Accelerated Cognitive Decline Associated With Hearing Loss and Bilateral Vestibulopathy: Insights From a Prospective Cross-Sectional Study Using the Repeatable Battery for the Assessment of Neuropsychological Status Adjusted for the Hearing Impaired in the DFNA9 Population

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Background: DeaFNess Autosomal dominant 9 (DFNA9) is a hereditary disorder known to affect both hearing and vestibular function in its carriers. Its phenotype is characterized by progressive sensorineural hearing loss (SNHL) and vestibular dysfunction evolving towards bilateral vestibulopathy (BV) by the 3rd to 5th life decade. Recent studies have identified the impact of hearing loss and vestibular dysfunction on cognitive functioning.

Objective: The main objective of this study was to investigate how the cognitive functioning of carriers of the p.Pro51Ser variant in the *COCH* gene is affected by the disease and compare these results with a matched healthy control group.

Study design: Forty-six carriers of the pathogenic p.Pro51Ser variant in the *COCH* gene were included in this study, of which 38 met the Bárány Society criteria and were thus diagnosed with BV. All subjects were between the age of 22 and 72 years old. Each control was individually matched based on age, gender, and education level. A cognitive, vestibular, and hearing assessment was performed in all subjects. All participants completed the Repeatable Battery for the Assessment of Neuropsychological Status, adjusted for the Hearing Impaired (RBANS-H), a cognitive test battery that includes subtests probing Immediate and Delayed Memory, Visuospatial/Constructional, Language, and Attention.

Results: Overall, the DFNA9 patients demonstrated significantly lower scores on the Immediate Memory subscale and lower Total Scale scores than their healthy matched controls. The total sample was divided into two groups: age <55 years old and age ≥55 years old. The DFNA9 group aged ≥55 years old obtained significantly lower scores on the Attention subscale and lower Total Scale scores than their matched controls. Cognition of DFNA9 patients aged <55 years old no longer differed significantly from their matched controls.

Conclusion: This cross-sectional study found that DFNA9 patients demonstrated cognitive deficits in comparison with their healthy matched controls. The DFNA9 group aged ≥ 55 years old obtained significantly lower scores on the Total Scale and Attention subscale. This finding; however, was not observed for the age group younger than 55 years old. Further research is needed on the individual trajectory of SNHL and vestibular function, and how hearing rehabilitation affects cognitive functioning.

Key words: Cognition, DeaFNess Autosomal Dominant 9, Hearing impairment, Vestibular dysfunction.

Abbreviations: AC = air conduction; BC = bone conduction; BV = bilateral vestibulopathy; dB HL= decibel hearing level; DFNA9 = DeaFNess autosomal dominant 9; ENG = electronystagmography; LIST = leuven intelligibility sentences test; MCI = mild cognitive impairment; PTA = pure-tone average; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; RBANS-H = Repeatable Battery for the Assessment of Neuropsychological Status, adjusted for the Hearing Impaired; SCC = semi-circular canals; SNHL = sensorineural hearing loss; SPIN = Speech In Noise; SPV= Slow Phase Velocity; SRT= Speech Reception Threshold; vHIT = video Head Impulse Test; VOR = Vestibulo-Ocular Reflex.

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INTRODUCTION

DeaFNess Autosomal dominant 9 (DFNA9) is a non-syndromic dominant hereditary disorder. Numerous mutations in the *COCH* gene, which encodes for cochlin, are causing DFNA9 (Manolis et al. 1996; Robertson et al. 1997). Cochlin is expressed in the spiral ligament and spiral limbus of the inner ear and plays important, though not entirely elucidated roles

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in both architectural as well as immune function (Khetarpal 2000; Robertson et al. 2001; Gallant et al. 2013). It is believed that cochlin plays a role in regulating the innate immune system and maintaining the extracellular matrix of the inner ear. Furthermore, it has a key role in maintaining ion homeostasis in the endolymph, the regulation of the cochlear blood flow, and immune response in the cochlea (Peeleman et al. 2020). Its phenotype is therefore characterized by a progressive sensorineural hearing loss (SNHL) with a high-frequency onset and it is also often associated with vestibular dysfunction evolving towards Bilateral Vestibulopathy (BV) (Fransen et al. 2001; Bom et al. 2003; Bischoff et al. 2005; Bae et al. 2014). BV is characterized by a severe bilateral loss of function of vestibular sensors which causes oscillopsia, gait imbalance, spatial disorientation, increased risk of falling, etc. (Kremmyda et al. 2016; Strupp et al. 2017; Lucieer et al. 2018; Paredis et al. 2021).

Verhagen et al. (1988) first described DFNA9 in a Dutch patient that presented with adult-onset rapid progression of hearing and vestibular dysfunction. Although several mutations have been described in all continents, the p.Pro51Ser variant in *COCH* is by far the most prevalent mutation in Belgium and The Netherlands (Manolis et al. 1996; de Kok et al. 1999; Fransen et al. 2001; Van Rompaey et al. 2022). The pathophysiology of the p.Pro51Ser variant in *COCH* is not yet fully elucidated, although recent studies concluded that the onset of sensorineural hearing deterioration starts around the 3rd decade followed by vestibular function decline (JanssensdeVarebeke et al. 2021a, 2021b).

Hearing loss, gradually rising in prevalence and severity with age, is the most frequently reported sensory deficit and affects 400 million people worldwide (WHO 2021). It not only has a significant impact on quality of life and society in general, but recent studies have identified a significant correlation between patients' hearing status and their cognitive abilities. Increasing hearing thresholds (i.e. poorer hearing level) correlate with lower cognitive performance. Different studies have observed that hearing loss is associated with accelerated cognitive decline (Claes et al. 2016; Livingston et al. 2017; Wei et al. 2017). Individuals with hearing loss have a 24% increased risk of cognitive impairment (Lin et al. 2011, 2013). For this reason, hearing loss has been identified as an independent modifiable risk factor for accelerated cognitive decline, cognitive impairment, and even dementia in older adults (Livingston et al. 2017).

There is growing evidence in both human and animal studies suggesting that not only hearing loss, but also vestibular dysfunction may result in cognitive deficits, which has been shown for spatial cognition in particular (Smith et al. 2005; Bigelow & Agrawal 2015; Smith 2017). Furthermore, due to their close anatomical relationship within the labyrinth, there is a high prevalence of hearing loss in patients with vestibular dysfunction and vice versa. Vestibular loss is therefore also associated with cognitive impairment and may also be a risk factor for dementia (Previc 2013; Harun et al. 2016; Dobbels et al. 2019a, b; Bosmans et al. 2021).

Cognitive decline may be slowed down by adequate treatment of hearing loss with hearing aids (for patients with moderate to severe SNHL) or cochlear implants (for patients with profound SNHL) and thus decreasing the risk of developing dementia by 9.1% (Livingston et al. 2017; Claes et al. 2018a, 2018b). Unfortunately, to date there is no commercially available treatment for BV and DFNA9 patients cannot be prevented from developing this condition with age (Guyot & Perez Fornos 2019).

Since DFNA9 patients are affected by both hearing loss and vestibular loss, their cognition may be affected by the disease as well. According to a recent literature review, cognition has never been explored in DFNA9 patients (De Belder et al. 2018). This study aimed to assess the cognitive abilities of DFNA9 patients using the Repeatable Battery for the Assessment of Neuropsychological Status, adjusted for Hearing impaired patients (RBANS-H) (Randolph et al. 1998; Claes et al. 2016).

MATERIALS AND METHODS

Study Design

The present study was a single-center, prospective, cross-sectional study in which both hearing and vestibular function as well as a cognitive assessment were performed at the Antwerp University Hospital (UZA). Inclusion started on February 5, 2019 and was finalized on September 9, 2021. Three International Conference on Harmonisation-Good Clinical Practive-accredited clinical researchers (H.G., J.B., and J.M.) conducted the 2-hr assessment in a single session. Both DFNA9 patients and healthy controls underwent hearing, vestibular, and cognitive assessments.

Subjects

A total of 46 genetically confirmed heterozygous carriers of the p.Pro51Ser variant in the *COCH* gene, henceforth called "DFNA9 patients/population," all degrees of hearing loss and vestibular impairment combined, and 46 control subjects (matched for sex, age, and education level) were included in this cross-sectional study. Demographic details of both study groups are found in Table 1. All subjects were divided into six age groups (3rd decade: 18 to 29 years of age; 4th decade: 30 to 39 years; 5th decade: 40 to 49 years; 6th decade: 50 to 59 years; 7th decade: 60 to 69 years; and 8th decade: 70 to 80 years). The number of patients in each of these age groups, including their age distribution, is found in Table 2.

The DFNA9 population and control subjects were recruited from the Otorhinolaryngology, Head and Neck Surgery department of the Antwerp University Hospital (UZA). DFNA9 patients were recruited from the *DFNA9-evolution* study (B300202042807). Healthy controls were recruited from the *GECkO* study (Gehoor, Evenwicht, COgnitie) (B300201938949) (Bosmans et al. 2020) and the *ERP-Norm* study (Event-Related Potentials) (B300201630244). All participants gave written initial informed consent in accordance with the Declaration of Helsinki before participation. The Committee for Medical Ethics of the Antwerp University Hospital and the University of Antwerp approved all studies.

Inclusion Criteria

The following inclusion criteria for the DFNA9 population were applied: (1) aged ≥18 years at the time of investigation, (2) Dutch native speaking, (3) no cochlear implantation or other implantable hearing devices, (4) no known neurological disorders (e.g. mild cognitive hearing loss, or dementia), and (5) confirmed p.Pro51Ser variant carrier. Each control subject was individually matched based on age, sex, and education level. The following additional inclusion criteria were applied for

TABLE 1. Demographic information of the DFNA9 patients and control subjects

	DFNA9 Patients (n = 46)	Control Subjects (n = 46)	*p*
Gender (n: female/male)	26/20	26/20	
Age (mean [range])	53.56 [22 to 75]	52.91 [22 to 72]	0.823
HLs (dB HL: mean [range]):	62.35 [1.67 to 120.00]	12.01 [–1.67 to 35.00]	**<0.001**
PTA (1 kHz, 2 kHz, 4 kHz) right	60.01 [5.00 to 120.00]	11.67 [–1.67 to 36.67]	
PTA (1 kHz, 2 kHz, 4 kHz) left			
video Head Impulse Test (vHIT) (mean [range])	0.53 [0.01 to 1.00]	0.89 [0.68 to 1.19]	**<0.001**
VOR-gain Left Lateral	0.55 [0.02 to 1.11]	0.95 [0.75 to 1.13]	
VOR-gain Right Lateral			
Education level (n: elementary/lower secondary/higher secondary/ higher education/unknown)	1/4/12/22/7	0/0/17/29/0	0.054

The non-parametric Wilcoxon tests confirmed the matching of age, sex and education level of the study group (DFNA9 population) with the control group. The DFNA9 population showed significantly worse scores on hearing and vestibular function.
dB HL, decibel HL; DFNA9, DeaFNess Autosomal dominant 9; vHIT, video Head Impulse Test; VOR, vestibulo-ocular reflex; PTA, Pure-Tone Average; PTA (1 kHz, 2 kHz, and 4 kHz) = average of hearing thresholds at 1 kHz, 2 kHz, and 4kHz.

TABLE 2. The number of patients in each age decade (N) including mean age, SD, and age range for the control subjects and DFNA9 patients

	Control Subjects			DFNA9 Patients		
Decade	N	Age (mean ± SD)	Age range	N	Age (mean ± SD)	Age range
3rd	1	22.00	—	1	22.00	—
4th	5	36.8 ± 1.64	35–38	6	37.33 ± 1.51	35–39
5th	9	43.78 ± 2.49	40–47	7	45.00 ± 2.08	41–47
6th	17	54.35 ± 2.69	50–59	17	53.94 ± 2.68	50–59
7th	13	64.46 ± 2.40	60–68	13	64.54 ± 2.44	60–68
8th	1	72.00	—	2	73.50 ± 2.12	72–75

DFNA9, DeaFNess Autosomal dominant 9.

control subjects: (1) normal hearing defined by hearing thresholds for both ears at 0.250 Hz up to 8 kHz within the normal range based on age and sex, as defined by the BS 6954:1988, EN 27029:1991, and ISO 7029-1984 standards and (2) absence of BV confirmed by a lateral VOR-gain >0.6, assessed with video Head Impulse Testing (vHIT). Only control subjects aged 55 years and older (recruited through the *GECkO* study) underwent vHIT testing to confirm normal vestibular function. Control subjects' medical history was questioned during anamnesis and all reported no history of vertigo and no balance problems.

Cognitive Assessment

Cognition was evaluated using the Dutch RBANS-H, an instrument developed and validated for individuals with severe hearing loss (Claes et al. 2016). The RBANS-H is a modified version of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) to minimize the effect of hearing loss on cognitive testing and it can be used to detect mild forms of cognitive disorders (Randolph et al. 1998; Randolph 2012). To use this test in a population who are hard of hearing with visual stimuli using an accompanying PowerPoint presentation were added to the oral instructions to make sure the patient is able to understand the instructions correctly (Claes et al. 2016). Assessment of the RBANS-H takes approximately 30 minutes on average. The RBANS-H consists of a set of 12 subtests each combined to assess five [cognitive domains]: "List Learning," "Story Memory" [Immediate Memory], "Figure Copy," "Line Orientation" [Visuospatial Construction], "Picture Naming," "Semantic Fluency" [Language], "Digit Span," "Coding" [Attention], "List Recall," "List Recognition," "Story Recall," and "Figure Recall" [Delayed Memory]. The raw total scores of the subtests are needed for the conversion to an index score for each cognitive domain. The sum of all index scores can be converted to an age-corrected standard score (total index scale) with a mean equal to 100 and an SD of 15. A scaled score (either total index scale or subtest index score) of below or equal to 85 (mean of 100—SD of 15) indicates a lower-than-expected cognitive result, making them at risk for mild cognitive impairment (MCI) (Cassel 1963; Albert et al. 2011). MCI is defined as cognitive decline greater than expected for an individual's age and education level but the individual is still able to perform their activities of daily life (Gauthier et al. 2006). Both the DFNA9 patients and the control subjects underwent cognitive assessment using the RBANS-H.

AUDIOLOGICAL ASSESSMENT

Pure-Tone Audiometry

Hearing thresholds were assessed using pure-tone audiometry for both air and bone conduction (resp. AC and BC) according to the present clinical standards (ISO 8253-1, 2010). To determine hearing thresholds in decibels hearing level (dB HL), the Hughson-Westlake methodology was performed (Carhart & Jerger 1959; Poling et al. 2016). Air conduction was performed in a sound-treated booth at 125 Hz, 250 Hz, 500 Hz, 1 kHz, 2 kHz, 3 kHz, 4 kHz, 6 kHz, and 8 kHz using insert earphones and a two-channel AC-40 Audiometer (Interacoustics, Assens, Denmark). Bone conduction was performed at frequencies

between 250 Hz and 8 kHz. AC and BC hearing thresholds were collected from both ears for each subject. Pure-tone average (PTA) was calculated for 1000 Hz, 2000 Hz, and 4000 Hz (PTA [1, 2, and 4 kHz]). Due to output-level equipment limits, an arbitrary fixed value of 120 dB HL was assigned to cases where no measurable hearing level was detected.

VESTIBULAR ASSESSMENT

Different semi-circular canals (SCC) were measured at different angular accelerations: to obtain vestibulo-ocular reflex-gain (VOR-gain) of all three SCC the vHIT was used; horizontal (lateral), anterior (superior), and posterior SCC, as a measure for high-frequency stimulation (4 to 5 Hz) of the SCC, and electronystagmography (ENG) using both rotatory chair and caloric tests to obtain the gain and bi-thermal maximal sum of slow phase velocity (SPV) as a measure of the middle (0.01 to 1.32 Hz) and low (0.001 to 0.003 Hz) frequency stimulation of the horizontal SCC, respectively.

video Head Impulse Test (vHIT) • vHIT was administered by a clinical audiologist in a well-lit room. Participants were instructed to focus on a fixation dot placed at eye-level 1.5 meter in front of them while the clinical audiologist was standing behind the participant. Patients underwent passive short, quick head impulses in the direction of all six SCC (lateral, superior, and posterior). The head was moved randomly in both directions of the functional SCC pairs: right and left for the horizontal SCC (RL and LL), left anterior and right posterior SCC, and right anterior and left posterior SCC. Ten valid head impulses were required for each canal.

Eye velocity was determined using an infrared camera recording the right eye, and angular head velocity by three mini-gyroscopes, all incorporated in vHIT goggles (Otometrics, Taastrup, Denmark). In addition, the ICS Impulse software (Otometrics, Natus, Pleasanton, California, USA) was used in which the VOR-gain (by evaluating the relation between eye and head velocity), SD of VOR-gain, saccades (none, gathered, and scattered) and the velocity of the head (°/s) were analyzed. All DFNA9 patients underwent vHIT testing. Since the vHIT test was not routinely used in the *ERP-Norm* study, only control subjects that were recruited through the *GECkO* study underwent vHIT testing.

Electronystagmography (ENG) • Electronystagmography was performed only in DFNA9 patients in a semi-darkened room. At first, eye movements were calibrated. Then, bilateral caloric irrigation (with water) was used to evaluate low-frequency lateral SCC function. The patients were positioned in supine position, with their head elevated 30° to align the lateral SCC vertically for maximal stimulation. Bi-thermal caloric irrigation at 30°C (cold irrigation) and 44°C (warm irrigation) were performed in a 30-second time span for both stimulations. A minimum of 5-minute interval was kept between caloric irrigations. After that, the torsion swing test was performed using sinusoidal rotation at 0.05 Hz with a peak velocity of 60°/s to evaluate low- to mid-frequency vestibular function. Finally, eye movements were recorded using ENG (Nystagliner Toennies, Germany).

According to the Bárány Society criteria, the diagnosis of BV is based on bilaterally reduced vestibular responses documented by (1) a bilaterally pathological lateral VOR-gain <0.6, measured by the vHIT and/or (2) reduced caloric response (sum of bi-thermal, 30 and 44°, maximum peak SPV) on each side <6°/sec, and/or (3) reduced horizontal angular VOR-gain <0.1 upon sinusoidal stimulation on a rotatory chair (0.1 Hz, V_{max} = 50°/sec) (Strupp et al. 2017; Agrawal et al. 2019).

Only the DFNA9 population group underwent all three mentioned vestibular tests. Vestibular function in the control group was assessed by means of the vHIT only.

Dizziness Handicap Inventory (DHI) • The DHI is a validated questionnaire, designed to assess the self-perceived effect of dizziness on the quality of life. It consists of 25 items, which are grouped into three subscales evaluating the respondent's performance along emotional, functional, and physical aspects of daily life. The higher the score, the more symptoms a patient experiences (range 0 to 100), and the lower the quality of life (Tamber et al. 2009). Within a range from 30 to 60 DHI scores, a moderate self-perceived handicap is present. DHI scores above 60 points at a severe handicap (Jacobson & Calder 2000). The questionnaire was administered before the outpatient visit. DHI data for both the DFNA9 patient group and the control group are presented in Table 3.

STATISTICAL ANALYSIS

Data were stored in OpenClinica LLC (Waltham, MA), an online database for data registration and management specifically developed for clinical research and only accessible with a password. All statistical analyses were conducted using JMP Pro 16 software (JMP, Version 16. SAS Institute Inc., Cary, NC, 2021). Data were checked for normal distribution, using the Shapiro-Wilk test. In addition, histograms were used to determine normality visually. The normality of the data was not confirmed. Therefore, non-parametric tests were used.

Demographic data were analyzed with the appropriate non-parametric tests. RBANS-H scores of DFNA9 patients and controls were compared using the non-parametric Wilcoxon rank-sum test. In addition, the total sample was split into two groups: participants younger than 55 years old on the one hand and participants 55 years and older. Because the age of 55 is the youngest mean age in which the presence of hearing loss is shown to increase dementia risk, this cutoff age was used to analyze both age groups (Gallacher et al. 2012). The decision to analyze both age groups (between 55 and over and under 55) was made before the data were collected. Demographic data of these subgroups are presented in Table 4.

The two-tailed results were reported. The significance level was set at $\alpha = 0.05$. To correct for multiple testing, a Bonferroni correction was applied to the α-level to control the overall Type I error rate (α: 0.05/6 tests = 0.008).

RESULTS

Hearing and Vestibular Status of DFNA9 Patients

To visualize the progression of hearing decline across decades using observed measurements of hearing levels in both the control group and the DFNA9 group, mean hearing thresholds (dB HL) (AC) were plotted for each measured frequency (125 Hz to 8 kHz). Figure 1A represents measured hearing threshold progression across decades in 46 control subjects and Figure 1B represents measured hearing threshold progression across decades in 46 p.Pro51Ser carriers. DFNA9 patients have

TABLE 3. Data from the Dizziness Handicap Inventory for the control group and the DFNA9 patient group

	<55 (n = 21)		≥ 55 (n = 20)		Total (n = 41)	
DHI Scores	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Range
Controls						
DHI Emotional	0.29 ± 0.96	0–4	0.30 ± 0.98	0–4	0.29 ± 0.96	0–4
DHI Physical	0.29 ± 0.96	0–4	2.10 ± 2.71	0–8	1.17 ± 2.19	0–4
DHI Functional	0.48 ± 1.40	0–6	1.50 ± 3.30	0–12	0.98 ± 2.53	0–12
DHI total	1.05 ± 2.80	0–12	3.90 ± 5.56	0–20	2.44 ± 4.55	0–20
DFNA9						
DHI Emotional	9.52 ± 9.78	0–30	11.10 ± 9.19	0–32	10.29 ± 9.41	0–32
DHI Physical	10.00 ± 8.83	0–24	12.80 ± 8.24	0–26	11.37 ± 8.56	0–26
DHI Functional	11.24 ± 11.46	0–30	14.90 ± 9.99	0–34	13.02 ± 10.80	0–34
DHI Total	30.76 ± 29.23	0–84	38.80 ± 25.04	0–92	34.68 ± 27.23	0–92

DHI, dizziness handicap inventory; DFNA9, DeaFNess Autosomal dominant 9.

TABLE 4. Demographic information of the control subjects and DFNA9 patients, divided in age-subgroups of below 55 yrs old and 55 yrs and older

	Control Subjects (n = 46)		DFNA9 Patients (n = 46)	
	<55 y/o	≥55 y/o	<55 y/o	≥ 55 y/o
Gender (n: female/male)	13/10	13/10	12/13	14/7
Age (mean ± SD)	N = 23	N = 23	N = 25	N = 21
Age range	44.17 ± 7.78 [22 to 54]	61.65 ± 4.94 [55 to 72]	45.44 ± 7.94 [22 to 54]	63.23 ± 5.25 [55 to 75]
HLs (dB HL: mean [range]):	N = 23	N = 23	N = 25	N = 21
PTA right	7.10 [–1.67 to 21.67]	16.93 [3.00 to 35.00]	45.53 [1.67 to 120.00]	85.95 [60.00 to 120.00]
PTA left	7.46 [–1.67 to 15.00]	16.46 [–1.67 to 36.67]	39.15 [5.00 - 85.00]	84.84 [60.00 to 120.00]
vHIT (mean [range])	—	N = 13	N = 24	N = 18
VOR-gain Left Lateral		0.89 [0.68 to 1.19]	0.72 [0.01 to 1.00]	0.28 [0.05 to 0.67]
VOR-gain Right Lateral		0.95 [0.75 to 1.13]	0.76 [0.04 to 1.11]	0.26 [0.02 to 0.85]

dB HL, decibel HL; DFNA9, DeaFNess Autosomal dominant 9; vHIT, video Head Impulse Test; VOR, vestibulo-ocular reflex; PTA, Pure-Tone Average; PTA (1 kHz, 2 kHz, and 4 kHz) = average of hearing thresholds at 1 kHz, 2 kHz, and 4kHz.

an overall higher hearing level (dB HL) for each measured frequency and for each age decade. These differences in hearing levels per frequency are significant for every age decade, except the 3rd age decade and some of the lower frequencies (125 Hz, 250 Hz, and 1 kHz) in the 4th age decade.

In the DFNA9 patient group, 81% (n = 38) (mean age = 56.42; range [38 to 72]) presented with definite BV, based on the diagnostic criteria of the Bárány Society. Twenty-six percent of BV patients (mean age = 60.56; range [51 to 67]) met all Bárány Society criteria: a bilaterally reduced response on vHIT, caloric testing, and rotatory chair test. In 34% of BV patients (mean age = 59.58; range [44 to 72]) two of three criteria were fulfilled, and in the remaining 40% of BV patients (mean age = 50.13; range [38 to 63]) only one criterium was fulfilled (Fig. 2). The remaining 19 % (n = 8) of DFNA9 patients did not meet the Bárány Society criteria for BV and had normal vestibular function tests (vHIT, ENG) except for 1 patient who had a unilateral VOR gain of 0.41. All control subjects reported no balance problems as documented with the DHI (Table 3), had no history of vertigo, and had vHIT gains >0.6 where results were available (Table 4). To visualize hearing levels (PTA) and vestibular function (vHIT) across ages, a scatter plot is shown in Figures 3 and 4.

Cognitive Performance Using the RBANS-H

Scores on all RBANS-H subscales were compared between groups. Scores on the Immediate Memory subscale (p = 0.003), the Visuospatial/Constructional subscale (p = 0.043), the Attention subscale (p = 0.018), the Delayed Memory subscale (p = 0.014), and the Total Scale (p = 0.002) differed significantly between groups, with DFNA9 patients scoring lower than control subjects on all subscales (Table 5). After the Bonferroni correction, the Immediate Memory subscale and the Total Scale remained significantly different. DFNA9 patients obtained significantly lower scores on the Immediate Memory subscale (107.83 ± 14.01) in comparison to the control subjects (116.24 ± 14.73) (p = 0.003). DFNA9 patients had significantly lower total percentile scores (52.46 ± 28.13) than the controls (69.72 ± 21.98) (p = 0.002, r = −0.45) (Figs 5 and 6).

An index score was calculated for each of the five cognitive domains, as explained in the previous section. DFNA9 patients had an overall lower index score on all the RBANS-H subscales in comparison to their matched controls. Even though not a single included p.Pro51Ser carrier of the DFNA9 population had a history of neurological disease, six of them presented with index scores less than 85 and thus a total percentile score under 16, making them at risk of MCI (Cassel 1963; Albert et al. 2011).

In addition, the total sample was split into two groups: participants aged younger than 55 years old on the one hand and participants aged 55 years and older. Different results were retrieved from this analysis: in the age group younger than 55 years old the DFNA9 patients obtained significantly lower scores (112.44 ± 10.53) on the Immediate Memory subscale in

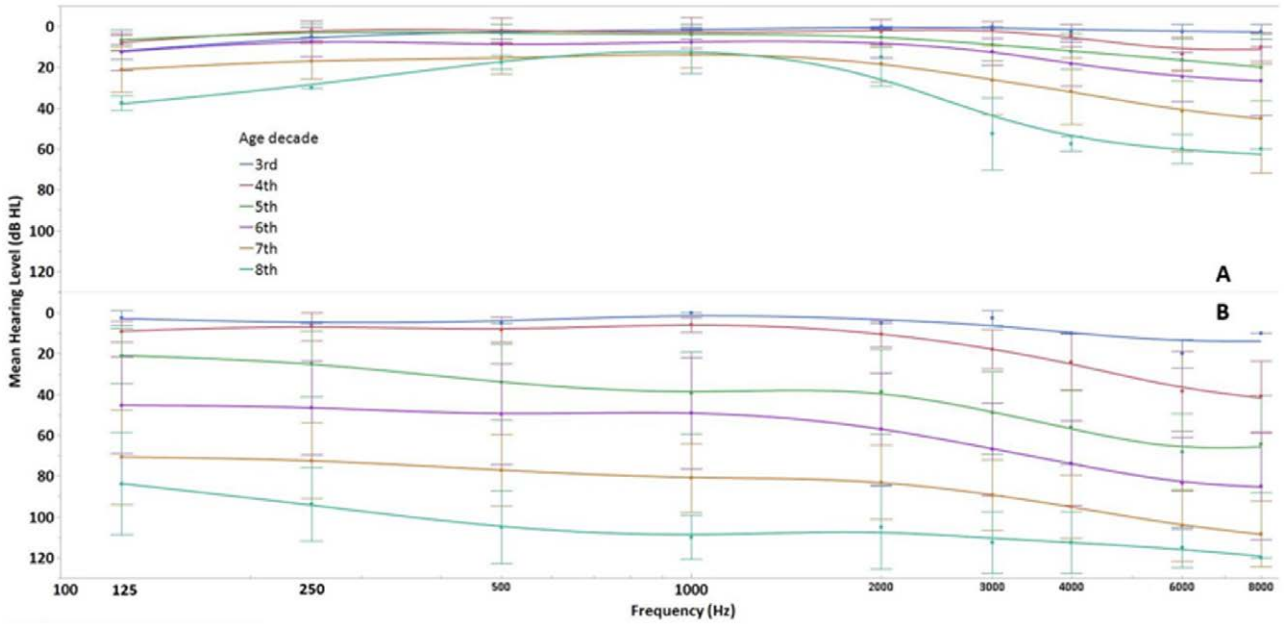

Fig. 1. The evolution of hearing decline across decades for the control group (A) and p.Pro51Ser carriers (B), based on observed data from 46 DFNA9 patients and 46 control subjects (184 ears). This figure shows the progression of the hearing decline across the different age decades (3rd to 8th age decade). Mean hearing thresholds (dB HL) (air-conduction) were plotted for each measured frequency (125–8 kHz). Each line represents one age decade. Error bars represent SDs of the mean HL for each frequency. DFNA9, DeaFNess Autosomal dominant 9.

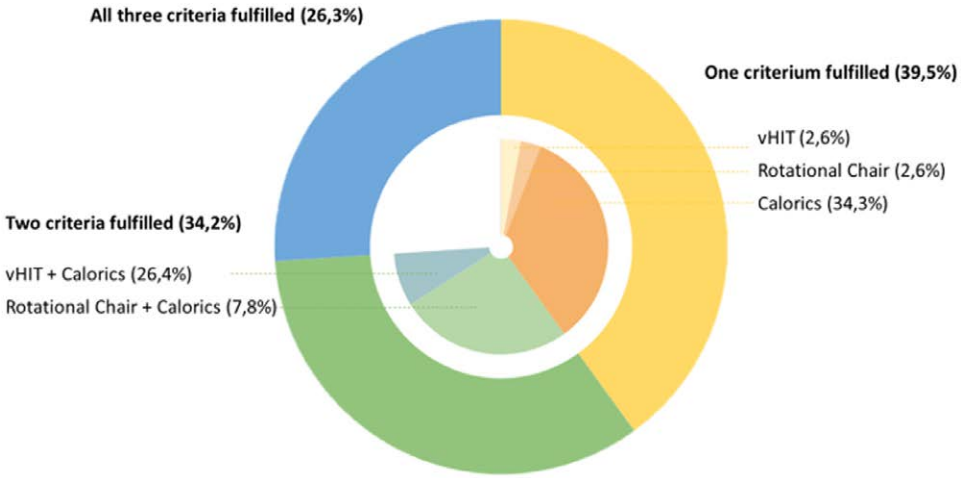

Fig. 2. This figure presents the percentages of BV patients (n = 38) in the DFNA9 population group (n = 46) that fulfilled all three Barany Society criteria or less. Bilateral Vestibulopathy is defined by a hypofunction measured by means of vHIT, Rotational Chair or Caloric Irrigation. DFNA9, DeaFNess Autosomal dominant 9.

comparison to the control subjects (118.48 ± 11.67) ($p = 0.031$). This difference was no longer significant after the Bonferroni correction (Table 6). In the age group aged 55 and older, scores on the Immediate Memory subscale ($p = 0.020$), the Visuospatial/Constructional subscale ($p = 0.013$), the Attention subscale ($p = 0.005$), and the Total Scale ($p = 0.006$) differed significantly between groups, with DFNA9 patients scoring lower than control subjects on all subscales (Table 7). After the Bonferroni correction, the Attention subscale and the Total Scale remained significantly different. DFNA9 patients had significantly lower Attention subscale scores (86.62 ± 14.77) in comparison with the controls (100.26 ± 13.58) ($p = 0.005$). Also, their total percentile scores (41.43 ± 30.60) were significantly lower than the ones of the control subjects (67.78 ± 21.45) ($p = 0.006$). The trend shown in Figure 5 indicates that the group differences in RBANS-H Total Percentile increase with advancing age. The total percentile scores of all three analyses are presented in Figure 6.

DISCUSSION

To the best of our knowledge, this is the first study evaluating cognitive performance in 46 carriers of the p.Pro51Ser variant in the *COCH* gene, all degrees of hearing loss and vestibular impairment combined, compared with their healthy matched controls. The RBANS-H is a cognitive test battery that can detect a mild cognitive disorder and is designed to exclude any bias from hearing loss (Randolph et al. 1998). The study aims to investigate how cognitive performance was affected in DFNA9 patients.

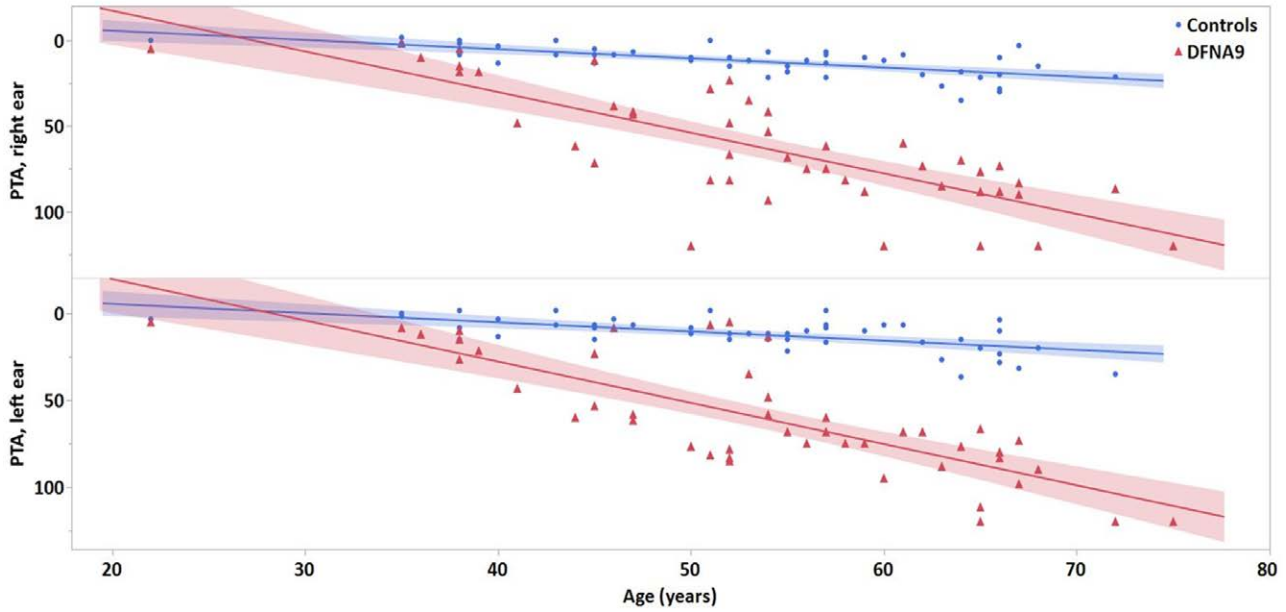

Fig. 3. HLs (PTA) across age for the control group and DFNA9 patients. PTA, Pure-Tone Average. DFNA9, DeaFNess Autosomal dominant 9.

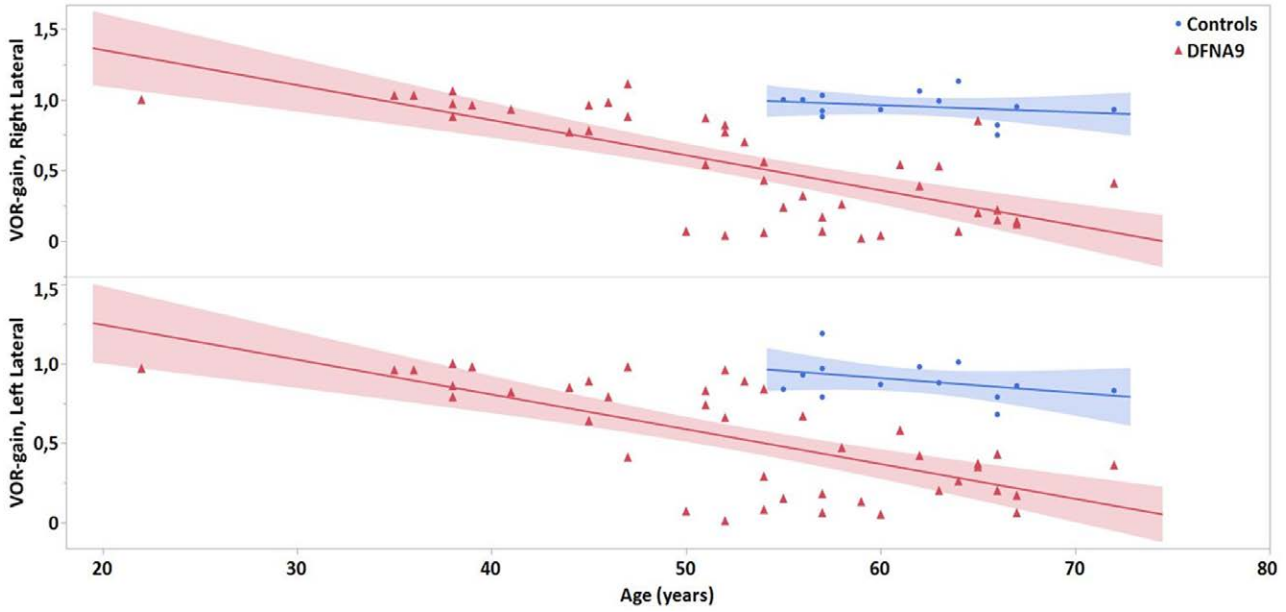

Fig. 4. Vestibular function (VOR-gain) across age for the control group and DFNA9 patients. DFNA9, DeaFNess Autosomal dominant 9; VOR, vestibulo-ocular reflex.

In the analysis, a cutoff age of 55 years old was chosen. Since DFNA9 patients are affected not only with hearing loss, known to increase dementia risk from the age of 55 (Gallacher et al. 2012), but also vestibular loss, the cutoff age could therefore be different in this particular DFNA9 population. Another possibility could be to analyze the data by age decade instead of using a specific cutoff age in the analysis.

The phenotype of DFNA9 is characterized by a progressive SNHL and is also often associated with progressive vestibular dysfunction evolving toward BV (Fransen et al. 2001; Bom et al. 2003; Bischoff et al. 2005; Bae et al. 2014). Increasing age is thus associated with the more advanced decline of both hearing and vestibular function. DFNA9 patients aged 55 years and older showed significantly lower scores on RBANS-H. In contrast, there was no statistically significant difference after Bonferroni correction in RBANS-H scores between those carriers aged younger than 55 years old and their healthy matched controls.

The DFNA9 patient group in our study obtained significantly lower scores on all subscales, except the Language subscale. After the Bonferroni correction, only the Immediate Memory subscale and Total Scale remained significantly different. A study evaluating the link between cognition, hearing, and vestibular dysfunction in patients with acquired BV found similar results, namely that hearing loss was linked with worse scores on the Immediate Memory subscale (Dobbels et al. 2019a, b).

TABLE 5. RBANS-H Subscale Scores for DFNA9 and control subjects

RBANS-H Subscales	DFNA9 Patients (n = 46) (mean ± SD)	Control Subjects (n = 46) (mean ± SD)	W_S	z	*p*
Immediate Memory	107.83 ± 14.01	116.24 ± 14.73	1752.0	–3.03	**0.003***
Visuospatial/Constructional	96.30 ± 17.02	104.22 ± 10.87	1880.0	–2.03	0.043*
Language	102.57 ± 12.50	102.91 ± 10.53	2096.0	–0.33	0.740
Attention	94.87 ± 15.70	101.89 ± 13.85	1836.0	–2.37	0.018*
Delayed Memory	102.11 ± 11.93	105.63 ± 16.49	1824.0	–2.46	0.014*
Total Scale	101.28 ± 15.68	109.54 ± 10.98	1750.0	–3.04	**0.002***

DFNA9 patients scored significantly worse on all subscales, except for the Language subscale, compared with the control group.
** indicates statistical significance (α = 0.05), p values in bold indicate statistical significance after Bonferroni correction (α = 0.008).*
DFNA9, DeaFNess Autosomal dominant 9; RBANS-H, Repeatable Battery for the Assessment of Neuropsychological Status, adjusted for the Hearing Impaired.

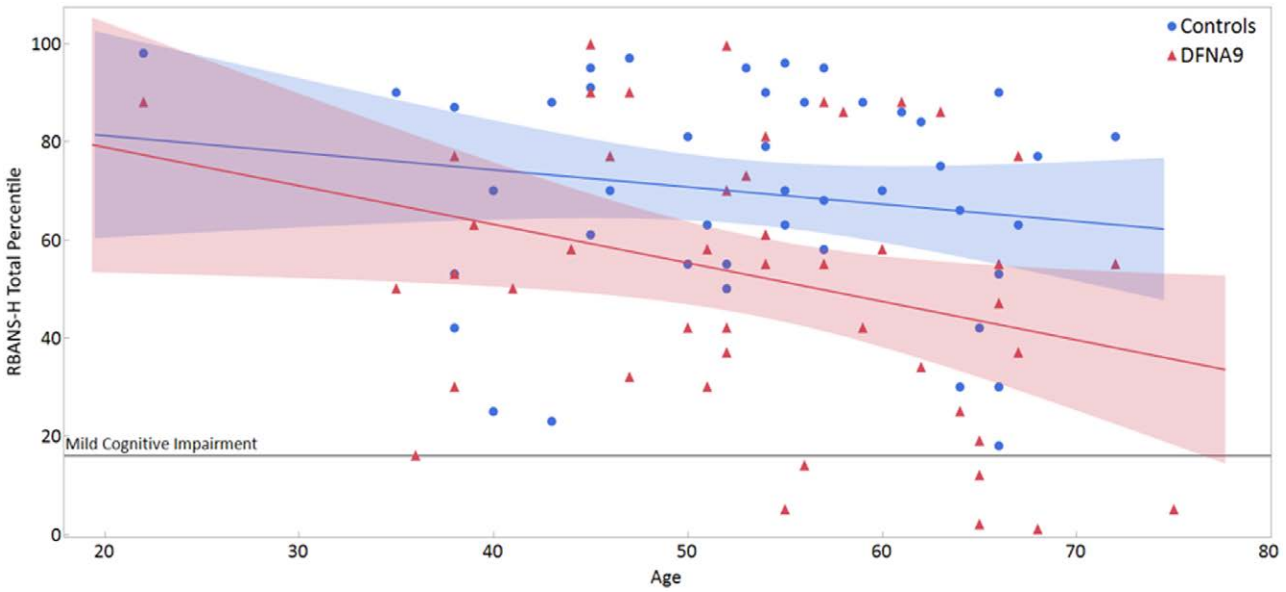

Fig. 5. Scatterplot of RBANS-H total percentile scores and age with individual data points for DFNA9 patients (red triangles) and controls(blue dots). Also the linear regression line with (95%) confidence interval is shown (Controls: y = 88.23–0.3498*age; DFNA9: y = 94.57–0.7861*age). An additional reference line indicates RBANS-H Total Percentile 16, indicating the presence of Mild Cognitive Impairment below this line. DFNA9, DeaFNess Autosomal dominant 9; RBANS-H, Repeatable Battery for the Assessment of Neuropsychological Status, adjusted for the Hearing Impaired.

On the other hand, the vestibular loss was associated with worse scores on the RBANS-H Attention subdomain, a result that we also found in our analyses of the age group of 55 years and older. Another recent study from Bosmans et al. (2022) evaluating cognitive function by use of the RBANS-H in acquired BV patients (including 11 DFNA9 carriers of the p.Pro51Ser mutation), matched with healthy controls for hearing status, also had similar findings. Both studies did not perform post-hoc Bonferroni corrections. Therefore, the discrepancies in the main findings between previous studies and the present study could be explained by different approaches toward correcting for multiple testing.

None of the analyses in the two subdivisions of age found a significant difference in the Visuospatial/Constructional domain between the DFNA9 patients and healthy controls. In future studies, it would be beneficial to include alternative spatial-cognitive assessments since the two tasks assessing spatial cognition in the RBANS-H rely more on visuomotor constructive skills, which are considered less dependent on vestibular function than navigation and spatial memory. Spatial cognitive tasks of the RBANS-H are potentially not sensitive enough to identify cognitive deficits in the DFNA9 population, including patients with BV. Spatial cognition has been studied in patients with vestibular dysfunction using the Virtual Morris Water Task (VMWT) (Brandt et al. 2005; Hüfner et al. 2007; Kremmyda et al. 2016), an adapted version of the gold standard to test spatial cognition in rodents, the Morris Water Maze (Hamilton et al. 2002, 2009). The VMWT is among the most used tasks to assess spatial cognition in patients with BV. Originally, the VMWT was included in the study protocol of the *GECkO* study (B300201938949) (Bosmans et al. 2020). However, preliminary data demonstrated that healthy control participants were unable to sufficiently complete this task, leading to unreliable results. Therefore, this task was removed from the protocol as it did not reliably represent a measure of spatial cognition.

An alternative could be the use of the Sea Hero Quest mobile application, a promising virtual reality navigation task designed to detect cognitive changes in spatial navigation (Coutrot et al. 2019; Coughlan et al. 2020).

The lower RBANS-H scores of DFNA9 patients in the older subgroup can be explained by the fact that for the p.Pro51Ser variant in *COCH*, both hearing and vestibular dysfunction begins in the 4th life decade. SNHL starts at the age of 32.8 years on average with an annual threshold deterioration of 3 dB HL per year (1 to 24 dB HL/year) (JanssensdeVarebeke et al. 2021b). By the time these carriers reach the age of 76 years on

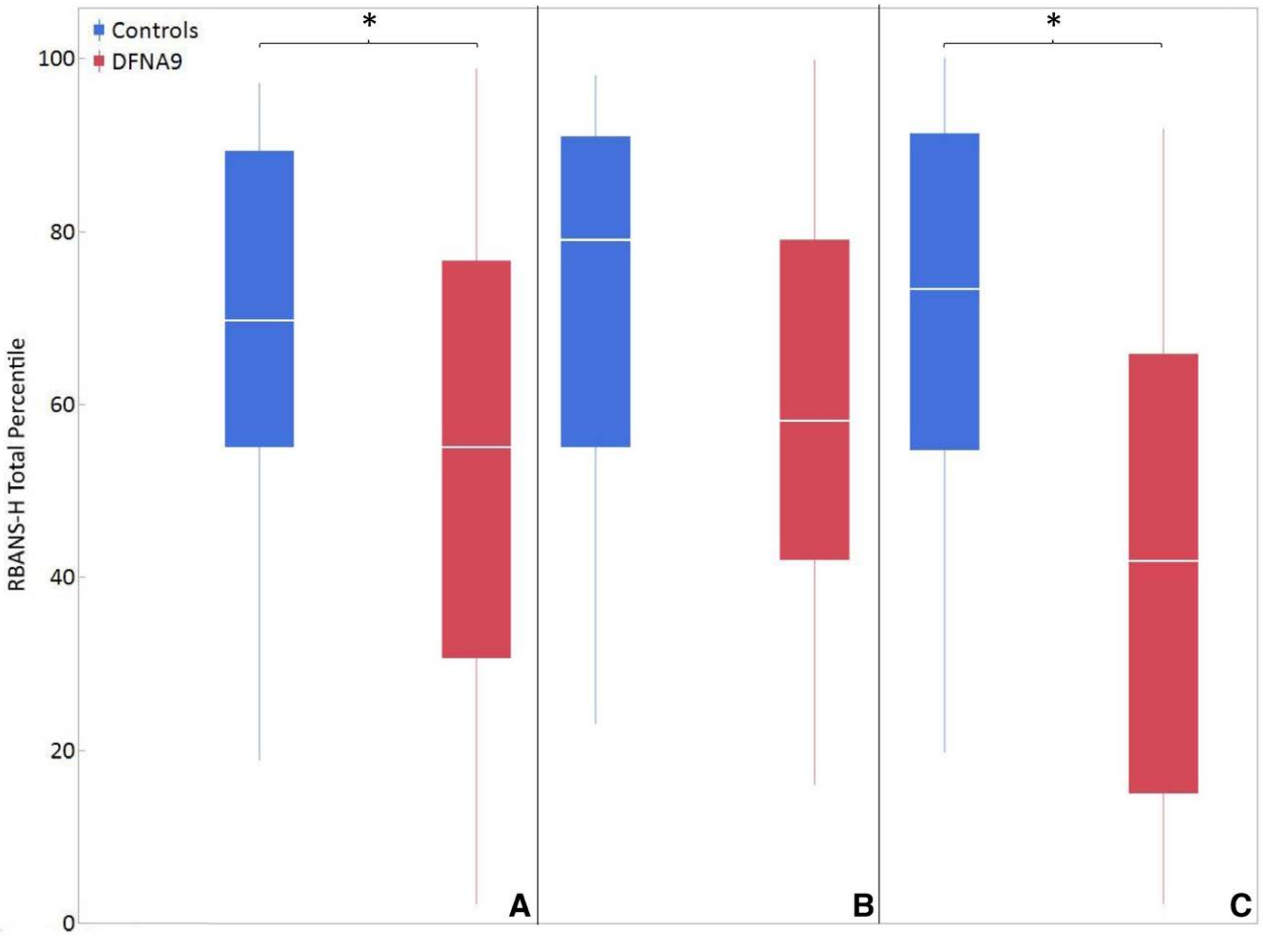

Fig. 6. Comparison of RBANS-H Total Percentile scores between controls (blue) and DFNA9 patients (red) of all ages (A), aged <55 yrs old (B) and aged 55 yrs, and older (C). Boxplots represent RBANS-H Total Percentile Scores. The boxplots show the minimum, first quartile, median, second quartile, and maximum scores. * indicates statistical significance. DFNA9, DeaFNess Autosomal dominant 9; RBANS-H, Repeatable Battery for the Assessment of Neuropsychological Status, adjusted for the Hearing Impaired.

TABLE 6. RBANS-H Subscale Scores for DFNA9 and control subjects below age 55

RBANS-H Subscales	DFNA9 Patients (n = 25) (mean ± SD)	Control Subjects (n = 23) (mean ± SD)	W_s	z	*p*
Immediate Memory	112.44 ± 10.53	118.48 ± 11.67	667.5	2.16	0.031*
Visuospatial/Constructional	100.32 ± 16.12	103.30 ± 11.00	582.0	0.37	0.709
Language	103.48 ± 13.63	102.87 ± 11.78	563.0	0.00	1.000
Attention	101.80 ± 13.08	103.52 ± 14.22	608.5	0.92	0.356
Delayed Memory	104.08 ± 7.51	103.04 ± 21.86	634.5	1.46	0.144
Total Scale	106.36 ± 13.65	110.91 ± 11.75	641.5	1.60	0.109
Total Percentile	60.89 ± 23.26	71.65 ± 22.81	641.5	1.60	0.109

DFNA9 patients below age 55 had no significant different total percentiles scores in comparison to their matched controls, except for the index score on the Immediate Memory subscale for which control subjects obtained higher index scores
** indicates statistical significance (α = 0.05), p values in bold indicate statistical significance after Bonferroni correction (α = 0.008).*
DFNA9, DeaFNess Autosomal dominant 9; RBANS-H, Repeatable Battery for the Assessment of Neuropsychological Status, adjusted for the Hearing Impaired.

average, they present with profound SNHL. The onset of vestibular dysfunction is estimated at around 34 to 40 years with BV observed between 49 and 60 years (JanssensdeVarebeke et al. 2019). DFNA9 patients aged 55 years and older are therefore for longer periods suffering from sensory deprivation of hearing function and vestibular function, both known to affect cognition negatively.

Six p.Pro51Ser carriers achieved lower than expected total scores on the RBANS-H and were therefore at risk for MCI and all were aged 55 years and older. MCI diagnosis requires a full neurological evaluation, including medical history and a physical examination, in combination with neuropsychological testing of which the RBANS-H is one of the few tests that are normed in a population with impaired loss. Therefore, a formal diagnosis of MCI cannot be made based only on the results of the RBANS-H. However, it highlights that these patients are to be considered at risk for MCI and should be closely monitored for further cognitive decline.

A significant strength of the present study is the matching of both populations for age, sex, and education level and it

TABLE 7. RBANS-H Subscale Scores for DFNA9 and control subjects aged 55 yrs and older

RBANS-H Subscales	DFNA9 Patients (n = 21) (mean ± SD)	Control Subjects (n = 23) (mean ± SD)	W_S	z	*p*
Immediate Memory	102.33 ± 15.82	114.00 ± 17.23	373.5	–2.32	0.020*
Visuospatial/Constructional	91.52 ± 17.19	105.13 ± 10.90	366.5	–2.49	0.013*
Language	101.48 ± 11.24	102.96 ± 9.38	443.0	–0.68	0.494
Attention	86.62 ± 14.77	100.26 ± 13.58	352.0	–2.83	**0.005***
Delayed Memory	99.76 ± 15.55	108.22 ± 8.02	389.5	–1.95	0.051
Total Scale	95.24 ± 16.09	108.17 ± 10.23	354.5	–2.76	**0.006***
Total Percentile	41.43 ± 30.60	67.78 ± 21.45	354.5	–2.76	**0.006***

DFNA9 patients had significantly lower scores on all subscales, except the Language subscale.
** indicates statistical significance (α = 0.05), p values in bold indicate statistical significance after Bonferroni correction (α = 0.008).*
DFNA9, DeaFNess Autosomal dominant 9; RBANS-H, Repeatable Battery for the Assessment of Neuropsychological Status, adjusted for the Hearing Impaired.

is, therefore, able to eliminate any influence of these factors. DFNA9 patients are affected with both progressive vestibular dysfunction and hearing loss, which can affect cognitive functioning negatively. It still remains a matter of debate to determine to which extent their cognitive performances are solely affected by their vestibular and hearing deficits or if their cognition may be influenced by a combined detrimental effect of both sensory deficits. Therefore, some confounder effects of hearing loss and/or vestibular dysfunction on cognition cannot be excluded. Subsequently, the included subjects in the present study were not individually matched for HL and vestibular function. DFNA9 causes progressive otovestibular decline starting in the 3rd to 5th life decade. Because of the higher than expected age-related decline in vestibular and hearing functioning, no valuable control subjects were found to match for HL and vestibular function level as well as for age, sex, and education level. For these reasons, one has to rely on currently available data in the literature reporting on the influence of hearing loss or vestibular loss on cognition separately. The majority of available studies looked at the relationship between hearing loss and cognition (Fulton et al. 2015; Castiglione et al. 2016; Claes et al. 2016; Livingston et al. 2017; Wei et al. 2017). So far, little attention has been paid to the hearing status of patients with vestibular dysfunction when evaluating their cognitive performance, as pointed out by a review from Smith (2022). The study from Dobbels et al. (2019a, b) was the first study that took both sensory modalities into account. Another recent study from Bosmans et al. (2022) looked at the impact of BV on cognition and they matched their participants for hearing status as well.

Several hypotheses have been proposed and studied on the causal relationship between peripheral hearing loss and cognitive decline (Lindenberger & Baltes 1994; Baltes & Lindenberger 1997; Arlinger et al. 2009). The most popular hypothesis states that sensory deprivation of peripheral hearing loss and the secondary atrophy of cortical areas causes cognitive decline in patients with hearing loss (Wayne & Johnsrude 2015). An important role has been suggested for hippocampal atrophy as a neuro-biological correlate for cognitive decline in patients with hearing loss (Uchida et al. 2018; Armstrong et al. 2019, 2020). Multiple studies observed that hearing loss is related to a decreased brain volume, including temporal lobe and hippocampal volume (Eckert et al. 2012; Li et al. 2012; Yang et al. 2014; Alfandari et al. 2018; Uchida et al. 2018; Wang et al. 2018). As a result of decreased auditory input, ongoing reduced hippocampal neurogenesis would impair learning and memory.

However, the impact of BV on cognition is less well-known and frequently overlooked in patients with SNHL (Dobbels et al. 2019a, b). Vestibular dysfunction can be linked to reduced topographical orientation and memory and has been suggested as a risk factor for AD (Previc et al. 2014). Different areas in the hippocampus, which are especially active in cognitive domains such as spatial and non-spatial memory and learning, have been suggested to be involved in hearing and vestibular functioning and are affected by sensory loss (Kremmyda et al. 2016; Harun et al. 2017). Also, a direct association between hippocampal volume, vestibular decline, and impaired (spatial) cognition has been put forward (Brandt et al. 2005; Göttlich et al. 2016). Similar to the impact of SNHL on cognition, the sensory deprivation hypothesis may also apply to the link between BV and cognition (Dobbels et al. 2019a, b).

Limitations of the present study involve the small amount of included p.Pro51Ser carriers aged under 35 (n = 1) which makes these carriers underrepresented in this study. This patient presented with normal hearing (PTA high right/left = 5.00) and normal vestibular function (vHIT VOR-gain left lateral = 0.97; vHIT VOR-gain right lateral = 1.00). Therefore, this specific population subgroup, being presymptomatic carriers, could not be analyzed separately. Additional analyses, in which the data of this pre-symptomatic carrier were removed, were performed. The same results could be retrieved from these analyses and are therefore not further described in detail within this manuscript. Another limitation of this study is that the inclusion criterium of normal vestibular function for the control group was only assessed by using vHIT (VOR-gain > 0.6). Caloric testing and rotatory chair testing were not performed in the control group because it is time-consuming and control subjects with preserved vestibular function could experience negative side effects such as dizziness and nausea when undergoing caloric testing and rotatory chair testing. However, a recent systematic review and meta-analysis by Vallim et al. (2021) pointed out that vHIT does not fully substitute for caloric testing. Also, no cervical Vestibular-Evoked Myogenic Potentials were performed. Accordingly, it is preferable in future studies to perform the full vestibular test battery. Control subjects' medical history was questioned during anamnesis and all reported no history of vertigo and no balance problems. Therefore, there was no indication of any vestibular problems in the control group. A third limitation is that information about hearing aid use is lacking. It would be beneficial to include this information in future research to look at differences in cognitive performance between treated and untreated patients with hearing loss. This is important because of the observed positive effect of hearing aids on cognition (Acar et al. 2011; Amieva et al. 2015; Dawes et al. 2015).

To protect DFNA9 patients against potential accelerated cognitive decline, early identification of DFNA9 carriers is warranted. In that way, adequate treatment with hearing aids or cochlear implantation may reduce the adverse effects of hearing loss on cognition (Cosetti & Lalwani 2015; Wei et al. 2017; Claes et al. 2018a, 2018b). The development of a vestibular implant also seems to be a promising treatment option (Perez Fornos et al. 2017; Guyot & Perez Fornos 2019). The complexity of the association between hearing loss and vestibular loss on cognition must be clarified by future research taking both hearing function and vestibular function into account.

CONCLUSIONS

In conclusion, this cross-sectional study found that DFNA9 patients demonstrated cognitive deficits in comparison with their healthy matched controls. The DFNA9 group aged ≥55 years old obtained significantly lower scores on the Total Scale and Attention subscale. This finding; however, was not observed for the age group younger than 55 years old. Further work is needed to investigate the subclinical period more profoundly since pre-symptomatic carriers are underrepresented in the literature. To further refine the present findings, a prospective longitudinal study of both otovestibular functioning and cognitive performance may help to provide better insights into this matter.

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