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Cognitive performance in DFNA9 patients

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Content

List of abbreviations

AC	Air Conduction
AD	Alzheimer's Disease
BV	Bilateral Vestibulopathy
BC	Bone Conduction
COCH	Coagulation factor C Homology gene
c-VEMP	cervical Vestibular Evoked Myogenic Potential
DSM	Diagnostic and Statistical Manual of Mental Disorders
ENG	Electronystagmography
HADS-D	Hospital Anxiety and Depression Scale – Depression data
HL	Hearing Loss
ISO	International Organisation for Standardisation
Ivd	Intervening Domain
LARP	Left Anterior – Right Posterior semicircular canals
LCCL	Limulus factor C, Cochlin late gestation lung protein Lgl1
MCI	Mild Cognitive Impairment
MMSE	Mini-Mental State Examination
PHQ-9	9-item Patient Health Questionnaire scale
PTA	Pure Tone Audiometry
RALP	Right Anterior – Left Posterior semicircular canals
RBANS-H	Repeatable Battery for the Assessment of Neuropsychological Status adjusted for Hearing-impaired individuals
SCC	Semicircular Canals
SCD	Semicircular Duct
SCM	Sternocleidomastoid Muscle
SD	Standard Deviation
SNHL	Sensorineural Hearing Loss
SP	Signal Peptide
SPIN	Speech-In-Noise Test
SPL	Sound Pressure Level
vHIT	video Head Impulse Test
vMWMT	virtual Morris Water Maze Task
VNG	Videonystagmography
VOR	Vestibulo-Ocular Reflex
VSR	Vestibulospinal Reflex

vWFA	von Willebrand factor A-like
WHO	World Health Organisation

Abstract

Background: DFNA9 is a hereditary disease caused by mutations in the *COCH* gene. This progressive disease is characterised by a late-onset Sensorineural Hearing Loss (SNHL) and an evolution towards Bilateral Vestibulopathy (BV). Literature has indicated that HL contributes as a risk factor for cognitive decline. Evidence of a higher prevalence of HL in people suffering from dementia has already been published. In addition, previous studies have shown the independent association between HL and age-related cognitive decline. Furthermore, BV is suggested to contribute as a risk factor for cognitive decline. A correlation has been reported between the severity of hippocampal atrophy, which is a biomarker for Alzheimer's Disease (AD), and the degree of spatial memory loss in patients with BV in human, as well as in animal models. Moreover, a higher prevalence of vestibular loss has been observed in people suffering from cognitive impairment. A recent study outlined the fact that SNHL is highly prevalent in BV patients (range from 31% to 44%), yet only limited studies are performed to investigate whether cognitive deficits in BV patients are solely due to BV or (partially) due to SNHL. In addition, a link between SNHL, BV and depression is suggested. Besides, depression might also be related to cognitive decline. However, the co-occurrence of SNHL, BV and depression has frequently been overlooked, which might have resulted in unwarranted conclusions.

Design: The study includes 46 DFNA9 patients and 46 healthy controls. Healthy controls are individually matched based on age, sex and educational level. Of the 46 DFNA9 patients, 29 are diagnosed with BV according to the Bárány society criteria. The primary outcome measure is cognition measured by the Total Scale and index scores of the Repeatable Battery for the Assessment of Neuropsychological Status adjusted for Hearing-impaired individuals (RBANS-H). The secondary outcome measure is depression evaluated by the total score of the Hospital Anxiety and Depression Scale – depression data (HADS-D).

Objective: The primary objective of this cross-sectional study is to investigate the effects of both HL and BV on cognition. This is achieved by evaluating cognitive performance in a DFNA9 population with the p.Pro51Ser variant in the *COCH* gene and comparing it to the cognitive performance of healthy matched controls. The secondary objective is to compare cognitive performance of DFNA9 patients who are diagnosed with BV according to the Bárány society criteria and DFNA9 patients without BV. The third objective is to compare HADS-D scores between DFNA9 patients and healthy matched controls.

Results: DFNA9 patients obtained a lower score on the RBANS-H Total Scale and index scores compared to healthy matched controls. The difference was significant for the Total Scale score and all subdomains (Immediate Memory, Visuospatial/Construction, Attention and Delayed Memory), except Language. No significant differences were found in the RBANS-H Total Scale and index scores between DFNA9 patients with and without BV. Lastly, DFNA9 patients obtained a significantly higher score on the HADS-D compared to healthy matched controls.

Conclusion: According to this study, DFNA9 patients showed deficits in the Total Scale score of the RBANS-H, which was most pronounced in cognitive subdomains Immediate Memory, Visuospatial/Construction, Attention and Delayed Memory. In contrast, subdomain Language remained preserved. These results support the evidence that HL, BV and possibly their interaction contribute as risk factors for cognitive decline and dementia. No significant differences were observed between DFNA9 patients with and without BV. Furthermore, evidence of a link between depression and DFNA9 can be supported, since a higher score was obtained by DFNA9 patients on the HADS-D.

Part I

GENERAL INTRODUCTION

1. Introduction

1.1 DFNA9

Worldwide more than 440 million people suffer from Hearing Loss (HL), which is therefore the most frequent sensory deficit in the human population (Olusanya *et al.*, 2019). Some types of HL are hereditary, which can be divided into syndromic HL on the one hand, and non-syndromic HL on the other hand. Additionally, HL can be classified as Sensorineural HL (SNHL), conductive or mixed HL. (Zahnert, 2011, Verdoodt *et al.*, 2021). DFNA9 is a progressive, autosomal dominant, hereditary, non-syndromic and late-onset disease characterised by SNHL and an evolution towards Bilateral Vestibulopathy (BV). However, the penetrance of vestibular impairment varies between patients (Ihtijarevic *et al.*, 2019, Verdoodt *et al.*, 2021). DFNA9 refers to the ninth locus that has been associated with a DeaFNess Autosomal dominant disorder (Janssens de Varebeke *et al.*, 2019). This disease is caused by mutations in the Coagulation factor C Homology (*COCH*) gene, which is found on the long arm of chromosome 14 (14q12-q13) (Verdoodt *et al.*, 2021). This gene encodes for the cochlin protein, which can be found abundantly in the spiral ligament and spiral limbus of the inner ear, but also in the spleen and even at very low levels in the kidney, liver, eyes, cerebellum and brainstem (De Belder *et al.*, 2017, Verdoodt *et al.*, 2021). The average age of HL onset lies between the third and fifth decade (Figure 1). Nevertheless, the age of onset depends on the mutation. In addition, Janssens de Varebeke *et al.* (2021) reported similar, however slight differences in age of HL onset between male and female carriers. More precisely, third-decade onset is more associated with females (average of 38 years), whereas the fifth-decade onset is more linked to males (average of 46 years). Nevertheless, these differences can be due to more stringent age-referenced limits in male carriers. DFNA9 patients first lose the ability to hear higher frequencies. They experience an average deterioration of 3 dB HL per year, which progressively evolves towards deafness around the 7th decade (De Belder *et al.*, 2017, Janssens de Varebeke *et al.*, 2021). Vestibular symptoms mostly occur a few years after the onset of SNHL or in some cases simultaneously or even prior to SNHL. Initially, patients complain about vertigo spells, which progressively evolves towards BV at an average age of 53 years (Janssens de Varebeke *et al.*, 2021).

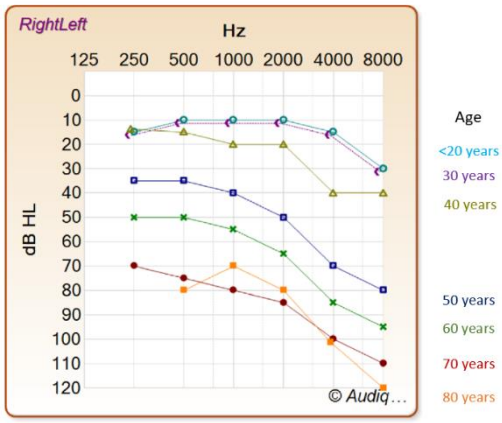

Figure 1. Representation of the cumulative age-related typical audiogram based on bilateral averaged hearing levels of DFNA9 patients with a p.Pro51Ser variant in the *COCH* gene. DFNA9 patients first lose the ability to hear higher frequencies. The onset of hearing loss lies between the third and fifth decade, which progressively evolves towards deafness around the seventh decade (Janssens de Varebeke et al., 2021).

1.1.1 The COCH gene

The *COCH* gene contains the following domains: an N-terminal signal peptide (SP) for secretion, a Limulus factor C, Cochlin, and late gestation lung protein Lgl1 (LCCL) domain, two von Willebrand factor A-like (vWFA) domains (vWFA1 and vWFA2) and two short intervening domains (ivd) as seen in Figure 2 (Robertson *et al.*, 2014). These domains are connected by cysteine residues that form disulphide bonds and are responsible for the structural integrity of the protein (Street *et al.*, 2005). Although the physiological function of cochlin remains unclear, it is known that it contributes to the maintenance of balance in the inner ear and that it assists in the structural support of the extracellular matrix and sound processing. For example, the vWFA2 domain is involved in cell adhesion of extracellular matrix proteins, such as collagen (Whittaker and Hynes, 2002). Since the vWFA domains are present in several major components of the extracellular matrix it is suggested that cochlin plays a structural role in the extracellular matrix of the cochlea (Robertson *et al.*, 1998). Furthermore, The LCCL domain is suggested to play a role in host defence mechanisms, since *COCH* expression by follicular dendritic cells in mouse spleen and lymph nodes has been reported (Py *et al.*, 2013). In addition, the involvement of cochlin in the innate immune response has been demonstrated by Py *et al.* (2013). Moreover, the LCCL domain has been associated with cytokine production, macrophage activation, and immune cell recruitment after pathogen exposure. (Jung *et al.*, 2019).

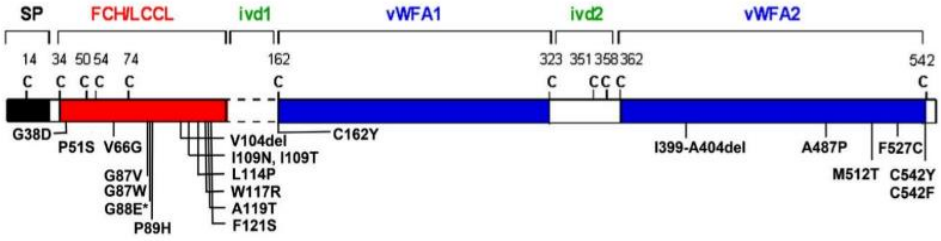

Figure 2. Schematic representation of the cochlin protein consisting of a signal peptide (SP), a Limulus factor C, Cochlin, late gestation lung protein Lgl1 (LCCL) domain, two von Willebrand factor A-like (vWFA) domains (vWFA1 and vWFA2) and two short intervening domains (ivd). These domains are connected by cysteine residues (C) that form disulphide bonds, which are responsible for the structural integrity of the protein (Robertson et al., 2014). The LCCL domain plays a role in the innate immune system (Py et al., 2013). The vWFA2 domain is involved in cell adhesion of extracellular matrix proteins, such as collagen (Whittaker and Hynes, 2002). There are 22 known mutations in the *COCH* gene that can cause DFNA9 (Janssens de Varebeke et al., 2019). Potential mutations are indicated in bold (Robertson et al., 2014).

1.1.2 Mutations in the COCH gene

DFNA9 can be caused by one of the 22 known mutations in the *COCH* gene. These known pathogenic variants are located at different domains of the *COCH* gene, with all slightly different phenotypes. The p.Pro51Ser mutation is most frequently found in Belgium and the Netherlands. Hence, only carriers of the p.Pro51Ser mutation are included in this study (Janssens de Varebeke *et al.*, 2019, Verdoodt *et al.*, 2021). The role of mutated cochlin is not yet fully understood. Nonetheless, several studies suggest that mutated cochlin aggregates interfere with the interactions between extracellular matrix proteins (Robertson *et al.*, 2001, Robertson *et al.*, 2003, Bhattacharya, 2006). Moreover, mutated cochlin is hypothesised to have a toxic effect on the dendritic processes of spiral ganglion cells and vestibular neurons, which may lead to the disruption of ionic cycling, especially in the spiral ligament (Merchant *et al.*, 2000). The characteristic pathology in temporal bones of DFNA9 patients, such as accumulation of acellular eosinophilic deposits throughout the labyrinth, as well as diffuse degeneration of the spiral ligament and spiral limbus, can be explained by the belief that *COCH* gene mutations affect the intracellular trafficking of cochlin (Verdoodt *et al.*, 2021). Mutations in the vWFA domains are associated with an earlier onset of disease, due to their effect on intracellular trafficking of cochlin.

Most of these variants in the vWFA domains have limited or complete absence of vestibular symptoms, because of the intracellular accumulation of mutant cochlin, which leads to early cell death. In contrast, mutations in the LCCL domain will not affect the intracellular trafficking but will lead to misfolding of the LCCL domain. Mutations in this domain give rise to progressive SNHL and are associated with more pronounced vestibular dysfunction, due to the misfolding of mutant cochlin. Nonetheless, patients with the same mutation can still show different phenotypes. This indicates that the pathogenesis is not yet fully elucidated and further research is warranted (Janssens de Varebeke *et al.*, 2021, Bae *et al.*, 2014).

1.2 Sense of hearing

As seen in Figure 3, the human ear can be divided into three parts: the external, middle and inner ear (George and Bordoni, 2022). Sound waves enter the external ear canal and travel towards the tympanic membrane. Subsequently, the tympanic membrane starts to vibrate. These vibrations are then transferred along the three bony ossicles (malleus, incus and stapes) (Casale *et al.*, 2021). These ossicles allow the transmission and amplification of sound waves, by connecting the tympanic membrane to the inner ear. So, vibrations of the tympanic membrane result in movement of the bony ossicles, leading to a displacement of a fluid called the perilymph in the cochlea of the inner ear (George and Bordoni, 2022, Sliwinska-kowalska, 2015a). These vibrations travel up through the scala vestibuli to the apex of the cochlea and then through the scala tympani towards the base. Between the scala vestibuli and scala tympani lies the cochlear duct. The cochlear duct consists of a fluid known as the endolymph, which contains a higher positive potential than the surrounding perilymph. This positive potential is established by a higher K^+ and lower Na^+ ion concentration. The Reissner's and basilar membrane separate respectively the scala vestibuli and the scala tympani from the cochlear duct. The basilar membrane consists of the organ of Corti, which is a specialised structure that plays a key role in auditory transduction. Thus, the vibrations will travel from the perilymph in the scala vestibuli through the Reissner's membrane into the endolymph of the cochlear duct and will eventually vibrate the organ of Corti (Figure 4). The organ of Corti consists of hair cells that respond to these vibrations by brushing their stereocilia against a fixed structure called the tectorial membrane. This results in a depolarization of the attached nerve fibers. So, the organ of Corti converts acoustic stimuli into electrical nerve stimuli. These stimuli travel around the vestibulocochlear nerve towards the auditory cortex, where these nerve stimuli are converted into meaningful sounds. The frequency of the vibrations travelling through the perilymph will correspond to an area of the cochlea that is maximally stimulated. More specifically, high-pitched sounds will stimulate hair cells in the lower part of the cochlea, whereas low-pitched sounds stimulate the upper part. This allows interpretation of various frequencies. Human beings can detect sounds in a frequency range from 20Hz to 20.000Hz (Casale *et al.*, 2021, Sliwinska-kowalska, 2015a).

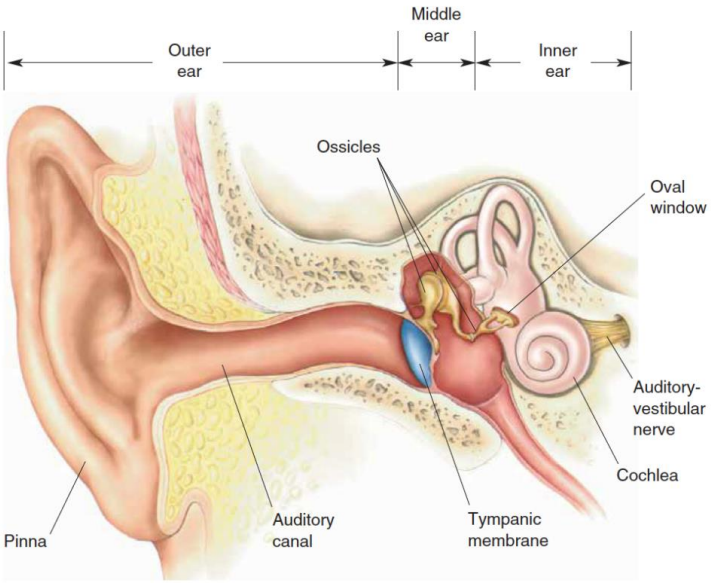

Figure 3. The human ear can be divided into three parts: outer, middle and inner ear (Bear, 2007).

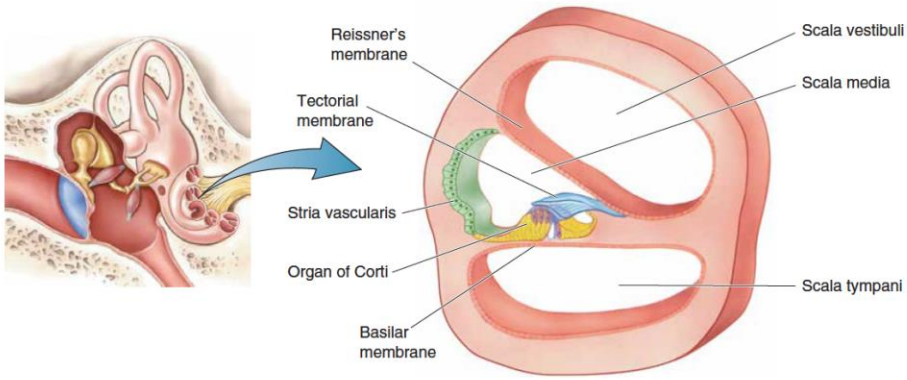

Figure 4. A cross-sectional representation of the three scalae of the cochlea located in the inner ear (Bear, 2007). The middle ear transfers sound vibrations into the cochlea of the inner ear. Subsequently, the fluids in the cochlea start to move, which stimulates the sensory hair cells located in the Organ of Corti, which can be found in the basilar membrane. Subsequently, hair cells convert acoustic stimuli into electric nerve stimuli. These stimuli travel around the vestibulocochlear nerve towards the auditory cortex, where they can be converted into meaningful sounds (Casale et al., 2021, Davies, 2020, Sliwinska-kowalska, 2015a).

1.2.1 Types of Hearing Loss (HL)

As mentioned earlier, a division can be made between different types of HL, namely SNHL, conductive or mixed HL. DFNA9 patients suffer from SNHL, which affects the conversion of mechanical sounds into neuroelectric stimuli in the inner ear or auditory nerve. Conductive HL, on the other hand, is characterised by problems involving the middle ear or tympanic membrane, which interferes with the transmission of sound and conversion to mechanical vibrations. Mixed HL is suggested when there is damage to both the middle and inner ear (Michels *et al.*, 2019).

1.2.2 Degree of Hearing Loss (HL)

According to the World Health Organisation (WHO), the severity of HL can be classified as mild, moderate, severe or profound. In Table 1, grades of HL and the corresponding audiometric ISO (International Organisation for Standardisation) values are indicated by best ear pure-tone average of hearing thresholds at frequencies of 500, 1000, 2000 and 4000 Hz. Mild HL is suggested when a hearing level of ≤25 dB is observed. A hearing level of 41-60 dB is considered moderate HL. Severe HL occurs with a 61-80 dB hearing level. Finally, a hearing level of ≥ 81 dB is characterised as profound HL (Olusanya, 2019).

Table 1. WHO's Grades of Hearing Loss (HL).[1]

Degree of Hearing Loss (in dB hearing level)	
Mild	≤ 25
Moderate	41-60
Severe	61-80
Profound	≥ 81

1.3 Vestibular function mechanism

The vestibular system serves a wide variety of functions, including the sensation of linear and angular acceleration of the head in three-dimensional space. Furthermore, the vestibular system is responsible for the Vestibulo-Ocular Reflex (VOR) and the Vestibulospinal Reflex (VSR), which allows the stabilisation of the visual image on the retina and the adjustment of posture during head movements. More precisely, the VOR permits the fixation of the eyes on a point while the head is moving, by making compensatory eye movements in the direction opposite of the head movements. An impaired VOR can lead to oscillopsia. In addition, the VSR allows the coordination of the spinal musculature with head movements to maintain balance and posture (Casale *et al.*, 2022, Hitier *et al.*, 2014). The inner ear, as seen in Figure 5, consists mainly of the bony labyrinth on the one hand, which consists of three Semicircular Canals (SCC) (anterior, lateral and posterior), the cochlea and the vestibule. The membranous labyrinth, on the other hand, is located within the bony labyrinth and consists of three Semicircular Ducts (SCD) and two otolith organs (saccule and utricle) within the vestibule (Davies, 2020). The bony labyrinth is filled with a fluid called perilymph, whereas the membranous labyrinth is filled with a fluid called endolymph (Casale *et al.*, 2022, Ciuman, 2009). In the saccule, receptors that are sensitive to linear movements along the vertical axis can be found, whereas the utricle is involved in horizontal movements and gravity. The three SCC, on the contrary, are involved in the sensation of rotational movements of the head (Ekdale, 2016). The neuroepithelium of the otolith organs is called the macula, whereas the neuroepithelium of the SCD is called the crista ampullaris. Both neuroepithelia contain hair cells, which are specialized mechanoreceptors. On top of these hair cells, a vast number of actin filaments, called stereocilia can be found. These stereocilia contain cation channels at their apex and are organised by their length. The tallest stereocilia are connected to the immobile kinocilium (Ciuman, 2011, Casale *et al.*, 2022, Khan and Chang, 2013). Acceleration of endolymph results in movement of the stereocilia. This movement can either cause depolarization or hyperpolarization depending on the direction. Movements towards the kinocilium open the cation channels, resulting in an influx of K^+ and depolarization. The depolarised hair cells will subsequently release glutamate to afferent nerve cells. Movements in the opposite direction of the kinocilium, on the contrary, result in closure of the cation channels and thus hyperpolarization, due to the lack of K^+ influx. This leads to an inhibition of glutamate release to afferent nerve cells (Ciuman, 2011, Khan and

[1] OLUSANYA, B. O., DAVIS A. C., HOFFMAN H. J. 2019. *Hearing loss grades and the International classification of functioning disability and health* [Online]. [Accessed 2022].

Chang, 2013, Kingma and van de Berg, 2016). Then, afferent nerve signals travel via the vestibulocochlear nerve towards the central vestibular system in the brain, where they can be interpreted. This results in eye, head and body motor responses for control of balance and orientation (Khan and Chang, 2013).

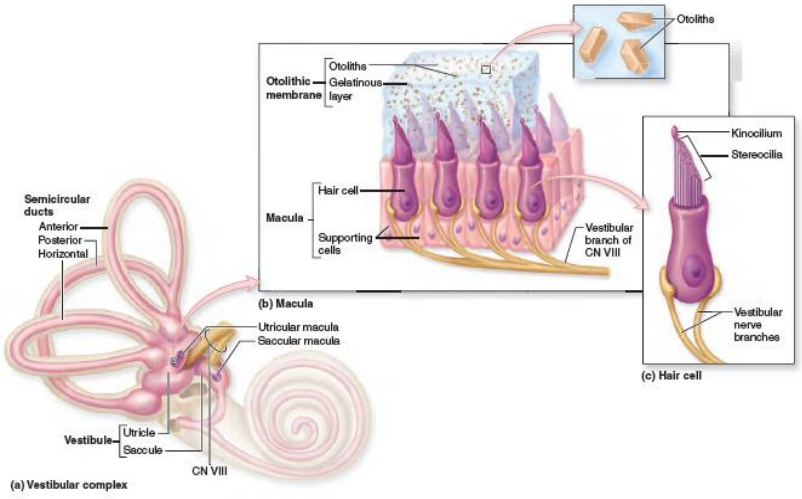

Figure 5. Schematic representation of the vestibular system (Hill, 2018). The vestibular apparatus consists of three Semicircular Canals (SCC) and two otolith organs (saccule and utricle), which are involved in the maintenance of balance and gaze stabilisation by detecting position and motion (Dobbels et al., 2019a). Endolymph within the Semicircular Duct (SCD) changes direction and/or speed upon movement of the head. This change is detected by the ampulla. The ampulla consists of sensory hair cells. At the top of these hair cells, small hairs, called stereocilia, can be found. The movement of endolymph results in movement of these stereocilia. Subsequently, neurotransmitters are released, which sends information about the plane of movement to the brain. This results in eye, head and body motor responses for control of balance and orientation (Khan and Chang, 2013).

1.3.1 Bilateral Vestibulopathy (BV)

Besides SNHL, DFNA9 patients also progressively suffer from BV. According to the Bárány Society criteria, BV is characterised by an impaired or absent VOR. In order to diagnose BV the following criteria should be present (Strupp *et al.*, 2017a):

A. Chronic vestibular syndrome with the following symptoms

1. Unsteadiness when walking or standing plus at least one of 2 or 3
2. Movement-induced blurred vision or oscillopsia during walking or quick head/body movements and/or
3. Worsening of unsteadiness in darkness and/or on uneven ground

B. No symptoms while sitting or lying down under static conditions

C. Bilaterally reduced or absent angular VOR function documented by

- bilaterally horizontal angular VOR gain <0.6, measured by the video Head Impulse Test (vHIT) and/or
- reduced caloric response (sum of maximal peak velocities of slow phase caloric-induced nystagmus on each side <6°/sec), measured by the Electronystagmography (ENG) and/or
- reduced horizontal angular VOR gain <0.1 upon sinusoidal stimulation on a rotatory chair (0.1 Hz, Vmax = 50°/sec), measured by the ENG

The techniques used to determine BV will be discussed in the Material and Methods section.

1.4 Cognition

Cognition can be defined as the mental action or process of acquiring knowledge and understanding through experiences, thoughts and the senses. Cognition encompasses six different domains, according to the Diagnostic and Statistical Manual of Mental Disorders. These domains include 'Learning and Memory', 'Language', 'Executive Function', 'Social Cognition', 'Complex Attention' and 'Perceptual Motor Function' (Figure 6). The Perceptual Motor Function domain is part of spatial cognition, whereas the other five domains are part of non-spatial cognition. Spatial cognition is defined as the way the mind processes and understands two-dimensional and three-dimensional space. This includes spatial navigation, as well as spatial memory. The former contains the ability to move through one's environment, which encompasses head direction. The latter integrates information about one's environment using different components, such as geometry, distance, relative position, coordinates, size and orientation (Bigelow and Agrawal, 2015).

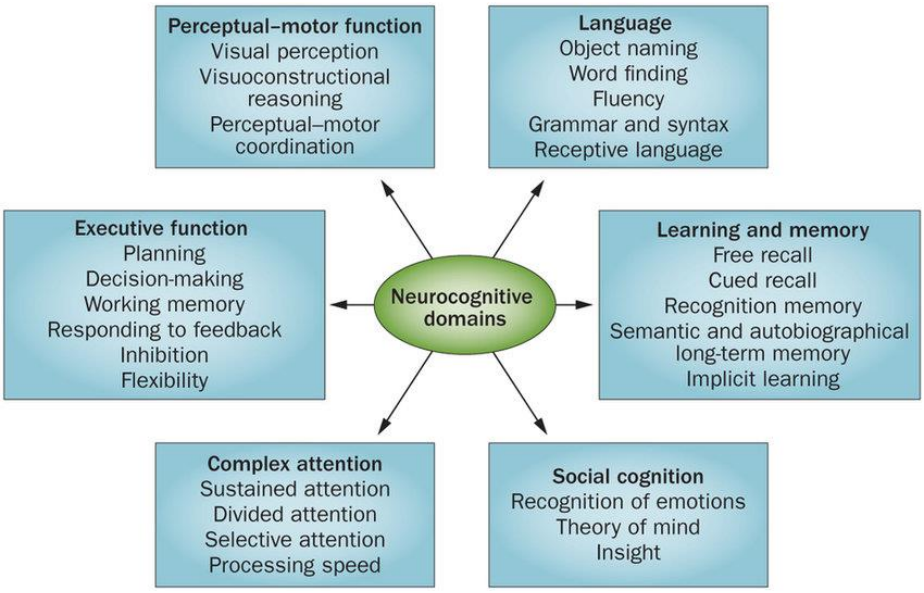

Figure 6. Schematic representation of cognition, which encompasses six different domains according to the Diagnostic and Statistical Manual of Mental Disorders. These domains include 'Learning and Memory', 'Language', 'Executive Function', 'Social Cognition', 'Complex Attention' and 'Perceptual Motor Function' (Sachdev et al., 2014).

1.4.1 Mild Cognitive Impairment (MCI) and Dementia

Mild Cognitive Impairment (MCI) is a decrease in cognitive function, where the ability to perform daily activities is not affected (Albert *et al.*, 2011). Dementia, on the contrary, is an umbrella term that includes all neurodegenerative diseases that are characterised by a decline in multiple cognitive domains, which also affects the ability to perform daily activities (Figure 7). Alzheimer's Disease (AD) accounts for 60-70% of all dementia cases and is therefore the most common type of dementia according to the WHO. Other dementia types include but are not limited to vascular dementia, dementia with Lewy Bodies and frontotemporal dementia (Greenblat, 2021). The WHO has recognised dementia as a public health priority due to the dramatically increasing prevalence, the enormous economic and social burden and the lack of cure or disease-modifying therapies. Since SNHL has been identified and BV has been suggested to contribute as a risk factor for cognitive decline and consequently dementia, further research unravelling these contributions and their possible interaction are warranted. In that way delaying the onset and progression of dementia can hopefully be achieved in the near future (Claes, 2018).

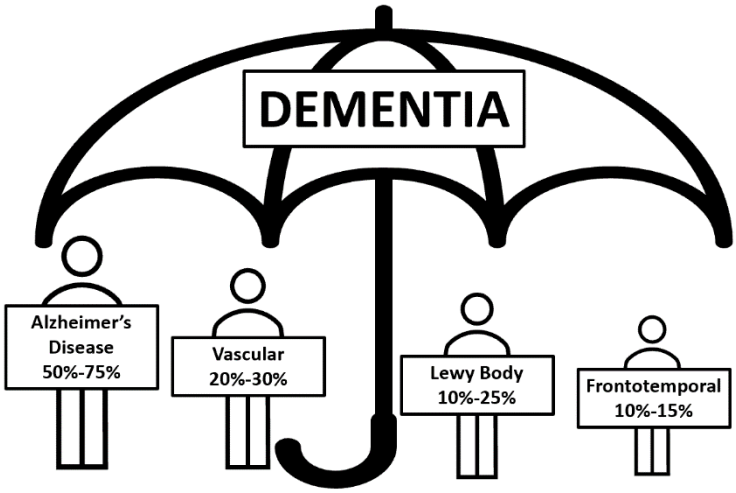

Figure 7. Dementia is an umbrella term that includes all neurodegenerative diseases that are characterised by a decline in multiple cognitive domains, which also affects the ability to perform daily activities. Alzheimer's Disease (AD) is the most common type of dementia, according to the WHO (Bogert, 2020). Other dementia types include but are not limited to vascular dementia, dementia with Lewy Bodies and frontotemporal dementia (Greenblat, 2021).

1.5 State-of-the-Art

1.5.1 Link between HL and cognitive decline

A possible association between HL and cognitive decline originates from decades ago (Uhlmann *et al.*, 1986, Thomas *et al.*, 1983). Research from Gates *et al.* (1996) has provided evidence that HL is more common in people suffering from dementia compared to healthy older adults. In addition, previous studies have shown the independent correlation between HL and age-related cognitive decline (Lin *et al.*, 2011b, Lin *et al.*, 2013, Gallacher *et al.*, 2012, Gurgel *et al.*, 2014, Fulton *et al.*, 2015, Wuyts *et al.*, 2016). Lin *et al.* (2013) performed a prospective observational study to assess the correlation between HL and accelerated cognitive decline. Cognitive performance of 1,984 older adults, from which 1,162 suffered from HL were evaluated. From the results, it could be concluded that HL is independently associated with accelerated cognitive decline and cognitive impairment. Moreover, an accelerated cognitive decline of 30-40% and a 24% increased risk of incident dementia was found in people suffering from HL. Besides, a more severe amount of HL resulted in an accelerated, as well as a higher risk for cognitive decline. Also, Harrison Bush *et al.* (2015) showed that peripheral HL accounted for small, yet significant changes in processing speed, executive function, memory and global cognitive status. Multiple other studies found similar associations, independent of age, sex, education or other confounding variables (Lin *et al.*, 2011a, Lin, 2011, Sugawara *et al.*, 2011). However, several studies could not confirm these findings (Bucks *et al.*, 2016, Tay *et al.*, 2006, Gussekloo *et al.*, 2005). Nonetheless, a recent study by Golub *et al.* (2020) showed a decrease in cognition with every 10 dB decline of hearing ability. A meta-analysis of ten prospective cohort studies was performed by Wei *et al.* (2017). These studies investigated if HL could be used as a predictor of MCI and dementia among older adults. Despite variations in hearing test protocols, assessment methods and outcome measures, all studies confirmed an association between HL on the one hand and cognitive decline on the other hand. Similar systematic reviews and meta-analyses have been published with consistent results (Zheng *et al.*, 2017, Thomson *et al.*, 2017, Loughrey *et al.*, 2018). To conclude, HL is a potentially modifiable risk factor for accelerated cognitive decline and cognitive impairment (De Belder *et al.*, 2017). However, the mechanistic basis of this relationship remains unclear. Investigating the role of HL in MCI and dementia is important, since hearing assessments may be performed to identify people at risk for cognitive decline. Moreover, hearing aids may be used among older adults in order to delay

the onset and progression of dementia. This hearing care might reduce the public health burden caused by MCI and dementia (Wei *et al.*, 2017). This topic will be further elaborated on in the Discussion section.

1.5.2 Link between BV and cognitive decline

In the past decades, numerous animal studies have shown a link between vestibular loss and spatial cognitive deficits (Wallace *et al.*, 2002, Zheng *et al.*, 2007, Zheng *et al.*, 2009, Zheng *et al.*, 2012, Zheng *et al.*, 2013, Baek *et al.*, 2010). However, only a few studies have been performed to assess the impact of BV on cognition in human patients (De Belder *et al.*, 2017, Bosmans *et al.*, 2022, Dobbels *et al.*, 2019a). Gizzi *et al.* (2003) performed an epidemiological study on 200 patients with a chief complaint of dizziness and concluded that there was no association between vestibular disease and cognitive impairment. However, Smith *et al.* (2005) did report a correlation, more specifically between the severity of hippocampal atrophy and the degree of spatial memory loss in patients with BV, as well as in animal models. Furthermore, several studies have shown that BV is correlated with hippocampal atrophy, as well as a decrease in spatial navigation, attention and memory impairment (Brandt *et al.*, 2005, Glasauer *et al.*, 2002, Göttlich *et al.*, 2016, Harun *et al.*, 2017, Kremmyda *et al.*, 2016, Popp *et al.*, 2017, Dobbels *et al.*, 2019b). Moreover, a decrease in spatial cognition could be predicted by the observed vestibular decline in patients with MCI and AD (Bosmans *et al.*, 2021). Besides, a significantly higher prevalence of vestibular decline was observed in spatially impaired patients with AD, compared to spatially normal patients with AD (Previc *et al.*, 2014, Wei *et al.*, 2018). Also, Harun *et al.* (2016b) investigated whether the vestibular function was impaired in individuals with MCI and AD. The results confirmed the emerging evidence of the link between vestibular decline and reduced cognitive performance. Lastly, Bosmans *et al.* (2022) explored if there was an association between BV and cognition. A total of 68 participants (55-84 years) were included of which 34 were diagnosed with BV and the remaining 34 were healthy controls matched based on age, sex and hearing performance. The results suggested an association between vestibular loss and cognitive decline. Hence, BV is hypothesised to contribute as a risk factor for cognitive decline. However, further research is necessary in order to determine the causal mechanisms underlying this association (Harun *et al.*, 2016b, Bosmans *et al.*, 2022).

1.5.3 Effect of HL and BV on cognition

As described before, several studies showed a link between HL and cognitive decline, as well as a link between BV and cognitive impairment. However, Dobbels *et al.* (2019a) outlined the fact that SNHL is highly prevalent in BV patients (range from 31% to 44%). In their study at least 85% of BV patients had abnormal hearing in at least one ear. Thus, their interaction should not be underestimated. Yet only limited studies are performed to investigate whether cognitive deficits in BV patients are solely due to BV or (partially) due to SNHL. In addition, a systematic literature review by Dobbels *et al.* (2019b), with the aim to evaluate the relationship between BV and cognition, mentioned that most of the studies did not take HL into account as a potential confounding variable. Consequently, further research is necessary. Therefore, Dobbels *et al.* (2019a) performed a cross-sectional study on 64 BV patients and 83 control participants. Both groups consisted of patients with different levels of hearing impairment. Cognition was evaluated by using the Repeatable Battery for the Assessment of Neuropsychological Status adjusted for Hearing-Impaired Individuals (RBANS-H), a cognitive test battery which will be described in the Material and Methods section. A correlation between HL and worse Total Scale on the RBANS-H, as well as on cognitive subdomains Immediate Memory and Language, was observed. In contrast, BV patients scored worse on cognitive subdomains Visuospatial/Construction and Attention. In addition, BV patients suffered from impaired spatial cognition, as well as impaired processing speed, Immediate Memory and executive function. To conclude, their results suggest a higher contribution of HL, than vestibular dysfunction to cognitive impairment (Dobbels *et al.*, 2019a, Brandt *et al.*, 2005).

Since DFNA9 patients suffer from both BV and SNHL, similar spatial and non-spatial cognitive impairment can be expected (Semenov *et al.*, 2016, Loughrey *et al.*, 2018).

1.5.4 Hypothesis

It can be hypothesised that there is a combined detrimental effect on cognition in patients with BV and SNHL, such as in DFNA9 patients (De Belder *et al.*, 2017). This indicates the importance of evaluating both vestibular and hearing function. Nevertheless, little research assessed both in their analysis. This leaves the question of whether the impact of HL on cognition might be related to concomitant BV (and vice versa) unanswered (Bosmans *et al.*, 2020).

1.5.5 Possible theories to explain the link between HL and cognitive decline

As already mentioned, the largest modifiable risk factor for dementia is HL and also vestibular loss is suggested to contribute as a risk factor for cognitive decline and consequently dementia. However, the underlying mechanisms are not yet fully elucidated, so further research is warranted. Four theories that elaborate on the effect of HL and vestibular loss on cognition will be discussed in more detail. A schematic overview of the hypotheses can be seen in Figure 8 (Rizk *et al.*, 2020, Mitchell *et al.*, 2020, Livingston *et al.*, 2020, Bosmans *et al.*, 2022).

1. **Cognitive load hypothesis**

The first hypothesis, namely the “cognitive load hypothesis”, suggests that HL increases the cognitive load in order to be able to understand the auditory stimulus. This is achieved by diverting cognitive resources to auditory processing at the expense of other cognitive resources (Campbell and Sharma, 2013, Erb and Obleser, 2013). Cognitive load in this context is the neural activity needed to understand the auditory stimulus (Martini *et al.*, 2014). In addition, this hypothesis can also be applied to elaborate on the effect of BV on cognition. In this regard, the hypothesis may also state that cognitive resources are diverted to maintain balance at the expense of other cognitive resources (Bigelow and Agrawal, 2015, Bosmans *et al.*, 2022).

2. **Deprivation or cascade hypothesis**

The second hypothesis is the “deprivation hypothesis” or “cascade hypothesis”. A study by Lin *et al.* (2014) showed that individuals with HL have accelerated whole-brain atrophy and a specific volume decline in the temporal regions of the brain, due to a reduced auditory input. These regions play a major role in spoken word processing, semantic memory and sensory integration (Peelle, 2012, Chételat *et al.*, 2005). It is also possible to apply this hypothesis to BV patients, where a reduced vestibular input leads to accelerated brain atrophy. Hippocampal atrophy, which is a biomarker for AD, is already observed in people with vestibular loss (Brandt et al., 2005, Göttlich et al., 2016, Bosmans et al., 2022). Interestingly to mention, BV can also lead to reduced physical activity, which in its turn leads to reduced vestibular input and subsequently to a decreased stimulation of the somatosensory and locomotor system. Hence, physical activity can be a possible predictor of cognitive decline (Domingos *et al.*, 2021, Radler *et al.*, 2021, Bosmans *et al.*, 2022).

3. **Social isolation hypothesis**

A third hypothesis is called the “social isolation hypothesis”, which states that people suffering from HL or BV isolate themselves. People with HL cannot contribute easily to a group conversation, due to difficulties with following the subject of the conversation (Mick *et al.*, 2014, Shankar *et al.*, 2013). In addition, people with BV often lead a more isolated life, due to their anxiety and fear of falling (Kirby and Yardley, 2012, Harun *et al.*, 2016a, Lin and Albert, 2014, Bosmans *et al.*, 2022).

4. Common cause hypothesis

The last hypothesis is the "common cause hypothesis". This theory suggests that one common genetic or environmental mechanism results in HL, vestibular loss and cognitive impairment. Possible common mechanisms and factors include neurodegenerative processes, age, vascular risk factors (e.g., diabetes and smoking) and social factors (e.g., educational level) (Lin and Albert, 2014, Previc, 2013, Bosmans *et al.*, 2022). If this last hypothesis is true, then HL and BV do not cause MCI and dementia. This would imply that hearing aids or vestibular rehabilitation do not reduce the risk of MCI and dementia, nor improve cognition. Hence, only neurogenerative processes could lead to cognitive improvement. However, this is very unlikely since several studies have already indicated that HL precedes MCI and dementia. Moreover, several researchers already observed a link between hearing aids and improved cognition (Zhan *et al.*, 2020, Sonnet *et al.*, 2017, Völter *et al.*, 2018, Claes *et al.*, 2018a, Mosnier *et al.*, 2015, Cosetti *et al.*, 2016, Dawes *et al.*, 2015).

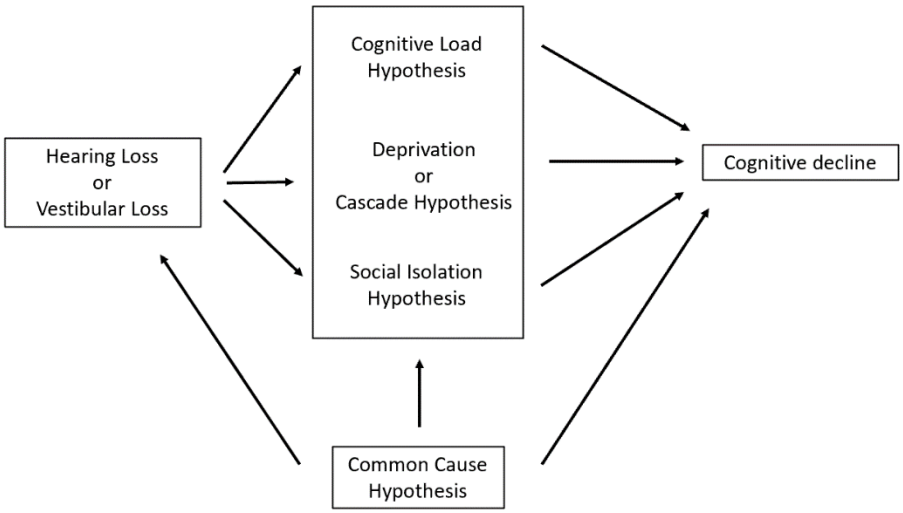

Figure 8. Theories that elaborate on the link between Hearing Loss (HL) or vestibular loss and dementia include the "cognitive load hypothesis", the "deprivation or cascade hypothesis", the "social isolation hypothesis" and the "common cause hypothesis" (Lin and Albert, 2014).

1.5.6 Link between HL and depression

Unfortunately, HL can impose an enormous economic and social burden on individuals (Campbell *et al.*, 1999). As already mentioned, HL can lead to social isolation, due to a decreased ability to communicate (Hogan *et al.*, 2009). Several studies have already indicated an association between HL and depression (Li *et al.*, 2014, Lawrence *et al.*, 2020, Rutherford *et al.*, 2018, Lucieer *et al.*, 2020, Huang *et al.*, 2010, Tambs, 2004, Keidser *et al.*, 2015). Depression is a common mental disorder, which affects approximately 264 million people around the world. According to the WHO, depression is characterised by sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, tiredness and poor concentration (World Health Organisation, 2019). Huang *et al.* (2010) performed a quantitative meta-analysis to assess the relationship between chronic diseases and risk for depression. The authors reported that HL is among the most common chronic conditions associated with depression in people aged 65 years or older. Furthermore, Li *et al.* (2014) investigated the link between depression and HL in 18,318 adults aged 18 years and older. Depression was evaluated by the 9-item Patient Health Questionnaire (PHQ-9) scale and HL was assessed by a self-report evaluation and an audiometric examination for participants aged 70 years and older. The results indicated a significant association between HL and an increased risk for depression in adults of all ages, however more pronounced in those aged 18 to 69 years. As such, untreated HL may have a negative impact on the social and psychological well-being of an individual. The results were consistent with

those of Tambs (2004), who performed a Norwegian population-based study on 50,398 adults aged 20 to 101 years. Nevertheless, few studies did not find a significant association among participants aged 50 to 70 years (Nachtegaal *et al.*, 2009, Bernabei *et al.*, 2011, Lee and Gomez-Marin, 1997). A study by Boorsma *et al.* (2012) reported that HL appeared to be protective among participants aged 85 years or older. This may indicate that different lifestyles, responsibilities and circumstances can result in different psychosocial issues. Additionally, research from Cosh *et al.* (2018) suggested that older adults may accept HL as part of the normal ageing experience and therefore adapt to changes in their hearing, which in turn mitigates the negative impact of HL on psychosocial experiences. Since studies reporting an association between HL and depression in older adults are often conflicting, Lawrence *et al.* (2020) performed a systematic review and meta-analysis of the evidence. Hence, 24 cross-sectional and 11 cohort designs were included. In general, HL was associated with a statistically significant increased risk to develop depression in older adults. However, it must be taken into account that ageing may also be associated with an increased risk for depression (Freeman *et al.*, 2016). In addition, Keidser *et al.* (2015) reported a significant association between HL and higher levels of depressive episodes, as well as depressive symptoms when controlling for age and sex. Nonetheless, a stronger association was observed in participants aged 40-49 years. In conclusion, the underlying mechanisms explaining the link between HL and depression are not yet fully understood and further research is warranted.

1.5.7 Link between BV and depression

Difficulties in performing routine daily activities, as well as chronic disequilibrium as a result of BV can harm the psychological well-being of an individual (Guinand *et al.*, 2012). Few studies have also indicated that patients with vestibular impairment are more prone to anxiety, depression and sleep disturbances (Bigelow *et al.*, 2016, Lahmann *et al.*, 2015, Smith *et al.*, 2019, Lucieer *et al.*, 2020). For example, Bigelow *et al.* (2016) performed a cross-sectional analysis to evaluate the association between vestibular vertigo on the one hand, and psychiatric diagnoses such as depression, anxiety and panic disorders on the other hand. Their results indicated a link between vestibular impairment and increased risk of psychiatric comorbidities. However, longitudinal studies need to be performed to further investigate a possible association between BV and depression.

1.5.8 Link between depression and cognition

Cognitive decline may also arise from the presence of neuropsychiatric comorbidities, such as depression. The term pseudodementia has been used in the literature to describe cognitive deficits in depression (Kiloh, 1961). A meta-analysis of Ownby *et al.* (2006) found an association between depression and a twofold increased risk of developing dementia later in life. In addition, an observational study by Sáez-Fonseca *et al.* (2007) indicated that moderate-to-severe depression in older adults contributes as a predictor of dementia. Moreover, a study by Hasselbalch *et al.* (2012) found that cognitive deficits are present in patients with a unipolar depressive disorder. The deficits are mostly observed in cognitive subdomain Attention and are characterised by impairment of processing speed and cognitive flexibility. Therefore, it may be hypothesised that there is an association between depression and cognitive decline.

1.6 Objectives

This master thesis aims to investigate the effect of both HL and BV simultaneously on cognition, since HL is highly prevalent in BV patients and vice versa (Figure 9). This is achieved by evaluating cognitive performance in 46 DFNA9 patients with a p.Pro51Ser mutation and 46 healthy controls, to see how the different cognitive subdomains are affected in these patients compared to healthy controls. The control group consists of individuals with preserved cognition individually matched based on age, sex and educational level. Data will be collected by performing hearing assessments, vestibular function assessments and a cognitive test battery. Cognition is evaluated by means of the RBANS-H Total Scale

and index scores. All assessments will be described in the Material and Methods section. It is hypothesised that DFNA9 patients will obtain a lower score on the RBANS-H Total Scale and index scores. In addition, BV is associated with a lower score on subdomains 'Attention' and 'Visuospatial/Construction', whereas SNHL is associated with a lower score on subdomains 'Language' and 'Immediate Memory' (Dobbels *et al.*, 2019a). Furthermore, since several studies indicated that HL, BV and cognitive decline are linked to depression, one may hypothesise that DFNA9 patients will obtain a significant higher score on the Hospital Anxiety and Depression Scale – Depression data (HADS-D) (Li *et al.*, 2014, Lawrence *et al.*, 2020, Rutherford *et al.*, 2018, Lucieer *et al.*, 2020).

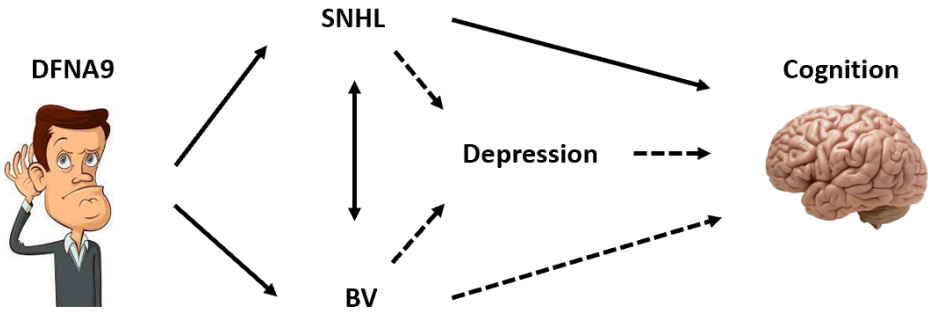

Figure 9. The aim of this master thesis is to investigate the effect of both Hearing Loss (HL) and Bilateral Vestibulopathy (BV) on cognition. This is achieved by evaluating cognitive performance in DFNA9 patients, since DFNA9 is associated with Sensorineural HL (SNHL) on the one hand, and BV on the other hand. It is important to assess both HL and BV simultaneously, since the co-occurrence of HL and BV is frequently been overlooked (Dobbels et al., 2019a).

As already mentioned, this master thesis aims to get insights into the effect of HL and BV on cognition. In total three research questions will be investigated:

Research question 1. Is there a significant difference in the RBANS-H Total Scale and index scores between DFNA9 patients and healthy matched controls?

Research question 2. Is there a significant difference in the RBANS-H Total Scale and index scores between DFNA9 patients with BV and DFNA9 patients without BV?

Research question 3. Is there a significant difference in the HADS-D score between DFNA9 patients and healthy matched controls?

Part II

MATERIAL AND METHODS

2. Material and methods

2.1 Study design

This study is a single-centre, cross-sectional study at the Department of Otorhinolaryngology-Head and Neck Surgery at Antwerp University Hospital (UZA) in Belgium and coordinated by the Department of Translational Neurosciences at the University of Antwerp. The assessments are performed by ICH-GCP-accredited researchers. All participants were assessed during one visit of approximately two hours. First, cognitive assessments are performed, in order to avoid fatigue and loss of attention. Afterwards, the vestibular assessments are conducted followed by the hearing assessments.

2.2 Study participants

In total 92 participants are recruited of which 46 DFNA9 patients with a p.Pro51Ser mutation in the *COCH* gene and 46 healthy controls (Figure 10). Each DFNA9 patient is individually matched with a healthy control based on age, sex and educational level. Of these DFNA9 patients, 29 are diagnosed with BV according to the Bárány Society criteria. Participants are recruited from the GECkO study (Gehoor, Evenwicht, COgnition) and the DFNA9 evolution study. The GECkO study is an ongoing prospective longitudinal study with the aim to evaluate the effect of HL, vestibular decline and their interaction on cognition (EC number B300201938949) (Bosmans *et al.*, 2020). The DFNA9 evolution study is an ongoing longitudinal study that investigates the evolution of the vestibular function and sense of hearing in DFNA9 patients (EC number B300202042807). All participants are aged 18 years or older.

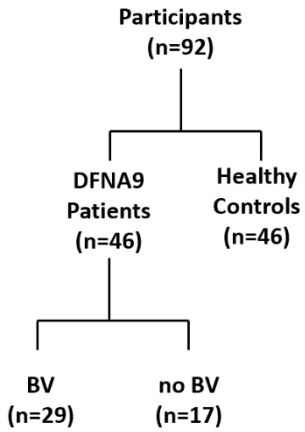

Figure 10. In total 92 participants are recruited of which 46 DFNA9 patients and 46 healthy matched controls. Of these DFNA9 patients, 29 are diagnosed with Bilateral Vestibulopathy (BV) according to the Bárány Society criteria. Participants are recruited from the GECkO study (Gehoor, Evenwicht, COgnition) and the DFNA9 evolution study.

2.3 Cognitive test battery

1. Mini-Mental State Examination (MMSE)

The MMSE is a simplified examination for cognitive mental status, which will be used as the first screening tool for cognitive impairment. This test evaluates an overall cognitive function in 5-10 minutes. The participants will need to answer 11 questions (Supplementary 1). The researcher asks the questions in the order listed and scores immediately (Folstein *et al.*, 1975). The MMSE covers different cognitive subdomains, namely Spatial and Temporal Orientation, Memory (immediate and delayed), Language, Visuospatial/Construction and Attention. A maximum score of 30 can be obtained (Folstein *et al.*, 1975). To enable vestibular assessment a total score >12 is needed (Harun *et al.*, 2017).

2. Repeatable Battery for the Assessment of Neuropsychological Status for Hearing-impaired individuals (RBANS-H)

The RBANS-H is a comprehensive neurophysiological assessment adjusted for hearing-impaired individuals to evaluate the general cognitive function (Claes *et al.*, 2016, Randolph *et al.*, 1998). This technique has a high sensitivity and age-corrected normative data (Duff *et al.*, 2005). This test is used to detect mild forms of cognitive disorders. The instructions and stimuli are simultaneously present in a visual and audible manner, to avoid potential bias due to HL. This is achieved by using an additional PowerPoint presentation shown on an external computer screen with written explanations and instructions (Claes *et al.*, 2016, Randolph *et al.*, 1998). The RBANS-H will evaluate five cognitive domains by using 12 subtests (Table 3 and Supplementary 2).

Immediate memory

Immediate memory is evaluated by the subtests 'List Learning' and 'Story Memory'. In 'List Learning' a list of 10 words is shown word by word for four times. After each round of 10 words, the participant is asked to recall as many words as possible. In 'Story Memory' a 12-item short story will be presented two times and after each time the participant is asked to recall the story.

Visuospatial/Construction

The Visuospatial/Constructional domain consists of subtests 'Figure Copy', on the one hand, and 'Line orientation', on the other hand. During 'Figure Copy', the participant needs to draw a complex geometric figure consisting of 10 items, which is shown to the participant during the entire drawing period. Afterwards, the 10 items are scored based on drawing and placement. During 'Line Orientation' participants need to match two lines according to their different degrees of orientation with a fan-shaped figure consisting of 13 numbered lines.

Language

'Picture Naming' and 'Semantic Fluency' subtests are used to assess language. The participant is asked to name 10 drawings, in the former. In the latter, the participant is asked to name as many fruit and vegetables/ zoo animals as possible in one minute.

Attention

Attention includes the subtests 'Digit span' and 'Coding'. In the subtest 'Digit Span' a string of digits is shown and the participant is asked to repeat the exact order of the digits. If the participant answered correctly the string of digits becomes longer. This exercise stops when the participant incorrectly answers twice or when the maximal score is obtained by successfully repeating the exact order of nine digits. Whereas in 'Coding' the participant is asked to fill in a page of symbols as much as possible in 90 seconds with the corresponding digits, that are found on top of the page.

Delayed memory

Delayed memory is assessed by asking the participant to recall the 10 words from the subtest 'List Learning', as well as the short story from 'Story Memory'. In addition, the participant is asked whether 20 words appeared in the 10-word list of 'List Learning'. Besides, the participant needs to redraw the complex figure from 'Figure Copy'. These subtests are called respectively 'List Recall', 'Story Recall', 'List recognition' and 'Figure Recall'.

Afterwards, index scores are calculated by converting the total scores of all the subtests. These index scores are normed based on the age of the participant. The Total Scale is subsequently calculated by using the sum of the index scores and can be converted into percentile scores. An RBANS-H Total Scale score <85 and a percentile <16 indicates a higher-than-expected cognitive impairment and is therefore used as the cut-off score (Albert *et al.*, 2011, Claes *et al.*, 2016).

Table 3. Table of the five cognitive domains and corresponding subtests of the Repeatable Battery for the Assessment of Neuropsychological Status adjusted for Hearing-Impaired Individuals (RBANS-H).[2]

Immediate memory	Visuospatial/Construction	Language	Attention	Delayed memory
- List Learning - Story Memory	- Figure Copy - Line Orientation	- Picture Naming - Semantic Fluency	- Digit Span - Coding	- List Recall - Story Recall - List Recognition - Figure Recall

2.4 Hearing assessments

1. Speech-In-Noise testing (SPIN)

Speech audiometry in noise is evaluated by using the Leuven Intelligibility Sentences Test (LIST) and is used to examine a participant's hearing ability in the presence of noise (van Wieringen and Wouters, 2008). During this test lists of 10 everyday sentences are presented bilaterally to the participant in a noisy environment (Supplementary 3) (Jansen *et al.*, 2013, Sliwinska-Kowalska, 2015b). This test is performed in a free field by using a loudspeaker at a distance of one meter and 0° azimuth (Carr, 2001). The participant is asked to repeat the sentence (Sliwinska-Kowalska, 2015b). The speech level will be adapted by the response of the participant, whereas the noise level will be set constant at 65 dB Sound Pressure Level (SPL). If the participant correctly repeats the keywords of the sentence, the speech level will be decreased by 2 dB SPL. On the contrary, when the participant incorrectly repeats the sentence, the speech level will be increased by 2 dB SPL. Minimally two lists with 10 sentences will be evaluated to be able to acquire the Speech Reception Threshold (SRT), which is defined as the lowest hearing level at which the participant can correctly repeat or identify the speech 50% of the time (Carr, 2001). In other words, the results indicate how loud the volume of the sentences needs to be turned up above the 65dB noise, in order for the participant to correctly repeat 50% of the sentence material (Sliwinska-Kowalska, 2015b). This threshold will be calculated by averaging the last five sentences and the imaginary 11th sentence of the last list (Portnuff and Bell, 2019).

2. Pure Tone Audiometry (PTA)

The PTA is considered the golden standard to evaluate hearing sensitivity. It is used to determine the lowest hearing threshold at which the participant responds to at least 50% of the auditory stimuli. In addition, PTA can determine the severity and type of HL. These pure tones are delivered to the ear via Air Conduction (AC) and Bone Conduction (BC) (Kung and Willcox, 2007). The thresholds are calculated for each ear separately. All tests are performed in a sound controlled environment (Carr, 2001). First, AC thresholds are measured for tonal stimuli at the frequencies of 125 Hz, 250 Hz, 500 Hz, 1000 Hz, 2000 Hz, 3000 Hz, 4000 Hz, 6000 Hz and 8000 Hz by using insert-earphones and a two-channel AC-40 audiometer (Interacoustics, Assens, Denmark) (Carr, 2001, Kung and Willcox, 2007). The participant is asked to respond to the auditory stimuli via hand-raising. The Hughson Westlake methodology will be used (Carr, 2001). Subsequently, BC thresholds are measured at 250 Hz, 500 Hz, 1000 Hz, 2000 Hz, 3000 Hz and 4000 Hz by using a headband with an oscillator (Kung and Willcox, 2007, Sliwinska-kowalska, 2015a).

[2] CLAES, A. J., MERTENS, G., GILLES, A., HOFKENS-VAN DEN BRANDT, A., FRANSEN, E., VAN ROMPAEY, V. & VAN DE HEYNING, P. 2016. The Repeatable Battery for the Assessment of Neuropsychological Status for Hearing Impaired Individuals (RBANS-H) before and after Cochlear Implantation: A Protocol for a Prospective, Longitudinal Cohort Study. *Front Neurosci,* 10, 512.

2.5 Vestibular function assessments

1. Video Head Impulse Test (vHIT)

The vHIT is used to evaluate the VOR in 10-15 minutes by using ICS Impulse (Otometrics, Natus, Pleasanton, California, USA) glasses with a built-in accelerometer and a video camera pointed at the right eye. This test is performed in a well-lit room (McGarvie *et al.*, 2015). By measuring the eye rotation response to an abrupt head movement in the direction of the SCC, the functional status of all six SCC can be evaluated separately. During this test, the vestibular system is stimulated at a high frequency (McGarvie *et al.*, 2015). The participants are instructed to avoid blinking as much as possible, as well as to relax their neck muscles (Jacobson *et al.*, 2020). To evaluate all six SCC individually, head impulses are delivered in the plane of the canals. There are three canal pairs, namely the two lateral canals, the Left Anterior – Right Posterior (LARP) and the Right Anterior – Left Posterior (RALP) canals (Figure 11). In order to test the LARP and RALP canal pairs, the head is rotated 30° to the right or left of the fixation dot respectively, while the participant is instructed to fixate on the dot, which is placed at eye level on one meter distance. All head movements are performed abruptly and unpredictably (McGarvie *et al.*, 2015). Measurements of interest are the VOR gain, the standard deviation (SD) of the VOR gain, the percentage and amplitude of the saccades, the amplitude of the head for all six SCC separately and a classification of the saccades as seen in Figure 12 (normal, gathered, scattered) (McGarvie *et al.*, 2015). The VOR gain is defined as the ratio of eye velocity to head velocity. In healthy subjects the VOR gain is around 1.0, whereas in BV patients the VOR gain is significantly less, namely <0.6. A VOR gain of 0.8-0.6 is considered normal in older participants due to ageing (Table 4) (Jacobson *et al.*, 2020).

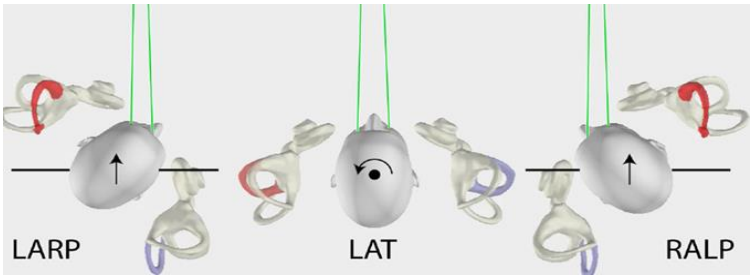

Figure 11. Schematic representation of head movements during the video Head Impulse Test (vHIT). All six Semicircular Canals (SCC) are evaluated separately. To evaluate the Left Anterior – Right Posterior (LARP) and Right Anterior – Left Posterior (RALP) canal pairs, the head of the participant is rotated 30° to the right or left respectively. The participant is always instructed to fixate on the dot, which is placed at eye level on one meter distance (McGarvie et al., 2015).

Table 4. The cut-off scores of the Vestibulo-Ocular Reflex (VOR) gain.[3]

vHIT VOR Gain		
Control	**Presbyvestibulopathy**	**BV**
1.0 – 0.8	0.8 – 0.6	<0.6

[3] MCGARVIE, L. A., MACDOUGALL, H. G., HALMAGYI, G. M., BURGESS, A. M., WEBER, K. P. & CURTHOYS, I. S. 2015. The Video Head Impulse Test (vHIT) of Semicircular Canal Function – Age-Dependent Normative Values of VOR Gain in Healthy Subjects. *Frontiers in Neurology,* 6.

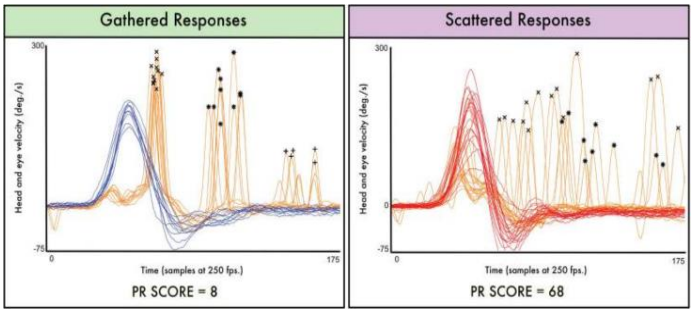

Figure 12. Saccades can be categorised in gathered or scattered saccades. The left figure shows a gathered saccade with isochronic impulses on a narrow time interval, whereas the right figure indicates a scattered saccade with asynchronic impulses on a wide time interval (Batuecas-Caletrio et al., 2017).

2. Cervical Vestibular Evoked Myogenic Potentials (c-VEMPs)

The c-VEMPs are electrical potential differences evoked by vestibular stimulation and recorded from the sternocleidomastoid muscle (SCM). They are used to evaluate the vestibular function of the saccule and inferior vestibular nerve by stimulating each ear separately with short tone bursts by using insert-earphones (Papathanasiou *et al.*, 2014). The presence of a response is independent of the severity of SNHL (Papathanasiou *et al.*, 2014). A validated neuroaudio device with electromyography feedback (Neurosoft) will be used to perform the c-VEMP (Fife *et al.*, 2017). Recordings will be made with an auditory evoked potential system equipped with electromyographic software (Neuro-Audio, Difra, Belgium). The participant is placed in a supine position to allow a higher muscle contraction. Afterwards, the participant is instructed to tilt his head to one side, thus contracting SCM, while the contralateral ear is stimulated. Subsequently, ipsilateral inhibiting muscle potentials are measured at the level of the contracted SCM. The evoked c-VEMPs are recorded with surface electrodes (Blue sensor, Ambu, Denmark) placed at the midpoint of the SCM and with the reference electrode on the upper part of the sternum and a ground electrode on the forehead (Figure 13). In a person with a normal saccule and inferior vestibular nerve function, two distinctive peaks can be observed, namely a positive peak at 13ms (range from 11.81 - 15.59 ms) (p13) and a negative peak at 23ms (range from 18.12 – 25.64ms) (n23) as seen in Figure 13 (Table 5). This indicates an intact reflex, where sound stimulates the saccule (Figure 14). The saccule then carries the signal through the ipsilateral inferior vestibular nerve to the vestibular nucleus from which the vestibulospinal pathway transmits a momentary inhibitory signal to the spinal accessory nerve supplying the ipsilateral SCM. A participant is considered to have an absent c-VEMP response, when no p13n23 is seen above 100dB acoustic clicks (Dobbels *et al.*, 2019a). However, not only the presence of this reflex is investigated, the threshold, as well as the latency of p13 and n23 and the amplitude for both ears are assessed (Fife *et al.*, 2017, Fife *et al.*, 2018, Janssens de Varebeke *et al.*, 2021). The larger the amount of muscle contraction, the larger the c-VEMP amplitude. This procedure should be replicated in order to verify the response presence (Papathanasiou *et al.*, 2014).

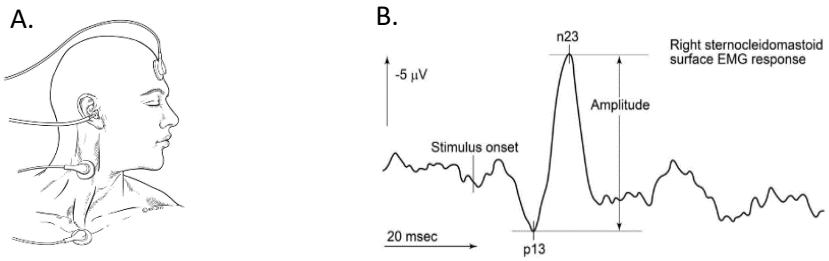

Figure 13. Figure A indicates the correct placement of the disposable Ag/AgCl electrodes (Blue Sensor type N-00-S) to record cervical Vestibular Evoked Myogenic Potentials (c-VEMP). Figure B shows the waveform of the c-VEMP in a healthy individual. Two distinctive peaks can be observed, namely a positive peak at 13 ms (p13) and a negative peak at 23 ms (n23) (Fife et al., 2017).

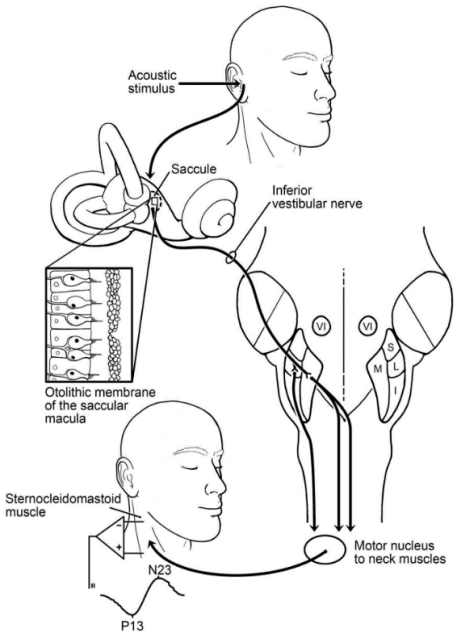

Figure 14. Reflex pathway mediating cervical Vestibular Evoked Myogenic Potential (c-VEMP) responses. Sound stimulates the saccule. The saccule carries the signal through the ipsilateral inferior vestibular nerve to the vestibular nucleus from which the vestibulospinal pathway transmits a momentary inhibitory signal to the spinal accessory nerve supplying the ipsilateral sternocleidomastoid muscle (SCM). Abbreviations: VI= abducens nucleus, S= superior vestibular nucleus, M= medial vestibular nucleus, L= lateral vestibular nucleus and I= inferior vestibular nucleus (Fife et al., 2017).

Table 5. Latencies of the cervical Vestibular Evoked Myogenic Potentials (c-VEMP). [4]

C-VEMP Latencies (ms)	
p13	**n23**
11.81 - 15.59 (mean=13.70)	18.12 – 25.64 (mean=21.90)

3. Electronystagmography (ENG)

Electronystagmography (ENG) is used to detect eye movements in order to evaluate the function of the vestibular and oculomotor nerves. In addition, the function of the right and left lateral SCC can be assessed separately by the caloric test and their interaction can be examined by the rotatory chair test. Eye movements are recorded by using electro-oculography (Kung and Willcox, 2007, Boyd, 2020). In total nine disposable Ag/AgCl electrodes (Blue Sensor type N-00-S) are placed on the head of the participant. One common ground electrode is placed on the forehead and the other electrodes are placed above, below, as well as on each side of both eyes and on each side of the nose to record electrical activity (Figure 15) (Van Der Stappen *et al.*, 2000, Gupta and Mundra, 2015).

[4] LI, C., ZUNIGA, M. G., NGUYEN, K. D., CAREY, J. P. & AGRAWAL, Y. 2014. How to interpret latencies of cervical and ocular vestibular-evoked myogenic potentials: Our experience in fifty-three participants. *Clin Otolaryngol,* 39**,** 297-301.

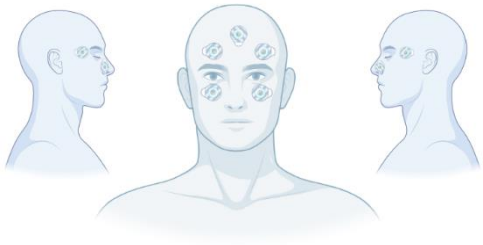

Figure 15. Placement of the electrodes to record Electronystagmography (ENG). In total nine disposable Ag/AgCl electrodes (Blue Sensor type N-00-S) are placed on the head of the participant. One common ground electrode is placed on the forehead and the other electrodes are placed above, below, as well as on each side of both eyes and on each side of the nose to record electrical activity. Created with BioRender (www.BioRender.com).

First, the calibration and the optokinetic tests are performed. Subsequently, the VOR function is evaluated by the rotatory chair test and caloric test. The rotatory chair test is performed to examine the interaction between the two lateral SCC. During this test, the participant is asked to sit in a chair, which rotates sinusoidally with a maximum angular velocity of 60°/s and a mid-frequency with a range of 0.01 – 0.64 Hz. This test takes two minutes, during which head movements are recorded by an angular rate sensor attached to the participant's head. The test is performed in total darkness and with closed eyes. In order to control the alertness, the participants are asked to perform a mental task. Participants with an intact VOR will show a slow phase eye velocity towards the direction opposite of the head velocity (Van Der Stappen *et al.*, 2000, Gupta and Mundra, 2015). A lateral VOR gain <0.1 upon sinusoidal stimulation on a rotatory chair implies BV (Strupp *et al.*, 2017b). Lastly, the caloric test is used to examine one lateral SCC independently of the other at a low frequency (Kung and Willcox, 2007). Caloric irrigation can identify the degree to which the vestibular system is responsive, as well as how symmetric the responses are between left and right (Strupp *et al.*, 2017b). During this test, the participant is placed in a dark room and in a supine position on a couch. The head end is raised 30 degrees above the horizontal to bring the lateral SCC in a vertical plane where they can be maximally stimulated (direction of gravity). The participant is asked to close his eyes and perform mental tasks, while both outer ear canals are consecutively irrigated with warm (44°C) and cold (30°C) water for 30s. This cold and warm water induces horizontal nystagmus by stimulating the lateral SCC. A cold stimulus results in nystagmus with the fast phase in the opposite direction, whereas a warm stimulus results in a nystagmus with the fast phase in the same direction. So, if a cold stimulus is applied to the left ear, the fast phase of the nystagmus will be directed to the right. In contrast, if warm water is applied the eyes will move rapidly towards the warm water and then slowly away. After each irrigation, a pause of 5 min follows to allow temperature stabilization in the labyrinth (Van Der Stappen *et al.*, 2000, Gupta and Mundra, 2015). A reduced caloric response and BV are implied when the sum of the bithermal maximum peak slow-phase velocity is <6°/s on each side (Strupp *et al.*, 2017b).

2.6 Patient-reported outcome

1. **Hospital Anxiety and Depression Scale (HADS)**

The HADS is a one-page questionnaire with a total of 14 items scored from zero to three (Supplementary 4). This questionnaire is a widely used instrument for detecting states of distress, depression and anxiety (Snaith, 1990). Hence, HADS is divided into an anxiety (HADS-A) and a depression (HADS-D) part, each consisting of 7 items. Only the HADS-D part is of interest for this master thesis. A higher score on the HADS-D is associated with a higher level of depression. More precisely, a score of 8-11 indicates a mild form of depression, whereas a score of 12-15 suggests a moderate form. A score of 15-21 indicates severe depression. A maximum score of 21 can be obtained (Table 6) (Zigmond and Snaith, 1983, Garaiman *et al.*, 2021).

Table 6. The cut-off scores of the Hospital Anxiety and Depression Scale – Depression data (HADS-D) Assessment.[5]

HADS-D		
Mild depression	**Moderate depression**	**Severe depression**
8-11	12-15	15-21

2.7 Overview methods

An overview of the used methods, as well as their corresponding requirements, cut-off scores an interpretation can be found in Table 7.

Table 7. Overview of the used methods, as well as their corresponding requirements, cut-off scores and interpretation. Abbreviations: MMSE= Mini Mental State Examination, RBANS-H= Repeatable Battery for the Assessments of Neuropsychological Status adjusted for Hearing-impaired individuals, MCI= Mild Cognitive Impairment, SPIN= Speech-In-Noise test, PTA= Pure Tone Audiometry, vHIT= Video Head Impulse Test, VOR= Vestibulo-Ocular Reflex, BV= Bilateral Vestibulopathy, c-VEMP= Cervical Vestibular Evoked Myogenic Potential, ENG= Electronystagmography and HADS-D= Hospital Anxiety and Depression Scale – Depression data.

Methods	Requirements	Cut-off scores	Interpretation
Cognitive test battery			
MMSE[6]	- One-page questionnaire (11 items)	<12	No enablement to vestibular assessments
RBANS-H[7]	- PowerPoint - Questionnaire with 12 subtests	Total scale <85 Percentile <16	MCI
Hearing Assessments			
SPIN[8]	- Loudspeaker - Leuven Intelligibility Sentences Test - Free field		
PTA[8]	- Sound controlled environment - Two-channel AC-40 audiometer (Interacoustics, Assens, Denmark) - Insert-earphones - Headband with oscillator		

[5] ZIGMOND, A. S. & SNAITH, R. P. 1983. The hospital anxiety and depression scale. Acta Psychiatr Scand, 67, 361-70.
[6] FOLSTEIN, M. F., FOLSTEIN, S. E. & MCHUGH, P. R. 1975. "Mini-mental state": A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research,* 12**,** 189-198.
[7] RANDOLPH, C., TIERNEY, M. C., MOHR, E. & CHASE, T. N. 1998. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity. J Clin Exp Neuropsychol, 20, 310-9.
[8] CARR, P. I. 2001. Development of an A elopment of an Audiological T udiological Test Procedure Manual for First e Manual for First

Vestibular function assessments			
vHIT[9]	- ICS Impulse (Otometrics, Natus, Pleasanton, California, USA) glasses - Accelerometer - Video camera pointed to the right eye	Bilaterally horizontal angular VOR gain: <0.6	BV
c-VEMP[10]	- Insert-earphones - 4 electrodes (Blue sensor, Amby, Denmark) - Neuroaudio device with electromyography feedback (Neurosoft) - Auditory evoked potential system equipped electromyographic software (Neuro-Audio, Difra, Belgium)	p13: 11.81 - 15.59 (mean= 13.70) n23: 18.12 – 25.64 (mean= 21.90)	Normal saccular and inferior nerve function
ENG[11]	- 9 Ag/AgCl electrodes (Blue sensor type N-00-S) - Electro-oculography - Rotatory chair - Water	Sum of maximal peak velocities of slow phase caloric induced nystagmus on each side: <6°/s Horizontal angular VOR gain: <0.1	BV
Patient reported outcome			
HADS-D[12]	- One-page questionnaire (14 items)	8-11 12-15 15-21	Mild depression Moderate depression Severe depression

[9] MCGARVIE, L. A., MACDOUGALL, H. G., HALMAGYI, G. M., BURGESS, A. M., WEBER, K. P. & CURTHOYS, I. S. 2015. The Video Head Impulse Test (vHIT) of Semicircular Canal Function – Age-Dependent Normative Values of VOR Gain in Healthy Subjects. *Frontiers in Neurology,* 6.

[10] FIFE, T. D., COLEBATCH, J. G., KERBER, K. A., BRANTBERG, K., STRUPP, M., LEE, H., WALKER, M. F., ASHMAN, E., FLETCHER, J., CALLAGHAN, B. & GLOSS, D. S., 2ND 2017. Practice guideline: Cervical and ocular vestibular evoked myogenic potential testing: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology, 89, 2288-2296.

[11] STRUPP, M., KIM, J. S., MUROFUSHI, T., STRAUMANN, D., JEN, J. C., ROSENGREN, S. M., DELLA SANTINA, C. C. & KINGMA, H. 2017b. Bilateral vestibulopathy: Diagnostic criteria Consensus document of the Classification Committee of the Bárány Society. J Vestib Res, 27, 177-189.

[12] ZIGMOND, A. S. & SNAITH, R. P. 1983. The hospital anxiety and depression scale. Acta Psychiatr Scand, 67, 361-70.

2.8 Statistical Analysis

All data is stored in OpenClinica LLC (Waltham, MA, United States). OpenClinica is an online password-protected case report form database used for data registration and management. For statistical analysis JMP Pro 16 statistics software (Medmenham UK) and for boxplot creation RStudio statistical program version 1.4.1103 are used. For the sample size calculation, a power analysis is performed. Therefore, a Two-Tailed T-test is used to estimate the required sample size to be able to detect significant differences in the primary outcome variable (RBANS-H Total Scale and index scores) between DFNA9 patients and healthy matched controls. The results suggest a sample size of 34 subjects per group with a power of 80%, SD of 8 and a significance level of α=0.05. In order to get more reliable data a total of 46 DFNA9 patients and 46 healthy matched controls are included. For the primary outcome, the difference between independent measurements will be compared. Two groups, namely one continuous (RBANS-H score) and one categorical (DFNA9/control) variable will be used. First assumptions will be checked (Figure 16). In order to verify if the data is normally distributed, histograms are plotted and a Shapiro-Wilk Test will be performed. Subsequently, to check for equal variances, a Levene's Test will be carried out. A Two-Sample Pooled T-test will be used if assumptions are met. If not, a non-parametric test, namely the Wilcoxon test, will be performed. A p-value <0.05 will be considered statistically significant. In that case, the null hypothesis will be rejected. A p-value >0.05 will not be considered statistically significant. Therefore, the null hypothesis will be accepted.

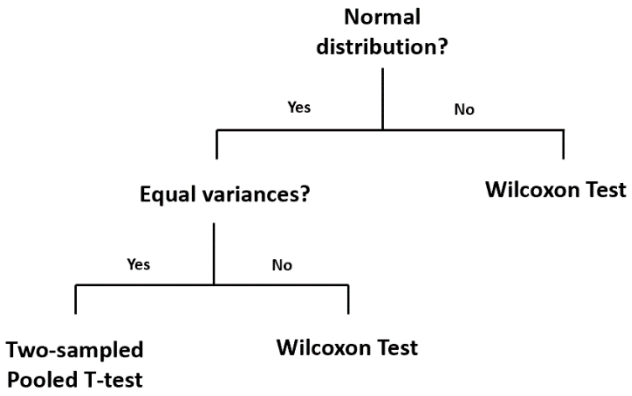

Figure 16. Schematic overview of the statistical analysis. First assumptions will be checked. If the data is normally distributed and has equal variances a Two-Sampled Pooled T-test will be performed. Otherwise, a non-parametric Wilcoxon test will be used.

Part III

RESULTS

3. Results

3.1 Assumptions check

3.1.1 Normal distribution

To check if the data is normally distributed, a histogram is plotted and a Shapiro-Wilk test is performed (Table 8).

Table 8. P-values of the Shapiro-Wilk Test to check if the data is normally distributed. Statistically significant results are indicated with an asterisk.

	p-Value Shapiro-Wilk Test
Study population (see 3.2)	
Age	0.0333*
Hearing Level	
FI_{high} best ear (unaided dB HL)	<0.0001*
Educational Level	0.1973
Research question 1 (see 3.3)	
Immediate Memory	0.0636
Visuospatial/Construction	0.0028*
Language	0.0138*
Attention	0.1869
Delayed Memory	<0.0001*
Total Scale	0.3779
Research question 2 (see 3.4)	
Immediate Memory	0.5067
Visuospatial/Construction	0.0375*
Language	0.1373
Attention	0.8472
Delayed Memory	0.0040*
Total Scale	0.3013
Research question 3 (see 3.5)	
HADS-D	<0.0001*

Study population. As seen in Table 8, Age and FI_{high} best ear (unaided dB HL) are not normally distributed (p-value of 0.0333 and <0.0001 respectively). Hence, a Wilcoxon test will be performed for this data. Educational Level, on the contrary, has a normal distribution (p-value of 0.1973). If equal variances are confirmed (see 3.1.2) a Two-Sampled Pooled T-test will be performed.

Research question 1. Immediate Memory, Attention and Total Scale data have a normal distribution (p-value of 0.0636, 0.1869 and 0.3779 respectively). For this data a Two-Sample Pooled T-test can be performed if the data has equal variances (see 3.1.2). Subdomains Visuospatial/Construction, Language and Delayed memory, on the contrary, are not normally distributed (p-value of 0.0028, 0.0138 and <0.0001 respectively). For this data a non-parametric Wilcoxon test will be performed.

Research question 2. Immediate memory, Language, Attention and Total Scale data have a normal distribution (p-value of 0.5067, 0.1373, 0.8472 and 0.3013 respectively). For this data a Two-Sample Pooled T-test can be performed if the data has equal variances (see 3.1.2). Subdomains Visuospatial/Construction and Delayed memory, on the contrary, are not normally distributed (p-value of 0.0375 and 0.0040 respectively). For this data a non-parametric Wilcoxon test will be performed.

Research question 3. HADS-D data is not normally distributed (p-value of <0.0001). Hence, a Wilcoxon test will be performed.

3.1.2 Equal variances

To check if the normally distributed data has equal variances, a Levene's Test will be performed.

Table 9. P-values of the Levene's Test to check for equal variances. Statistically significant results are indicated with an asterisk.

	p-Value Levene's Test
Study population (see 3.2)	
Educational Level	0.6212
Research question 1 (see 3.3)	
Immediate Memory	0.7134
Attention	0.6530
Total Scale	0.1639
Research question 2 (see 3.4)	
Immediate Memory	0.0069*
Language	0.4350
Attention	0.1660
Total Scale	0.1469

Study population. As seen in Table 9, Educational Level has equal variances (p-value of 0.6212). Thus, a Two-Sampled Pooled T-test will be performed.

Research question 1. RBANS-H subdomains Immediate Memory, Attention and Total Scale have equal variances (p-value of 0.7134, 0.6530 and 0.1639 respectively). Thus, a Two-Sampled Pooled T-test can be performed.

Research question 2. RBANS-H subdomain Language, Attention and Total Scale have equal variances (p-value of 0.4350, 0.1660 and 0.1469 respectively). Thus, a Two-Sampled Pooled T-test can be performed. In contrast, subdomain Immediate Memory has no equal variances (p-value of 0.0069). Hence, a non-parametric Wilcoxon test will be performed.

3.1.3 Overview of performed statistical tests

An overview of the performed statistical tests can be found in Table 10.

Table 10. Overview of the performed statistical tests for exploring demographic and clinical characteristics of the study population and each research question.

	Performed statistical tests
Study population (see 3.2)	
Age	Wilcoxon test
Hearing Level	
FI_{high} best ear (unaided dB HL)	Wilcoxon test
Educational Level	Two-Sampled Pooled T-test
Research question 1 (see 3.3)	
Immediate Memory	Two-Sampled Pooled T-test
Visuospatial/Construction	Wilcoxon test
Language	Wilcoxon test
Attention	Two-Sampled Pooled T-test
Delayed Memory	Wilcoxon test
Total scale	Two-Sampled Pooled T-test
Research question 2 (see 3.4)	
Immediate Memory	Wilcoxon test
Visuospatial/Construction	Wilcoxon test

Language	Two-Sampled Pooled T-test
Attention	Two-Sampled Pooled T-test
Delayed Memory	Wilcoxon test
Total Scale	Two-Sampled Pooled T-test
Research question 3 (see 3.5)	
HADS-D	Wilcoxon test

3.2 Study population

Table 11 describes the demographic and clinical characteristics of the study population. Differences in demographic and hearing covariates are explored, since they could have an influence on cognition (Bernardelli *et al.*, 2020). More specifically, studies have shown that sex and educational level are predictors of cognitive function. In that way, women are believed to be more resilient to age-related cognitive decline compared to men (McCarrey *et al.*, 2016, Gurvich *et al.*, 2020). In addition, a lower educational level is linked to a more rapid cognitive decline (Paddick *et al.*, 2014, van Hooren *et al.*, 2007). According to recent research, the total cognitive capacity improves with education, before reaching a plateau in late adolescence. At that moment, the brain reaches greatest plasticity, with relatively few further gains with education after the age of 20 years (Kremen *et al.*, 2019). Lastly, an association between increasing age and higher speed of cognitive decline has been reported as well (Lipnicki *et al.*, 2017, van Hooren *et al.*, 2007, Murman, 2015).

3.2.1 Results

Demographic and clinical characteristics of the study population can be found in Table 11.

Table 11. Demographic characteristics of the study population. Statistically significant results are indicated with an asterisk. Educational level indicates the type of education received and is categorised into 5 levels: 1 = no education, 2 = primary education, 3 = lower secondary education, 4 = upper secondary education and 5 = higher education. Abbreviations: M= Male, F= Female, SD= Standard Deviation, FI_{high}= Fletcher index high (mean 1 – 2 – 4 kHz) and dB HL= decibel Hearing Level.

	DFNA9 (n= 46)	Healthy Controls (n=46)	p-Value
Sex (n: M/F)	20/26	20/26	
Age (year: mean (SD))	53.57 (11.24)	52.91 (10.34)	0.824
Educational Level (level: mean (SD))	4.41 (0.79)	4.63 (0.49)	0.1186
Hearing Level			
FI_{high} best ear (unaided dB HL: mean (SD))	65.84 (32.21)	14.20 (9.11)	<0.0001*

3.2.2 Conclusion

The mean age and range for the study and control group were respectively 53.57 (22-75) and 52.91 (22-72) years. No significant difference in age and educational level was observed between both groups. Hence, the fact that healthy controls are matched based on age and educational level is confirmed. In contrast, a significant difference in hearing level, more precisely in the FI_{High} of the best ear, can be observed in DFNA9 patients with a mean (SD) of 65.84 (32.21) compared to healthy matched controls with a mean (SD) of 14.20 (9.11). Since DFNA9 patients suffer from progressive SNHL a difference in hearing level was expected.

3.3 Research question 1: Is there a significant difference in the RBANS-H Total Scale and index scores between DFNA9 patients and healthy matched controls?

3.3.1 Research hypothesis

Since HL contributes as a risk factor for cognitive decline and BV is suggested to contribute as a risk factor, it can be hypothesised that DFNA9 patients will obtain a significantly lower score on the RBANS-H Total Scale and index scores (Dobbels *et al.*, 2019a, Brandt *et al.*, 2005).

3.3.2 Results

Mean scores of the RBANS-H subtests and Total Scale scores of DFNA9 patients and their individually matched healthy controls, as well as their p-values can be found in Table 12.

Table 12. The results of the RBANS-H Total Scale and index scores of DFNA9 patients and their individually matched healthy controls using a Two-Sampled Pooled T-test or a non-parametric Wilcoxon test. Statistically significant results are indicated with an asterisk. Statistically significant results after the Holm-Bonferroni correction are indicated with two asterisks.

RBANS-H Index Score	DFNA9 Mean (SD) (n=46)	Healthy Control Mean (SD) (n=46)	p-Value Holm-Bonferroni	p-Value
Immediate Memory	107.83 (14.01)	116.24 (14.73)	0.0083	0.0061**
Visuospatial/Construction	96.30 (17.02)	104.22 (10.87)	0.0100	0.0426**
Language	102.57 (12.50)	102.91 (10.53)	0.0125	0.7397
Attention	94.87 (15.70)	101.89 (13.85)	0.0166	0.0253*
Delayed Memory	102.11 (11.93)	105.63 (16.50)	0.0250	0.0139*
Total Scale	101.28 (15.68)	109.54 (10.98)	0.0500	0.0043*

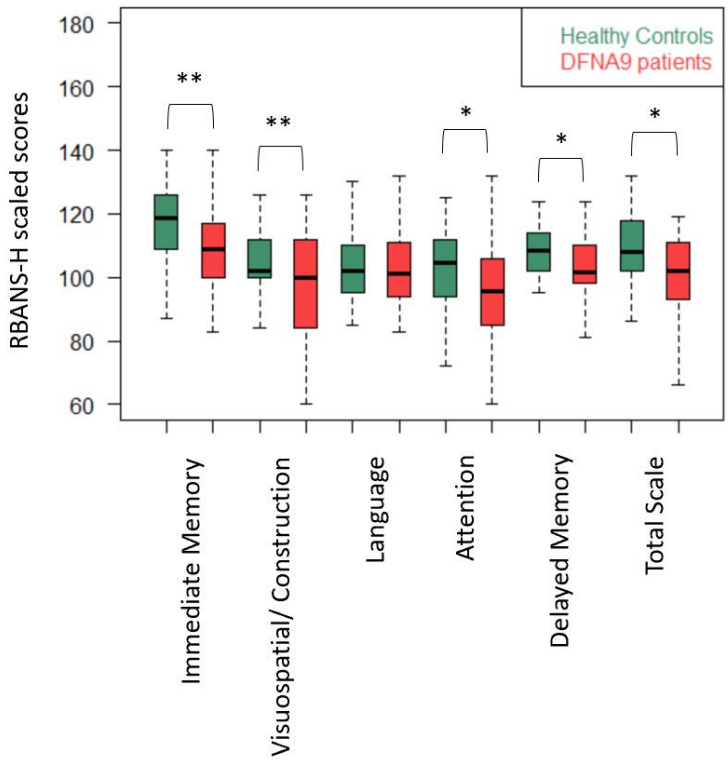

Figure 17. Comparison of the RBANS-H Total Scale and index scores between DFNA9 patients and their individually matched healthy controls. The minimum, as well as the maximum scores are visible. In addition, the first quartile, median and second quartile are indicated. Statistical significance is illustrated with an asterisk. Statistically significant results after the Holm-Bonferroni correction are indicated with two asterisks. Abbreviations: RBANS-H= Repeatable Battery for the Assessment of Neuropsychological Status adjusted for Hearing-impaired individuals.

3.3.3 Conclusion

Overall, DFNA9 patients obtained a significantly lower score on the RBANS-H Total Scale score compared to healthy matched controls (mean (SD) of 102.28 (15.68) compared to 109.54 (10.98)). In particular on cognitive subdomains Immediate Memory, Visuospatial/ Construction, Attention and Delayed Memory, while Language remained preserved. These outcomes may indicate a higher cognitive decline in DFNA9 patients, which might be a result of the fact that HL contributes as a risk factor and that BV is suggested to contribute as a risk factor for cognitive decline. These results are consistent with those observed in the literature, except for the fact that no statistically significant result was found on subdomain Language. After a Holm-Bonferroni correction, only subdomains Immediate Memory and Visuospatial/ Construction showed statistically significant results. This may be a result of the fact that the mean age of the study population is <55 years (mean (SD) of DFNA9 patients: 53.57 (11.24), healthy controls: 52.91 (10.34)), whereas 55 years is considered to be the cut-off score where HL is associated with increased dementia risk. In addition, six DFNA9 patients obtained a Total Scale score worse than expected for their age (score <85), revealing them at risk for MCI.

3.4 Research question 2: Is there a significant difference in the RBANS-H Total Scale and index scores between DFNA9 patients with BV and DFNA9 patients without BV?

3.4.1 Research hypothesis

Subject to any mistake, this cross-sectional study is the first to assess the cognitive difference in DFNA9 patients with and without BV. Therefore, the research hypothesis is based on the knowledge of the impact of the two characteristics of DFNA9, namely SNHL and BV, on cognition.

There is a significant age difference between DFNA9 patients with BV compared to DFNA9 patients without BV (p-value of <0.0001). DFNA9 patients with BV have a mean age (SD) of 59.93 (7.18) and DFNA9 patients without BV have a mean age of 42.71 (8.14). This difference is expected, since vestibular symptoms mostly occur a few years after the onset of SNHL (De Belder *et al.*, 2017). Since age is the most important risk factor to develop dementia, one may hypothesise that DFNA9 patients with BV will obtain a lower score on the RBANS-H Total Scale and index scores. Nonetheless, it is important to note that the RBANS-H is adjusted for age. In addition, a significant difference is observed in Fletcher Index high (FI_{high}) of the best ear (p-value of <0.0001). This index indicates the average HL at frequencies of 1000 Hz, 2000 Hz and 4000 Hz. DFNA9 patients with BV have a mean (SD) FI_{High} best ear of 82.59 (23.77), whereas DFNA9 patients without BV have a mean (SD) of 37.27 (23.84) (Smoorenburg, 1992). Since HL is a risk factor for cognitive decline, one may hypothesise that a more severe degree of HL (DFNA9 patients with BV) is associated with a more severe cognitive decline (Janssens de Varebeke *et al.*, 2019, Dobbels *et al.*, 2019a, Brandt *et al.*, 2005). Furthermore, research has shown that the age of 55 years is considered the mean age at which the presence of HL increases the risk of an accelerated cognitive impairment and dementia. Therefore, it can also be hypothesised that DFNA9 patients without BV, with a mean age (SD) below 55 years (42.71 (8.14)) are considered to not show the presence of cognitive decline (yet) (Lu *et al.*, 2021). In addition, the presence of BV is suggested to contribute as a risk factor for cognitive decline. In conclusion, it can be hypothesised that DFNA9 patients with BV will obtain a significantly lower score on the RBANS-H Total Scale and index scores (De Belder *et al.*, 2017, Popp *et al.*, 2017, Smith *et al.*, 2005).

3.4.2 Results

Mean scores of the RBANS-H subtests and Total Scale scores of DFNA9 patients with and without BV, as well as their p-values can be found in Table 13.

Table 13. The results of the RBANS-H Total Scale and index scores of DFNA9 patients with and without BV by using a Two-Sampled Pooled T-test.

RBANS-H Index Score	DFNA9 with BV Mean (SD) (n=29)	DFNA9 without BV Mean (SD) (n=17)	p-Value
Immediate Memory	105.28 (16.25)	112.18 (7.63)	0.0501
Visuospatial/Construction	94.83 (16.65)	98.82 (17.85)	0.4304
Language	102.52 (13.07)	102.65 (11.85)	0.9733
Attention	92.17 (17.26)	99.47 (11.68)	0.1296
Delayed Memory	100.59 (13.69)	104.71 (7.81)	0.4718
Total Scale	99.31 (18.01)	104.65 (10.22)	0.2698

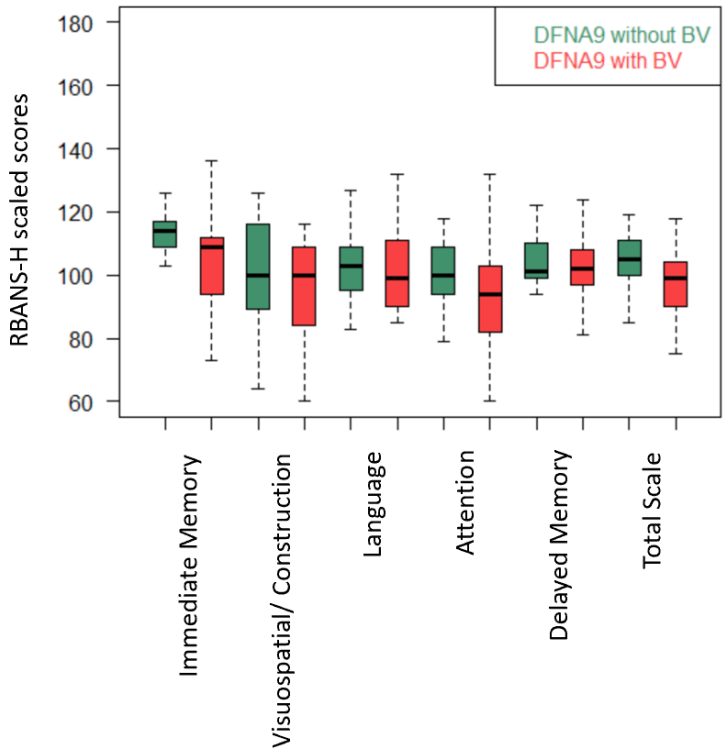

Figure 18. Comparison of the RBANS-H Total Scale and index scores between DFNA9 patients with and without BV. The minimum, as well as the maximum scores are visible. In addition, the first quartile, median and second quartile are indicated. No result was statistically significant. Abbreviations: RBANS-H= Repeatable Battery for the Assessment of Neuropsychological Status adjusted for Hearing-impaired individuals.

3.4.3 Conclusion

It can be concluded that there are no significant differences in the RBANS-H Total Scale and index scores between DFNA9 patients with BV, compared to DFNA9 patients without BV. It is important to note that the degree of BV is not taken into account. Therefore, BV patients can be in an early stage, which might explain why the lower obtained scores are not (yet) statistically significant. The degree of BV might be measured by making a subdivision of participants in groups who meet one, two or all three Bárány society criteria. However, further research is necessary, since according to my knowledge, this cross-sectional study is the first to assess the cognitive differences between DFNA9 patients with and without BV. Furthermore, all DFNA9 patients (n=6) who obtained a score lower than expected for their age (Total Scale score < 85) are diagnosed with BV according to the Bárány Society criteria.

3.5 Research question 3: Is there a significant difference in the Hospital Anxiety and Depression Scale – Depression data (HADS-D) between DFNA9 patients and healthy matched controls?

3.5.1 Research hypothesis

Several studies showed an association between HL and depression (see Introduction 1.5.6) (Li *et al.*, 2014, Lawrence *et al.*, 2020, Rutherford *et al.*, 2018, Lucieer *et al.*, 2020). Other studies have also indicated that BV patients are more prone to anxiety, depression and sleep disturbances (see Introduction 1.5.7) (Bigelow *et al.*, 2016, Lahmann *et al.*, 2015, Smith *et al.*, 2019, Lucieer *et al.*, 2020). These findings support the hypothesis that DFNA9 patients will obtain a significantly higher score on the HADS-D compared to healthy matched controls.

3.5.2 Results

Mean scores of the HADS-D questionnaire and the p-value can be found in Table 14.

Table 14. Comparison of the HADS-D scaled scores between DFNA9 patients and healthy matched controls. Statistically significant results are indicated with an asterisk.

	DFNA9 Mean (SD) (n=46)	Healthy control Mean (SD) (n=46)	p-Value
HADS - D	4.54 (4.19)	2.12 (2.34)	0.0099*

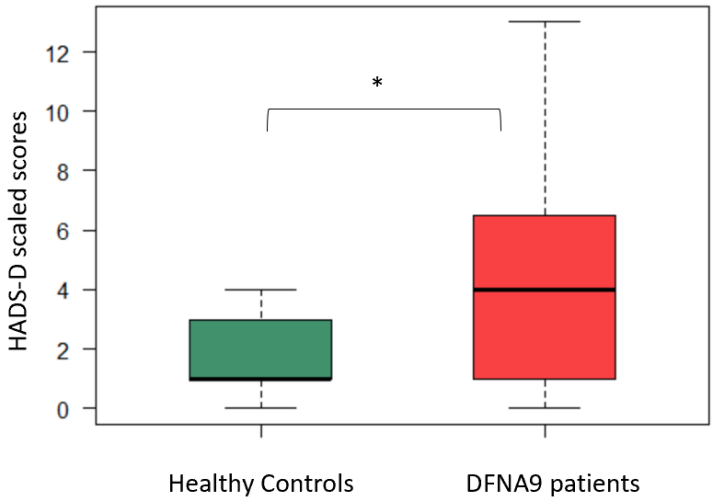

Figure 19. Comparison of the HADS-D scaled scores between DFNA9 patients and their individually matched healthy controls. The minimum, as well as the maximum scores are visible. In addition, the first quartile, median and second quartile are indicated. Statistical significance is illustrated with an asterisk. Abbreviations: HADS-D = Hospital Anxiety and Depression Scale – Depression data.

3.5.3 Conclusion

DFNA9 patients obtained a significantly higher score with a mean (SD) on the HADS-D of 4.54 (4.19) compared to 2.12 (2.34) for healthy matched controls. This result might be explained by the fact that people suffering from HL or BV are less likely to attend social activities, which can lead to feelings of loneliness, with a possible evolution towards depression (Li *et al.*, 2014, Lin and Albert, 2014, Rutherford *et al.*, 2018). In addition, these findings support the rising evidence of an association between DFNA9 and depression. Moreover, these findings must be taken into account when interpreting the results, since depression may also be linked to cognitive decline and thus partially explain the lower obtained scores by DFNA9 patients.

Part IV

DISCUSSION

4. Discussion

The primary aim of this cross-sectional study was to investigate the effect of both HL and BV on cognition. This was achieved by evaluating the cognitive performance in a DFNA9 population with the p.Pro51Ser variant in the *COCH* gene and comparing it to the cognitive performance of healthy matched controls. According to this study, DFNA9 patients showed deficits in the Total Scale score of the RBANS-H, which was most pronounced in cognitive subdomains Immediate Memory, Visuospatial/Construction, Attention and Delayed Memory (Table 12 and Figure 17). In contrast, subdomain Language remained preserved. These results are consistent with those observed in the literature, except for the fact that no statistically significant result was found on subdomain Language (Lin *et al.*, 2011b, Lin *et al.*, 2013, Gallacher *et al.*, 2012, Gurgel *et al.*, 2014, Fulton *et al.*, 2015, Wuyts *et al.*, 2016, Dobbels *et al.*, 2019b, Dobbels *et al.*, 2019a, Bosmans *et al.*, 2021). Furthermore, the outcome supports the evidence that HL and BV, and possibly their interaction, contribute as risk factors for cognitive decline and dementia.

The secondary aim was to compare the cognitive performance of DFNA9 patients who are diagnosed with BV according to the Bárány society criteria and DFNA9 patients without BV. According to my knowledge, this study was the first to assess the cognitive difference in DFNA9 patients with and without BV. Within the DFNA9 population, no significant differences were found on the RBANS-H Total Scale and index scores (Table 13 and Figure 18). However, the degree of BV was not taken into account.

Finally, the third aim was to compare HADS-D scores between DFNA9 patients and healthy matched controls. Evidence of a link between depression and DFNA9 can be supported, since a significant difference was found in the HADS-D score between DFNA9 patients and healthy matched controls (Table 14 and Figure 19). A higher score was obtained by DFNA9 patients, suggesting a correlation between DFNA9 and a higher risk for developing depression. Moreover, these findings must be taken into account when interpreting the results, since depression may also be linked to cognitive decline and hence partially explain the lower obtained scores by DFNA9 patients (Ownby *et al.*, 2006, Sáez-Fonseca *et al.*, 2007, Hasselbalch *et al.*, 2012).

4.1 Strengths and limitations

Since the co-occurrence of HL and BV has frequently been overlooked in the past, a first strength is the fact that this study assesses the impact of both HL and BV on cognition simultaneously. In addition, the cognitive function is evaluated by the RBANS-H, which is adjusted for hearing-impaired individuals. Therefore, potential bias due to HL is avoided. Subsequently, expected outcomes can support researchers to investigate the effect of hearing and vestibular function rehabilitation. Besides, this study includes a large sample size (n=92). According to the sample size calculation 34 individuals in each group would have been sufficient to obtain a significant result, however each group contains 46 individuals. Finally, expected outcomes may lead to audiological and vestibular screening protocols for patients at risk for dementia (Bosmans *et al.*, 2020).

Nevertheless, this study contains a few limitations. A first limitation is the fact that this is an open-label study, where both the researcher as well as the participant are aware of the presence of DFNA9. This knowledge can result in a researcher bias. Furthermore, the different assessments are not conducted by the same person, resulting in a possible performance bias. In addition, the RBANS-H form is collected and corrected by different researchers, which can result in variations in the interpretation of results and scoring of the RBANS-H, which may lead to an interviewer bias. However, the RBANS-H is a standardised tool so the expected differences are considered small and neglectable (Pannucci and Wilkins, 2010). Furthermore, some RBANS-H are taken in the afternoon, whereas others in the morning. Completing the RBANS-H tasks with time-of-day variations can result in differences in the RBANS-H scores. For example, results from Valdez (2019) showed that components of attention, working memory and executive function reach overall a low level in the morning (7h00 – 10h00), an

improvement towards noon (10h00 – 14h00) and after lunch a decrease (14h00 – 16h00), which is referred to as the "post-lunch dip". So, standardising the time at which the RBANS-H is performed may lead to a more reliable comparison of the results. However, interindividual differences can be observed as well, for example variation exists between morning-type and evening-type people, where the former show higher levels of attention in the morning and the latter in the evening. Besides, sleep deprivation is considered to have a detrimental effect on cognitive performance. Furthermore, it may be of added value to take subjective alertness and sleepiness into account, which refers to the subjective feeling of feeling alert or the need for sleep respectively. This may be achieved by using visual analogue scales for the former, and self-reported scales for the latter (Valdez, 2019, Schmidt *et al.*, 2007, Monk, 1989). Another limitation includes the fact that the c-VEMP often shows no response, which would indicate an impaired function of the saccule or inferior vestibular nerve. However, no response can be a result of incorrect placement of the electrodes or due to an insufficient contraction of the SCM muscle (Rahne *et al.*, 2014).

4.2 Socio-demographic characteristics

Rising evidence exists for the fact that risk factors in early-life (education), midlife (hypertension, HL, traumatic brain injury, alcohol abuse and obesity) and late-life (smoking, depression, physical inactivity, social isolation, diabetes and air pollution) can contribute to an increased risk to develop dementia (Sabia *et al.*, 2017, Singh-Manoux *et al.*, 2017). Some of these factors are taken into account in this master thesis, namely education, sex and age. However, it is important to mention that other possible risk factors are not taken into account in this master thesis. For instance, smoking, which is believed to play a role in cognitive decline. Ott *et al.* (1998) performed a population-based-follow-up study on 6,870 people aged >55 years. The participants were classified as "never smokers", "former smokers" and "current smokers". The results indicated an increased risk in smokers to develop dementia and particularly AD. Several other studies supported these findings (Agrawal *et al.*, 2006, Reitz *et al.*, 2007, Launer *et al.*, 1999, Juan *et al.*, 2004, Luchsinger *et al.*, 2005, Merchant *et al.*, 1999). There is also rising evidence that tinnitus contributes as a risk factor for cognitive decline (Chu *et al.*, 2020, Lee, 2020, Lee *et al.*, 2020). For example, Cheng *et al.* (2021) performed a retrospective case-control study. The results showed an increased risk for developing dementia in people with pre-existing tinnitus. Next, obesity is also a factor that may be associated with cognitive decline. Pedditzi *et al.* (2016) performed a meta-analysis of 21 studies. The authors concluded that obesity below the age of 65 years (mid-life obesity) correlates with the incidence of dementia, but not the late-life obesity (over 65 years). In addition, Kivimäki *et al.* (2018) analysed 1,349,857 people from 39 different cohorts. The authors observed that a higher BMI is associated with an increased risk to develop dementia in mid-life. Moreover, they described that this risk is reversed in late life and that a higher BMI could even be protective. Furthermore, an association between diabetes and an increased risk of cognitive decline is reported (Rawlings *et al.*, 2014, Chatterjee *et al.*, 2016, Luchsinger, 2010, Cheng *et al.*, 2012). Besides, hypertension is also related to a higher risk for cognitive decline and dementia. Nevertheless, the age of the participant seems to have an influence on the results. In participants aged 40-64 years, an association between a higher blood pressure and a higher risk for cognitive decline is observed. In participants aged >64 years, on the contrary, hypertension was linked to a lower risk for cognitive decline (Qiu *et al.*, 2005, Norton *et al.*, 2014, Sierra, 2020, Joas *et al.*, 2012, Kennelly *et al.*, 2009). Finally, rising evidence reveals that a greater exposure to air pollution is associated with an increased risk for dementia. However, all these associations are complex and not yet fully elucidated. So further research is necessary (Peters *et al.*, 2019, Clifford *et al.*, 2016, Chen *et al.*, 2017, Peters *et al.*, 2015). Since it is not possible to control and match for all possible risk factors, the aforementioned factors are not taken into account in this master thesis.

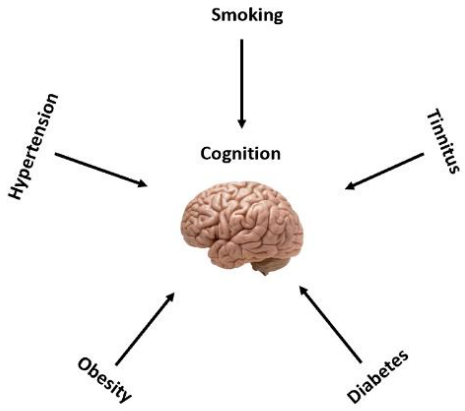

Figure 20. Five demographic characteristics that are suggested to contribute as a risk factor for cognitive decline.

4.3 Prevention of dementia

Prevention is never too late, nor too early. It requires both individually tailored interventions and public health programmes (Figure 21). The high-risk population should be encouraged to increase social, cognitive and physical activity (Livingston *et al.*, 2020). Social contact is an accepted protective factor that enhances cognitive reserve. One of the possible specific actions for risk factors across the life course includes the maintenance of systolic blood pressure of 130 mmHg or less in mid-life from around the age of 40 years. This can be achieved by implementing an antihypertensive treatment. In addition, one must encourage the use of hearing aids and the protection of ears from excessive noise exposure. Furthermore, the exposure to air pollution and second-hand tobacco smoke must be reduced. Above that, smoking cessation must be supported and smoking uptake must be avoided. Moreover, the use of alcohol must be limited, since alcohol misuse and the uptake of more than 21 units of alcohol weekly are associated with an increased risk for dementia. Besides, all children must be provided with primary and secondary education. Finally, obesity and the linked condition of type 2 diabetes must be reduced, which can be achieved by encouraging physical activity. Exercise is important since it not only reduces weight and diabetes risk, but also improves cardiovascular function (Livingston *et al.*, 2020, Chieffi *et al.*, 2017).

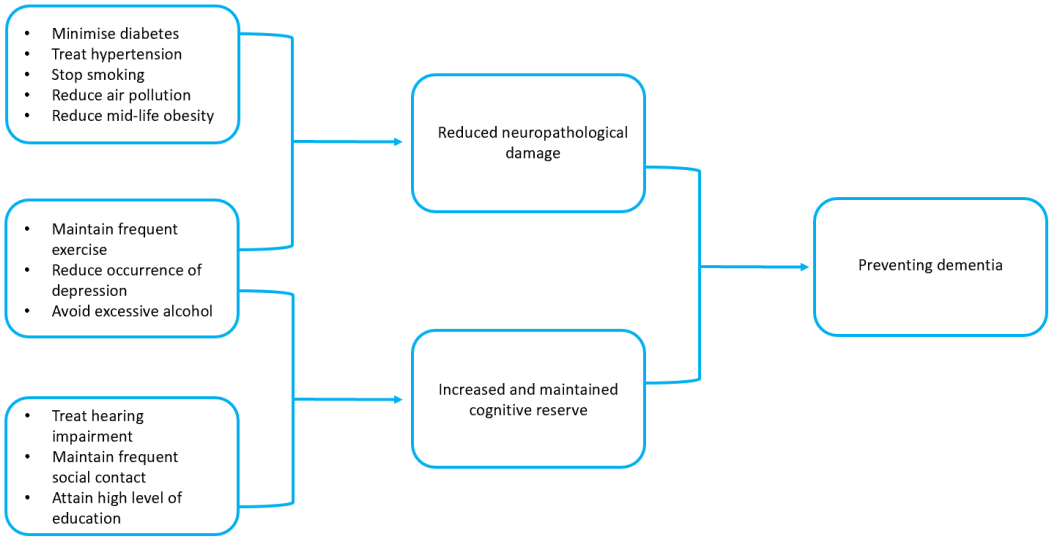

Figure 21. Possible prevention strategies in order to reduce the risk for developing dementia (Livingston et al., 2020).

4.4 What needs to be investigated in the future?

Age-related HL is considered to be a possible biomarker and modifiable risk factor for cognitive decline, cognitive impairment and dementia. Hence, additional research is warranted to investigate the effect of hearing treatments (Loughrey *et al.*, 2018). Possible hearing treatments include hearing aids and a Cochlear Implantation (CI). Acar *et al.* (2011) investigated the effect of hearing aids on cognitive functions and depressive signs in elderly people. It could be concluded that after three months of hearing aids, people suffering from HL showed a significant improvement in cognitive functions, as well as in psychosocial interactions. In addition, several studies have already investigated cognitive functions before and after CI. Their results showed cognitive improvement after CI (Zhan *et al.*, 2020, Sonnet *et al.*, 2017, Völter *et al.*, 2018, Claes *et al.*, 2018a, Mosnier *et al.*, 2015, Cosetti *et al.*, 2016, Claes *et al.*, 2018b). For example, research from Claes *et al.* (2018b) showed significant improvement in overall cognition 12 months after CI. Additionally, Mertens *et al.* (2021) compared the cognitive evolution of hearing-impaired adults after CI with that of matched hearing-impaired adults without CI. Their results showed improvement in overall cognitive functioning (particularly in subdomain Attention) after CI. However, a comparison between older CI users and matched controls with normal hearing still revealed a more impaired cognitive functioning of CI users. These results highlight the need for additional cognitive rehabilitation in the long term after CI. Unfortunately, the knowledge of the population on the fact that HL contributes as a risk factor for cognitive decline is very low, therefore it is crucial to educate people on this matter (Chou *et al.*, 2011). In addition, BV is suggested to contribute as a risk factor for cognitive decline. Consequently, BV treatment may reduce the risk of developing MCI and dementia. Possible vestibular treatments include vestibular implant and vestibular rehabilitation. Vestibular rehabilitation includes training to not stop walking while talking and balance exercises, which might decrease the cognitive load associated with balance performance. Sugaya *et al.* (2018) investigated the effect of vestibular rehabilitation in 60 people aged 20 years or older with chief complaint of dizziness. The results suggested a significant improvement in cognition. However, in the future further research on the effect of vestibular treatment on cognition, as well as possible vestibular treatments need to be conducted.

In order to know if the cognitive decline is solely due to HL or (partially) due to BV, the controls could also be matched based on either hearing or vestibular performance. However, this couldn't be achieved for this master thesis, because it is very hard to find controls for DFNA9 patients, both matched based on age and hearing or vestibular performance. The reason for this is that an individual's hearing and vestibular function more rapidly declines due to DFNA9 compared to age-related HL and BV. Hence, it remains a matter of debate whether the effect on cognition is solely due to HL or (partially) due to concomitant BV (Dobbels *et al.*, 2019a). So, further research investigating the underlying causal mechanisms is warranted.

4.5 Why vHIT and ENG?

Several theories can explain different results between the vHIT and ENG. According to Zellhuber *et al.* (2014), the variation might be the result of temporal frequency differences or due to the differing roles of regular and irregular fibers of the vestibular nerve. The authors explained that some animal studies show evidence that regular fibers drive the low-frequency VOR, whereas irregular fibers drive the high-frequency VOR. Another possible hypothesis suggests that healthy individuals can take different pathways to compensate for bilateral loss. For example, by raising the high-frequency gain at the expense of the low-frequency gain. Others do not increase their high frequency gain, but use covert saccades instead (Hain, 2021). This indicates the importance of performing both techniques to assess the function of the lateral SCC.

4.6 Are there better alternatives available?

The subtests 'Line Orientation' and 'Figure Copy' of the Visuospatial/Constructional cognitive domain of the RBANS-H can be less sensitive to detect spatial cognitive deficits in patients with BV. Hence, the virtual Morris Water Task (vMWT) can be used to assess navigation and spatial memory. The vMWT is a virtual version of the Morris Water Maze, which is the golden standard to evaluate spatial cognition in rodents. During this test, participants will have to navigate in a virtual pool as fast as possible towards a hidden platform (Dobbels *et al.*, 2019a). The GECkO protocol originally included the VMWT test, however most people of the older population (>55 years old) were unable to understand the instructions. Another possible alternative includes the app Sea Hero Quest originally led by Deutsche Telecom, alongside GLITCHERS, University College London, University of East Anglia and Alzheimer's research UK. This app is available for the public on mobile and tablet devices. During this multi-level adventurer game, participants will need to memorize a map and find and photograph sea creatures. In that way, the app will generate data about the spatial navigation capabilities of the participants (Spiers *et al.*, 2021).

Part V

CONCLUSION

5. Conclusion

In summary, according to this study, DFNA9 patients showed deficits in the Total Scale score of the RBANS-H, which was most pronounced in cognitive subdomains Immediate Memory, Visuospatial/Construction, Attention and Delayed Memory. In contrast, subdomain Language remained preserved. These results support and extend evidence on the association between HL, BV and cognitive decline. No significant differences were observed between DFNA9 patients with and without BV. Furthermore, evidence of a link between depression and DFNA9 can be supported, since a significant difference was found in the HADS-D score between DFNA9 patients and healthy matched controls. A higher score was obtained by DFNA9 patients, suggesting a correlation between DFNA9 and a higher risk for developing depression.

Currently, a causal relationship has not yet been found. The exploration and identification of causal mechanisms underlying the association between HL, BV and cognitive decline are recommended, since it may allow for early detection of people at risk for dementia. In addition, identification of the causal mechanisms may provide interventions to prevent or slow down the progression towards dementia. Furthermore, the results support researchers to investigate the effect of hearing and vestibular function rehabilitation. Finally, the results endorse audiological and vestibular screening protocols for patients at risk for developing dementia later in life.

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Supplementary

Supplementary 1. Mini-Mental State Examination (MMSE).

Gestandaardiseerde Mini-Mental State Examination

Naam patiënt :

Datum invullen : Naam invuller :

Ik ga u nu enkele vragen stellen en geef u enkele problemen om op te lossen. Wilt u alstublieft uw best doen omzo goed mogelijke antwoorden te geven.

noteer antwoord score:

ORIENTATION

1. a. Welk jaar is het?
   b. Welk seizoen is het?
   c. Welke maand van het jaar is het?
   d. Wat is de datum vandaag?
   e. Welke dag van de week is het? (0-5) _____

2. a. In welke provincie zijn we nu?
   b. In welke plaats zijn we nu?
   c. Wat is de naam van het ziekenhuis?
   d. Wat is de naam van deze afdeling?
   e. Op welke verdieping zijn we nu? (0-5) _____

REGISTRATION

3. Ik noem nu drie voorwerpen. Wilt u die herhalen nadat ik ze alle drie gezegd heb?Onthoud ze want ik vraag u over enkele minuten ze opnieuw te noemen.
   (Noem "appel, stuiver, tafel", neem 1 seconde per woord) (1 punt voor elk goed antwoord, herhaal maximaal 5 keer tot de patiënt de drie woorden weet)
   (0-3) _____

ATTENTION AND CALCULATION

4. Wilt u van de 100 zeven aftrekken en van wat overblijft weer zeven aftrekkenen zo doorgaan tot ik stop zeg?
   (Herhaal eventueel 3 maal als de persoon stopt, herhaal dezelfde instructie,geef maximaal 1 minuut de tijd) Noteer hier het antwoord.

of

Wilt u het woord "'worst" achterstevoren spellen?.Noteer hier het antwoord.

(0-5) _____

RECALL

5. Noemt u nogmaals de drie voorwerpen van zojuist.
   (Eén punt voor elk goed antwoord). (0-3) _____

LANGUAGE

6. Wat is dit? En wat is dat?
(Wijs een pen en een horloge aan. Eén punt voor elk goed antwoord). (0-2) _____

7. Wilt u de volgende zin herhalen: " Nu eens dit en dan weer dat ".
(Eén punt als de complete zin goed is) (0-1) _____

8. Wilt u deze woorden lezen en dan doen wat er staat'?
(papier met daarop in grote letters: "Sluit uw ogen") (0-1) _____

9. Wilt u dit papiertje pakken met uw rechterhand, het dubbelvouwen
en het op uw schoot leggen? (Eén punt voor iedere goede handeling). (0-3) _____

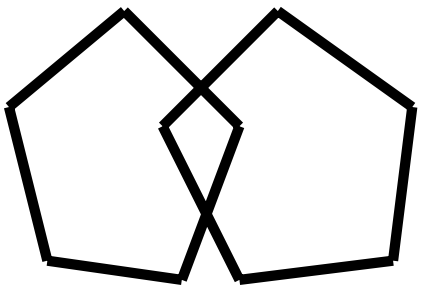
10. Wilt u voor mij een volledige zin opschrijven op dit stuk papier? (Eén punt wanneer de zin een onderwerp en een gezegde heeft
en betekenis heeft). (0-1) _____

VISUOSPATIAL FUNCTION

11. Wilt u deze figuur natekenen?
(Figuur achterop dit papier. Eén punt als figuur geheel correct is nagetekend.
Er moet een vierhoek te zien zijn tussen de twee vijfhoeken) (0-1) _____

TOTALE TEST SCORE: (0-30) _____

Sluit uw ogen



Supplementary 2. RBANS-H Record Form A and B.

RBANS-H

RECORD FORM A

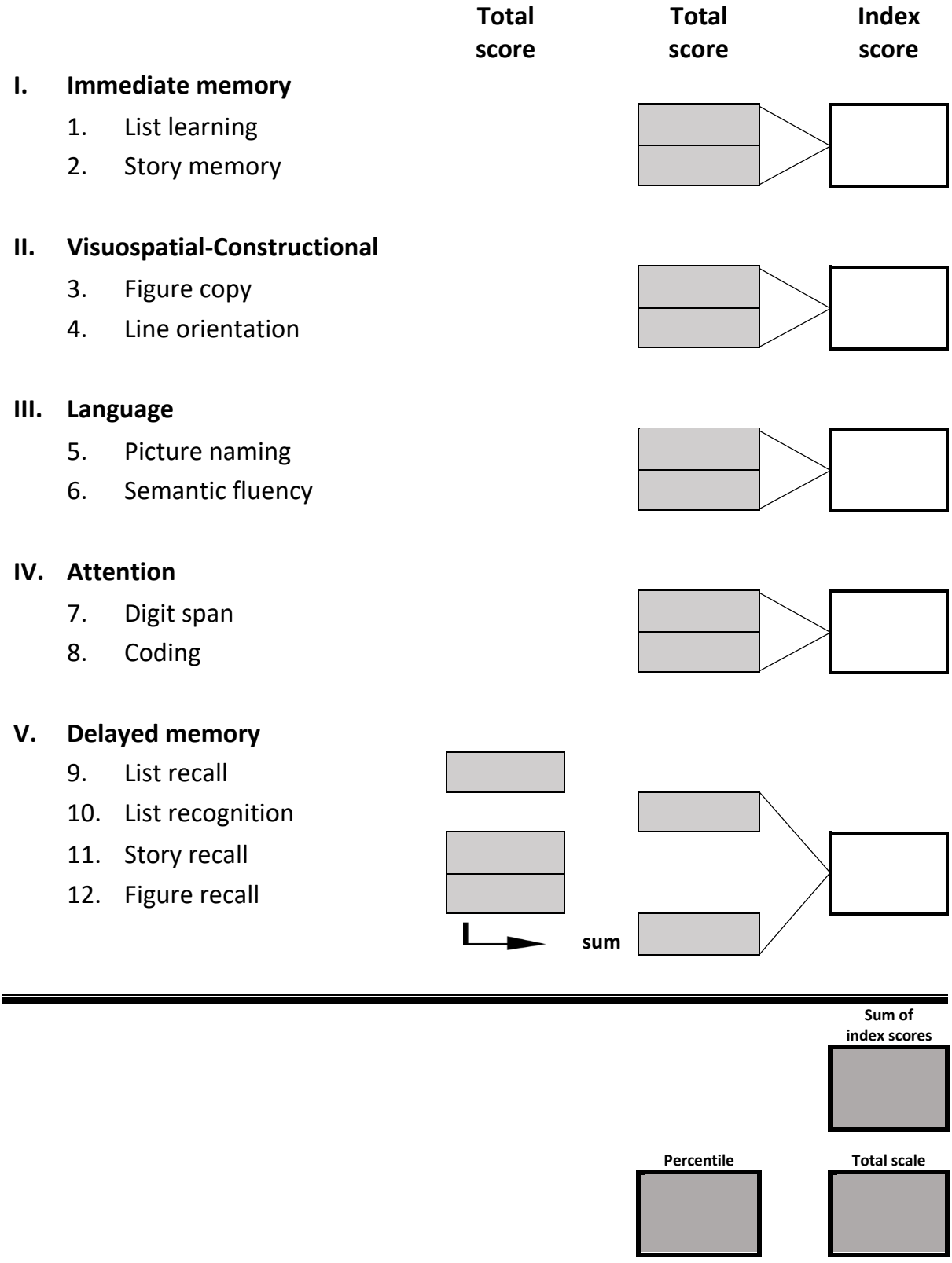
Person conducting the assessment:			
Date of assessment:			
	Day	*Month*	*Year*

Visit	☐ Baseline (T0)	☐ 12m (T1)	☐ 24m (T2)
Version RBANS-H	☐ A ☐ B		

Subject Identification			
Sex	☐ Male		☐ Female
Date of birth			
	Day	*Month*	*Year*
Years of education (quit – 6y)			
Education level	☐ Geen school/training ☐ Lagere school afgewerkt ☐ Lager secundair afgewerkt (eerste 3 jaren) ☐ Hoger secundair afgewerkt ☐ Hoger onderwijs ☐ Andere: _____		

Comments	

Score conversion page



1. list learning

LIST	TRIAL 1	TRIAL 2	TRIAL 3	TRIAL 4
Markt				
Pakje				
Elleboog				
Appel				
Verhaal				
Tapijt				
Luchtbel				
Autoweg				
Zadel				
Poeder				
Number correct				
			Total score (range=0-40)	

2. Story memory

STORY		RESPONSES	TRIAL 1 SCORE (0 or 1)	TRIAL 2 SCORE (0 or 1)	ITEM SCORE (0,1 or 2)
1.	Op **dinsdag**				
2.	**vier**				
3.	**mei**				
4.	ontstond in **Durbuy**				
5.	een **zware**				
6.	**brand**.				
7.	**Twee**				
8.	**hotels**				
9.	en een **restaurant**				
10.	waren **volledig uitgebrand** (volledig afgebrand/brandden volledig uit)				
11.	voordat de **brandweer** (de brandweermannen)				
12.	de brand kon **blussen**.				
			Total score (range=0-24)		

3. figure copy

ITEM		DRAWING (0 or 1)	PLACEMENT (0 or 1)	SCORE (0, 1 or 2)
1.	Rectangle			
2.	Diagonal cross			
3.	Horizontal line			
4.	Circle			
5.	Three small circles			
6.	Square			
7.	Curving line			
8.	Outside cross			
9.	Triangle			
10.	Arrow			
		Total score (range=0-20)		

3. Figure copy drawing page

4. line orientation

ITEM		RESPONSE	SCORE (0, 1 or 2)
0.	**1, 7**	*(sample item)*	
1.	**10, 12**		
2.	**4, 11**		
3.	**6, 9**		
4.	**8, 13**		
5.	**2, 4**		
6.	**1, 6**		
7.	**3, 10**		
8.	**5, 8**		
9.	**1, 3**		
10.	**11, 13**		
		Total score (range=0-20)	

5. picture naming

ITEM		SEMANTIC CUE	RESPONSE	SCORE (0 or 1)
1.	**Stoel**	Een meubel		
2.	**Potlood**	Om te schrijven		
3.	**(Water)put**	Je kunt er water uit halen		
4.	**Giraf**	Een dier		
5.	**Zeilboot**	Wordt gebruikt op het water (indien “boot”: “welke soort”?)		
6.	**Kanon**	Een wapen, gebruikt in de oorlog		
7.	**Tang** (notenkraker)	Een werktuig		
8.	**Trompet** (cornet)	Muziekinstrument		
9.	**Wasspeld**	Om de was op te hangen		
10.	**Vlieger**	Wordt opgelaten in de lucht		
			Total score (range=0-10)	

6. semantic fluency

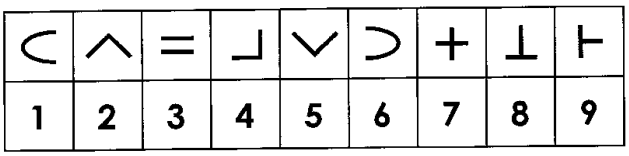
1.	11.	21.	31.
2.	12.	22.	32.
3.	13.	23.	33.
4.	14.	24.	34.
5.	15.	25.	35.
6.	16.	26.	36.
7.	17.	27.	37.
8.	18.	28.	38.
9.	19.	29.	39.
10.	20.	30.	40.
		Total score (range=0-40)	

7. Digit span

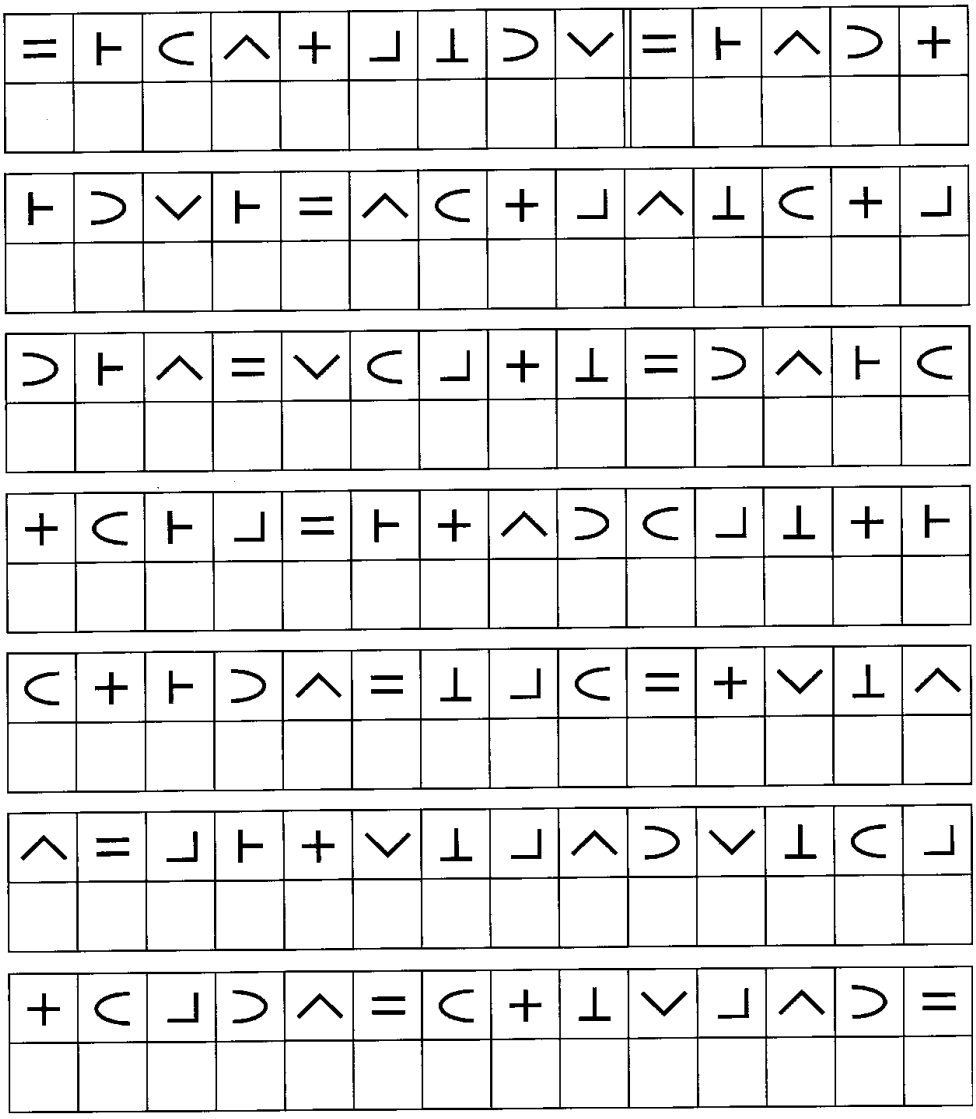
ITEM	FIRST STRING	SCORE (0 or 2)	SECOND STRING	SCORE (0 or 1)
1.	4 - 9		5 - 3	
2.	8 - 3 - 5		2 - 4 - 1	
3.	7 - 2 - 4 - 6		1 - 6 - 3 - 8	
4.	5 - 3 - 9 - 2 - 4		3 - 8 - 4 - 9 - 1	
5.	6 - 4 - 2 - 9 - 3 - 5		9 - 1 - 5 - 3 - 7 - 6	
6.	2 - 8 - 5 - 1 - 9 - 3 - 7		5 - 3 - 1 - 7 - 4 - 9 - 2	
7.	8 - 3 - 7 - 9 - 5 - 2 - 4 - 1		9 - 5 - 1 - 4 - 2 - 7 - 3 - 8	
8.	1 - 5 - 9 - 2 - 3 - 8 - 7 - 4 - 6		5 - 1 - 9 - 7 - 6 - 2 - 3 - 6 - 5	
			Total score (range=0-16)	

8. Coding

Total score (range=0-89)	



SAMPLE _____



9. list recall

LIST (Do not read)	**RESPONSE**	**SCORE** (0 or 1)
Markt		
Pakje		
Elleboog		
Appel		
Verhaal		
Tapijt		
Luchtbel		
Autoweg		
Zadel		
Poeder		
	Total score (range=0-10)	

10. List recognition

LIST (circle one)				**LIST** (circle one)			
1.	Appel	**YES**	no	11.	Luchtbel	**YES**	no
2.	Honing	yes	**NO**	12.	Polder	yes	**NO**
3.	Markt	**YES**	no	13.	Autoweg	**YES**	no
4.	Verhaal	**YES**	no	14.	Oester	yes	**NO**
5.	Weefsel	yes	**NO**	15.	Student	yes	**NO**
6.	Matroos	yes	**NO**	16.	Zadel	**YES**	no
7.	Fluweel	yes	**NO**	17.	Poeder	**YES**	no
8.	Tapijt	**YES**	no	18.	Engel	yes	**NO**
9.	Vallei	yes	**NO**	19.	Pakje	**YES**	no
10.	Elleboog	**YES**	no	20.	Weide	yes	**NO**
				Total score (range=0-20)			

11. Story recall

	STORY (Do not read)	**RESPONSE**	**SCORE** (0 or 1)
1.	Op **dinsdag**		
2.	**vier**		
3.	**mei**		
4.	ontstond in **Durbuy**		
5.	een **zware**		
6.	**brand**.		
7.	**Twee**		
8.	**hotels**		
9.	en een **restaurant**		
10.	waren **volledig uitgebrand** (volledig afgebrand/brandden volledig uit)		
11.	voordat de **brandweer** (de brandweermannen)		
12.	de brand kon **blussen**.		
		Total score (range=0-12)	

12. Figure Recall

ITEM		DRAWING (0 or 1)	PLACEMENT (0 or 1)	SCORE (0, 1 or 2)
1.	Rectangle			
2.	Diagonal cross			
3.	Horizontal line			
4.	Circle			
5.	Three small circles			
6.	Square			
7.	Curving line			
8.	Outside cross			
9.	Triangle			
10.	Arrow			
		Total score (range=0-20)		

12. Figure recall drawing page

RBANS-H

RECORD FORM B

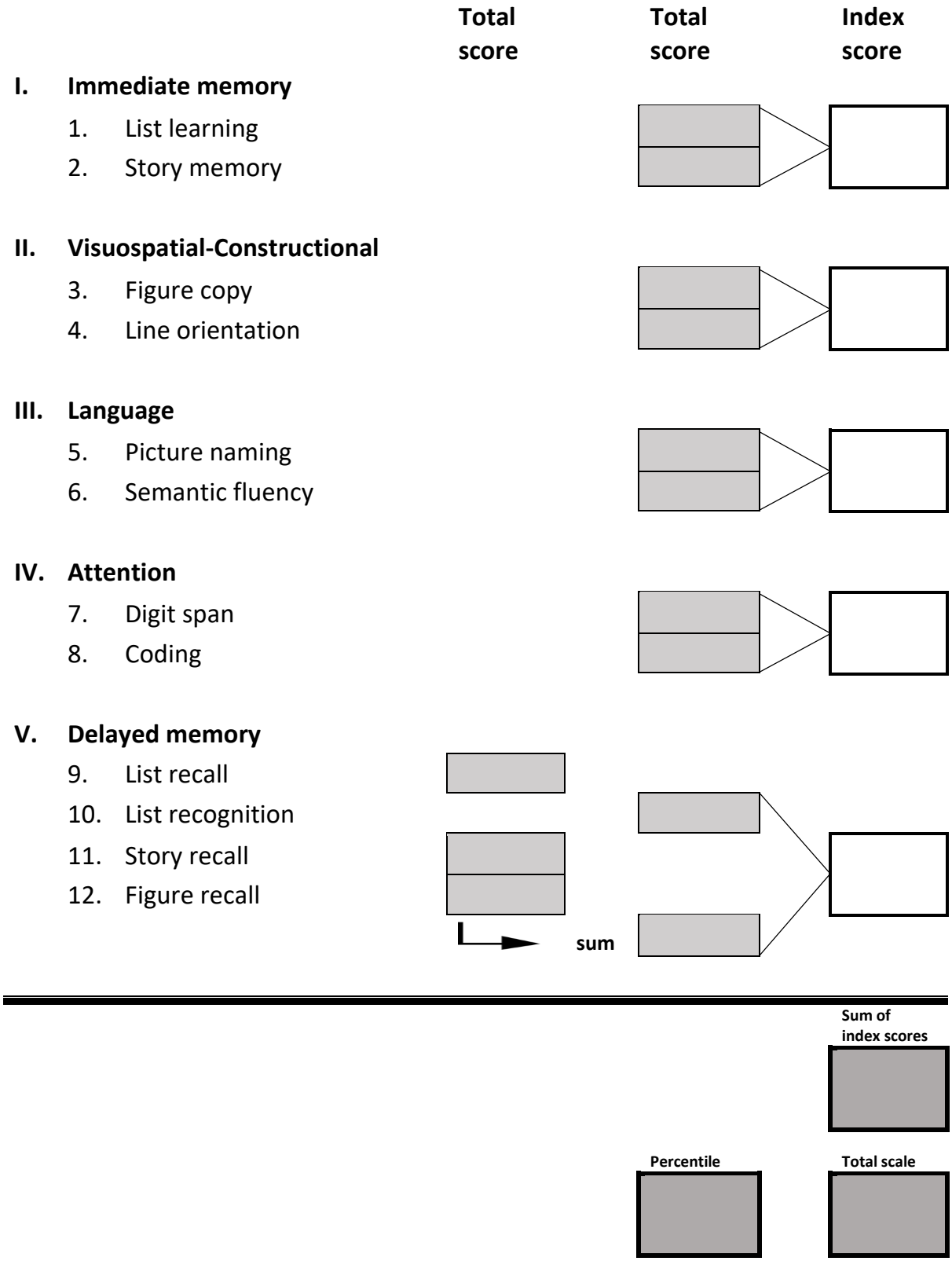
Person conducting the assessment:			
Date of assessment:			
	Day	*Month*	*Year*

Visit	☐ Baseline (T0)	☐ 12m (T1)	☐ 24m (T2)
Version RBANS-H	☐ A ☐ B		

Subject Identification			
Sex	☐ Male		☐ Female
Date of birth			
	Day	*Month*	*Year*
Years of education (quit – 6y)			
Education level	☐ Geen school/training ☐ Lagere school afgewerkt ☐ Lager secundair afgewerkt (eerste 3 jaren) ☐ Hoger secundair afgewerkt ☐ Hoger onderwijs ☐ Andere: _____		

Comments	

SCORE CONVERSION PAGE



1. list learning

LIST	TRIAL 1	TRIAL 2	TRIAL 3	TRIAL 4
Kaars				
Suiker				
Wagon				
Hotel				
Landbouwer				
Dorp				
Boterham				
Pluim				
Artiest				
Papier				
Number correct				
			Total score (range=0-40)	

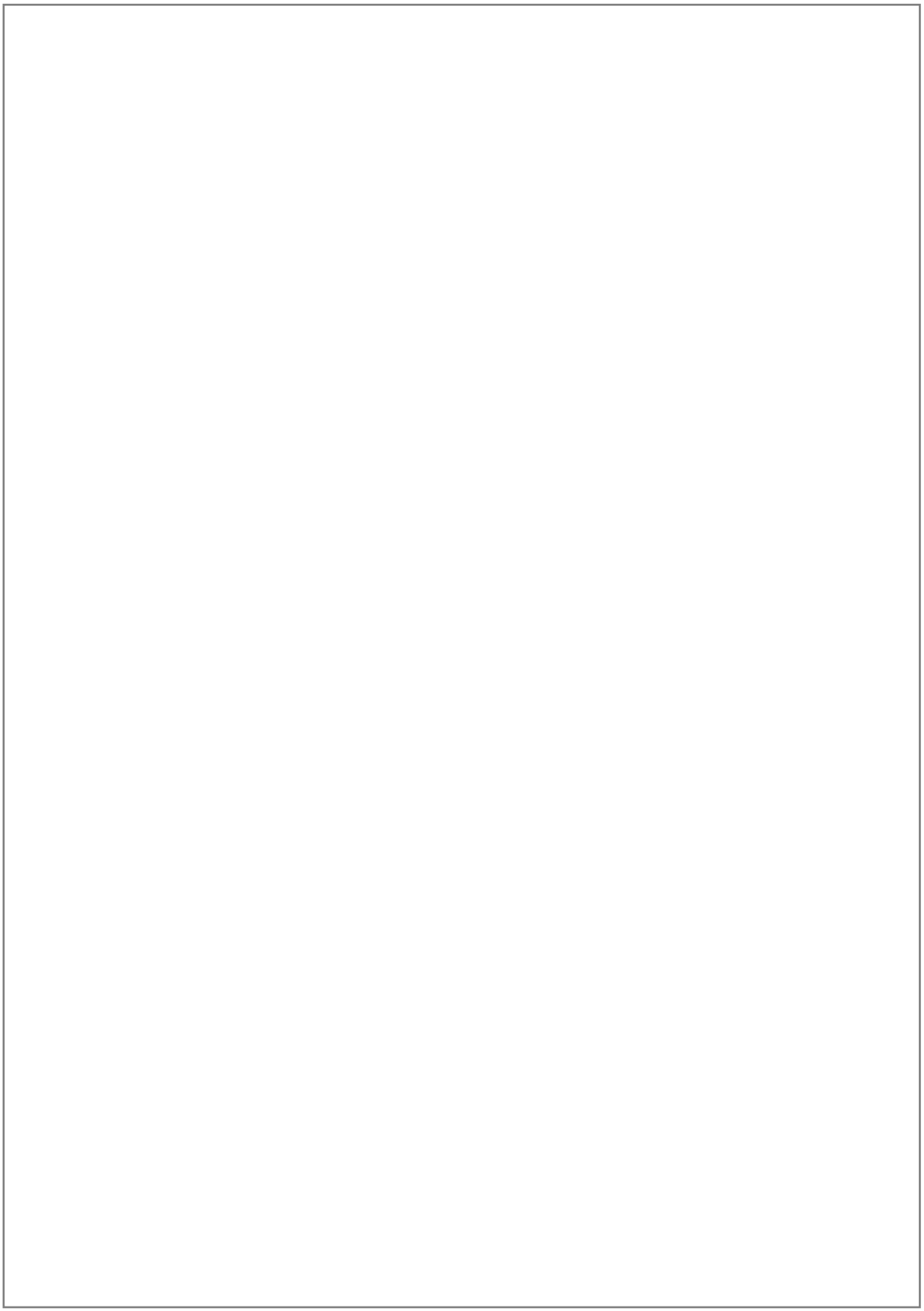
2. STORY MEMORY

STORY 1		**RESPONSE TRIAL 1**	**RESPONSE TRIAL 2**	**TRIAL 1 SCORE** (0 or 1)	**TRIAL 2 SCORE** (0 or 1)
1.	Op **maandag**				
2.	**vijf**				
3.	**maart**				
4.	werd **Oostende**				
5.	getroffen door een **storm**.				
6.	Hoewel er **twee miljoen** euro				
7.	**schade**				
8.	aan de **dijk (dijken)** was,				
9.	raakten slechts **zeven personen (zeven mensen/ zeven)**				
10.	**gewond (gekwetst/ gewonden/ gekwetsten)**,				
11.	en vielen er **geen (niemand)**				
12.	**doden (dood/ ~~kwam om het leven~~)**.				
			Sum (range=0-12)		
				+ 2	
			Total score (range=0-24)		

3. FIGURE COPY

ITEM		DRAWING (0 or 1)	PLACEMENT (0 or 1)	SCORE (0, 1 or 2)
1.	Rectangle			
2.	Diagonal cross			
3.	Horizontal line			
4.	Circle			
5.	Three small circles			
6.	Square			
7.	Curving line			
8.	Outside cross			
9.	Triangle			
10.	Arrow			
		Total score (range=0-20)		

3. FIGURE COPY DRAWING PAGE



4. LINE ORIENTATION

ITEM		RESPONSE	SCORE (0, 1 or 2)
0.	**1, 7**	*(sample item)*	
1.	**2, 5**		
2.	**4, 12**		
3.	**6, 11**		
4.	**7, 10**		
5.	**9, 12**		
6.	**2, 10**		
7.	**6, 12**		
8.	**3, 8**		
9.	**4, 7**		
10.	**2, 8**		
		Total score (range=0-20)	

5. PICTURE NAMING

ITEM		SEMANTIC CUE	RESPONSE	SCORE (0 or 1)
1.	**Bed**	Een meubel		
2.	**Paddestoel**	Iets dat gekweekt wordt, dat je kan eten		
3.	**Bloem**	Iets dat in de tuin groeit		
4.	**Strijkijzer**	Wordt gebruikt om kreuken uit je kleren te krijgen		
5.	**Schuur (garage, tuinhuis, bungalow, barak, chalet)**	Een soort gebouw		
6.	**Anker**	Wordt gebruikt op een boot		
7.	**Hamer**	Een werktuig		
8.	**Schaar**	Wordt gebruikt om te knippen		
9.	**Dobbelsteen**	Wordt gebruikt bij gezelschapspelletjes		
10.	**Zeepaardje**	Dier dat in de oceaan leeft		
			Total score (range=0-10)	

6. SEMANTIC FLUENCY

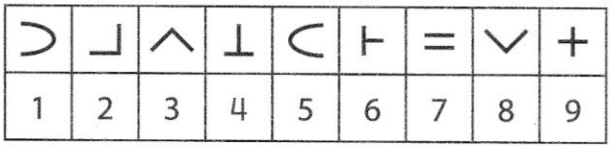
1.	11.	21.	31.
2.	12.	22.	32.
3.	13.	23.	33.
4.	14.	24.	34.
5.	15.	25.	35.
6.	16.	26.	36.
7.	17.	27.	37.
8.	18.	28.	38.
9.	19.	29.	39.
10.	20.	30.	40.
Number correct (range=0-40)		+ 4	**Total score** (range=4-40)	

7. DIGIT SPAN

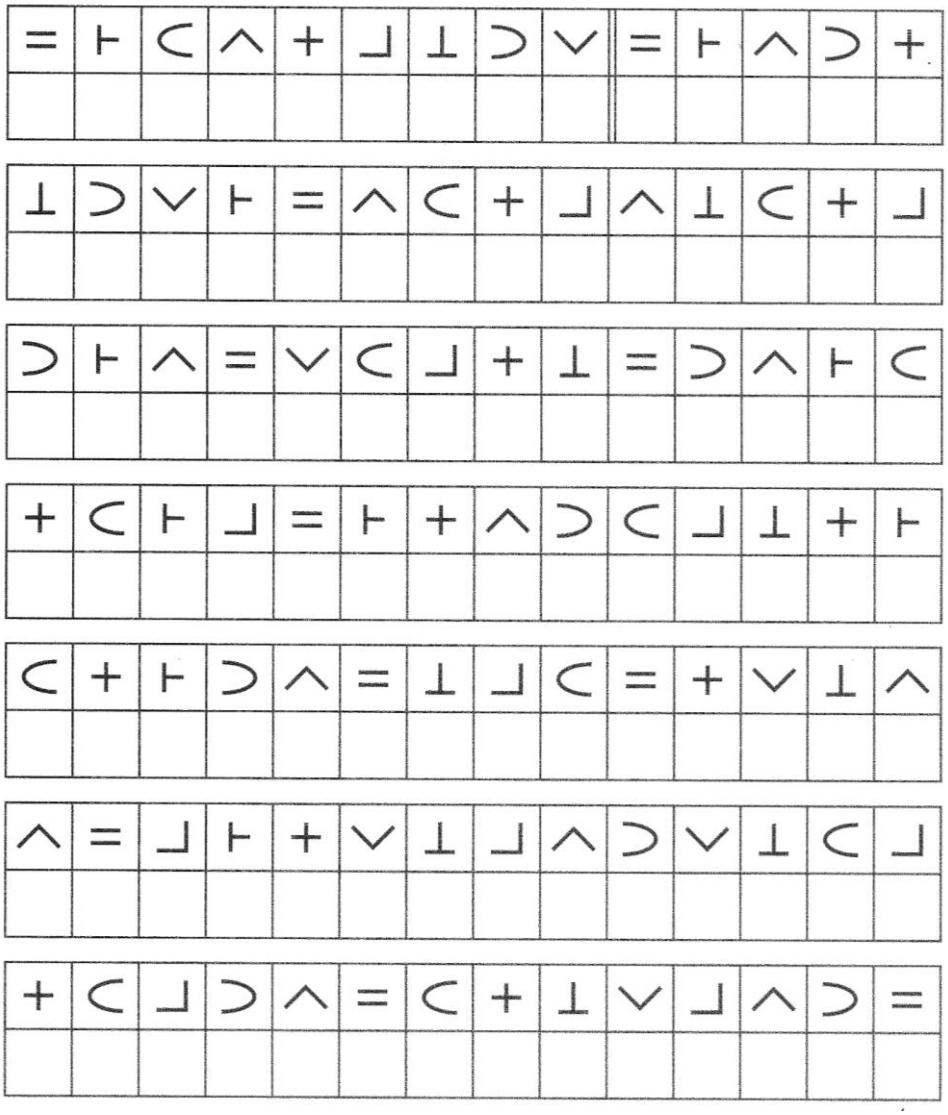
ITEM	FIRST STRING	SCORE (0 or 2)	SECOND STRING	SCORE (0 or 1)
1.	9 - 4		3 - 5	
2.	5 - 3 - 8		1 - 4 - 2	
3.	6 - 4 - 2 - 7		8 - 3 - 6 - 1	
4.	4 - 2 - 9 - 3 - 5		1 - 9 - 4 - 8 - 3	
5.	5 - 3 - 9 - 2 - 4 - 6		6 - 3 - 7 - 5 - 1 - 9	
6.	6 - 3 - 9 - 5 - 1 - 8 - 2		2 - 9 - 4 - 7 - 1 - 3 - 5	
7.	4 - 2 - 6 - 9 - 1 - 7 - 3 - 8		8 - 3 - 7 - 9 - 1 - 4 - 2 - 5	
8.	3 - 1 - 7 - 8 - 2 - 9 - 5 - 4 - 6		2 - 1 - 9 - 5 - 4 - 7 - 3 - 8 - 6	
			Total score (range=0-16)	

8. CODING

Total score (range=0-89)	



SAMPLE_____



9. LIST RECALL

LIST (Do not read)	**RESPONSE**	**SCORE** (0 or 1)
Kaars		
Suiker		
Wagon		
Hotel		
Landbouwer		
Dorp		
Boterham		
Pluim		
Artiest		
Papier		
	Total score (range=0-10)	

10. LIST RECOGNITION

LIST (circle one)				**LIST** (circle one)			
1.	Kaars	**YES**	no	11.	Hotel	**YES**	no
2.	Metaal	yes	**NO**	12.	Leerling	yes	**NO**
3.	Landbouwer	**YES**	no	13.	Artiest	**YES**	no
4.	Papier	**YES**	no	14.	Feest	yes	**NO**
5.	Paars	yes	**NO**	15.	Kasteel	yes	**NO**
6.	Seizoen	yes	**NO**	16.	Boterham	**YES**	no
7.	Gebouw	yes	**NO**	17.	Pluim	**YES**	no
8.	Wagon	**YES**	no	18.	Zomer	yes	**NO**
9.	Spiegel	yes	**NO**	19.	Dorp	**YES**	no
10.	Suiker	**YES**	no	20.	Insect	yes	**NO**
				Total score (range=0-20)			

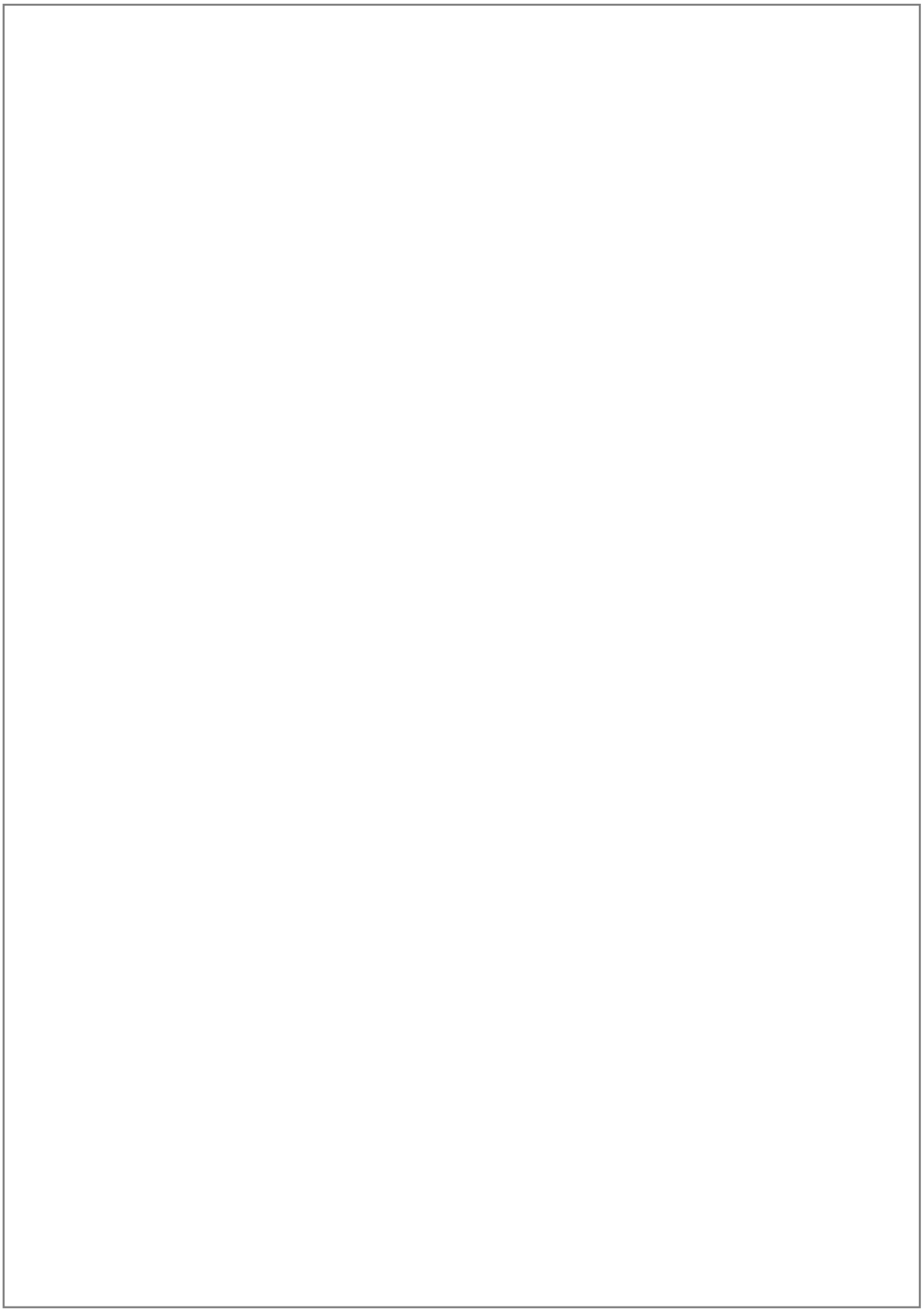
11. STORY RECALL

STORY (Do not read)		**RESPONSE**	**SCORE** (0 or 1)
1.	Op **maandag**		
2.	**vijf**		
3.	**maart**		
4.	werd **Oostende**		
5.	getroffen door een **storm**.		
6.	Hoewel er **twee miljoen** euro		
7.	**schade**		
8.	aan de **dijk (dijken)** was,		
9.	raakten slechts **zeven personen (zeven mensen/ zeven)**		
10.	**gewond (gekwetst/ gewonden/ gekwetsten)**,		
11.	en vielen er **geen (niemand)**		
12.	**doden (dood/ ~~kwam om het leven~~)**.		
		Total score (range=0-12)	

12. FIGURE RECALL

ITEM		DRAWING (0 or 1)	PLACEMENT (0 or 1)	SCORE (0, 1 or 2)
1.	Rectangle			
2.	Diagonal cross			
3.	Horizontal line			
4.	Circle			
5.	Three small circles			
6.	Square			
7.	Curving line			
8.	Outside cross			
9.	Triangle			
10.	Arrow			
		Total score (range=0-20)		

12. Figure recall drawing



Supplementary 3. List of used sentences for Speech-In-Noise (SPIN) test.

☐ **Adaptieve spraakaudiometrie** **Vaste ruiswaarde: _____** **Datum: _____**

☐ **Klassieke spraakaudiometrie**

Lijst 1:	**SNR:**	**./32**	**%**
Zijn **stem** is **schor**.		___dB	./2
Morgen gaan we naar de **stad**.		___dB	./3
De **leerling kwam te laat** op school.		___dB	./4
Hij **kreeg** een **wagen** van de **zaak**.		___dB	./3
De **operatie duurde vier uur**.		___dB	./4
Wij **wonen** in een **rustige buurt**.		___dB	./3
Gisteren hebben wij een **film gezien**.		___dB	./3
Deze **bakker** is **ook** op **zondag open**.		___dB	./4
De **secretaresse neemt** de **telefoon aan**.		___dB	./3
De **politie bevestigde** de **aanhouding**.		___dB	./3

Lijst 2:	**SNR:**	**./32**	**%**
Het **huis staat leeg**.		___dB	./3
De **kat sprong** op de **tafel**.		___dB	./3
Het **kind speelde** met de **bal**.		___dB	./3
Het **ijsje** was **al gesmolten**.		___dB	./3
Mijn **huis** wordt **bewaakt** door een **hond**.		___dB	./3
De **weg** was **niet goed aangegeven**.		___dB	./4
De **kinderen zwaaiden** naar de **auto's**.		___dB	./3
Hij **zat** naar de **televisie** te **kijken**.		___dB	./3
In het **weekend gebeuren vaak ongevallen**.		___dB	./4
De **conferentie** wordt in het **buitenland gehouden**.		___dB	./3

Lijst 3:	**SNR:**	**./32**	**%**
Hij **sloeg** de **deur dicht**.		___dB	./3
Het **apparaat** is **erg zwaar**.		___dB	./3
De **kapper heeft veel klanten**.		___dB	./4
Hij **moet veel reizen** voor zijn **werk**.		___dB	./4
Ze **schaamde** zich voor haar **gedrag**.		___dB	./2
Ik zal het **pakje** voor je **dragen**.		___dB	./2
Elke zaterdag ga ik naar de **markt**.		___dB	./4
Tijdens het **weekend** heb ik **veel geslapen**.		___dB	./4
De **consumentenbond vergelijkt producten**.		___dB	./3
Er was een **mooi programma** op de **televisie**.		___dB	./3

Lijst 4:	**SNR:**	**./33**	**%**
Ze **viel** van de **trap**.		___dB	./2
Fruit en **groenten** zijn **gezond**.		___dB	./3
Morgen gaat het **regenen**.		___dB	./3
Ze was **te ziek** om te **eten**.		___dB	./3
De **wandeling duurde drie uur**.		___dB	./4
Het **restaurant** is **goed**, maar **erg duur**.		___dB	./4
Ze **reed te hard** en **kreeg** een **bekeuring**.		___dB	./5
Hij **kreeg** een **bekeuring** van de **politie**.		___dB	./3
Ze **protesteerden** tegen de **kruisraketten**.		___dB	./2
Na de **ontsnapping namen** de **ministers ontslag**.		___dB	./4

Lijst 5:	**SNR:**	**./32**	**%**
Het **nieuws** is **schokkend**.		___dB	./2
Hij **maakte** haar **erg bang**.		___dB	./3
De **brandweer bluste** het **vuur**.		___dB	./3
Ze **berekenden** de **kosten**.		___dB	./2
Morgen wil ik **nog eens uitslapen**.		___dB	./5
Het **bedrijf** wordt **geprivatiseerd**.		___dB	./2
Na het **eten gaat** mijn **oma rusten**.		___dB	./4
Ze hebben de **kamer opnieuw geschilderd**.		___dB	./3
Het **parlement vergaderde** de **hele nacht**.		___dB	./4
Het **leger probeert** de **opstand** te **onderdrukken**.		___dB	./4

Lijst 6:	**SNR:**	**./32**	**%**
Lucht is **onzichtbaar**.		___dB	./2
De **dader wist** te **vluchten**.		___dB	./3
In een **kerk moet** men **stil** zijn.		___dB	./3
De **broodjes** waren **uitverkocht**.		___dB	./2
Ik **moet Frans leren** voor mijn **werk**.		___dB	./4
De **rente** is **gelukkig gedaald**.		___dB	./3
De **studenten bezetten** een **kraakpand**.		___dB	./3
Ik **moet** naar de **winkel** om **verf** te **kopen**.		___dB	./4
Tijdens de **middag** is het **kantoor gesloten**.		___dB	./4
Het **belangrijke nieuws** werd **meteen uitgezonden**.		___dB	./4

Lijst 7:	**SNR:**	**./32**	**%**
Hij **rookt** een **sigaar**.		___dB	./2
Ze **klopten** op de **deur**.		___dB	./2
De **blinde man draagt** een **stok**.		___dB	./4
Dat **café** is **erg gezellig**.		___dB	./3
Na de **winter gaat** de **boer zaaien**.		___dB	./4
Als het **lang vriest** kunnen we **schaatsen**.		___dB	./3
Het **rapport** wordt **maandag gepubliceerd**.		___dB	./3
Er is **ook** een **zwembad** en een **tennisbaan**.		___dB	./3
De **taxichauffeurs staken** voor een **beter loon**.		___dB	./4
In de **herfst** zijn er **veel paddestoelen** in het **bos**.		___dB	./4

Lijst 8:	**SNR:**	**./32**	**%**
Ze **sneed** de **taart aan**.		___dB	./2
Het **kopje viel** op de **grond**.		___dB	./3
Hij **werkt** al **meer** dan **tien jaar**.		___dB	./4
De **vrouw parkeerde** de **wagen**.		___dB	./3
Er wordt een **tunnel aangelegd**.		___dB	./2
Dagelijks drinkt hij een **liter melk**.		___dB	./4
Hij is **vrijwilliger** in het **zwembad**.		___dB	./2
De **firma besteedt veel geld** aan **reclame**.		___dB	./5
Het **conflict** is door de **vakbonden opgelost**.		___dB	./3
De **koninklijke familie woont** in een **paleis**.		___dB	./4

Lijst 9:	**SNR:**	**./32**	**%**
Het **gras** is **erg groen**.		___dB	./3
De **leraar deelde straf uit**.		___dB	./4
Hij **werkt** in het **buitenland**.		___dB	./2
We zijn **trots** op de **kampioen**.		___dB	./2
Mijn **kast** is een **grote puinhoop**.		___dB	./3
Iedere zondag gaat hij **vissen**.		___dB	./4
Het was een **heel ernstig treinongeval**.		___dB	./3
Het **motief** van de **dader** is **onbekend**.		___dB	./3
De **rechter neemt uiteindelijk** de **beslissing**.		___dB	./4
In de **meeste Europese landen** heerst **welvaart**.		___dB	./4

Lijst 10:	**SNR:**	**./33**	**%**
Zijn **broek** is **gescheurd**.		___dB	./2
Het **personeel kreeg opslag**.		___dB	./3
Veel vluchten zijn **volgeboekt**.		___dB	./3
Het **dak lekt** als het **erg regent**.		___dB	./4
In de **praktijk werkt** het **anders**.		___dB	./3
De **dokter schreef** een **medisch attest**.		___dB	./4
De **conducteur controleert** de **kaartjes**.		___dB	./3
De **gemeenteraad vergadert elke week**.		___dB	./4
Bij de **brand kwamen gevaarlijke gassen vrij**.		___dB	./4
De **minister** heeft **steekpenningen aangenomen**.		___dB	./3

Supplementary 4. Hospital Anxiety and Depression Scale (HADS).

Hospital Anxiety and Depression Score (HADS)

Denk niet te lang na over uw antwoord.
Uw eerste reactie op elke vraag is waarschijnlijk betrouwbaarder dan een lang doordacht antwoord.

A	**1. Ik voel me gespannen**	D	**8. Ik voel me alsof alles moeizamer gaat**
3	Meestal	**3**	Bijna altijd
2	Vaak	**2**	Heel vaak
1	Af en toe, soms	**1**	Soms
0	Helemaal niet	**0**	Helemaal niet
D	**2. Ik geniet nog steeds van de dingen waar ik vroeger van genoot**	A	**9. Ik krijg een soort benauwd, gespannen gevoel in mijn maag**
0	Zeker zo veel	**0**	Helemaal niet
1	Niet zo veel als vroeger	**1**	Soms
2	Weinig	**2**	Vrij vaak
3	Haast helemaal niet	**3**	Heel vaak
A	**3. Ik krijg een soort angstgevoel alsof er elk moment iets vreselijks zal gebeuren**	D	**10. Ik heb geen interesse meer in mijn uiterlijk**
3	Heel zeker en vrij erg	**3**	Zeker
2	Ja, maar niet zo erg	**2**	Niet meer zoveel als ik zou moeten
1	Een beetje, maar ik maak me er geen zorgen over	**1**	Waarschijnlijk niet zoveel
0	Helemaal niet	**0**	Evenveel interesse als vroeger
D	**4. Ik kan lachen en de dingen van de vrolijke kant zien**	A	**11. Ik voel me rusteloos en voel dat ik iets te doen moet hebben**
0	Net zoveel als vroeger	**3**	Heel erg
1	Niet zo goed als vroeger	**2**	Tamelijk veel
2	Beslist niet zoveel als vroeger	**1**	Niet erg veel
3	Helemaal niet	**0**	Helemaal niet
A	**5. Ik maak me vaak ongerust**	D	**12. Ik verheug me van tevoren al op dingen**
3	Heel erg vaak	**0**	Net zoveel als vroeger
2	Vaak	**1**	Een beetje minder dan vroeger
1	Af en toe maar niet te vaak	**2**	Zeker minder dan vroeger
0	Alleen soms	**3**	Bijna nooit
D	**6. Ik voel me opgewekt**	A	**13. Ik krijg plotseling gevoelens van panische angst**
3	Helemaal niet	**3**	Zeer vaak
2	Niet vaak	**2**	Tamelijk vaak
1	Soms	**1**	Niet erg vaak
0	Meestal	**0**	Helemaal niet
A	**7. Ik kan rustig zitten en me ontspannen**	D	**14. Ik kan van een goed boek genieten, of van een radio- of televisieprogramma**
0	Zeker	**0**	Vaak
1	Meestal	**1**	Soms
2	Niet vaak	**2**	Niet vaak
3	Helemaal niet	**3**	Heel zelden