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Association between saccule and semicircular canal impairments and cognitive performance among vestibular patients

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Abstract

Objectives—Growing evidence suggests that vestibular function impacts higher order cognitive ability such as visuospatial processing and executive functioning. Despite evidence demonstrating vestibular functional impairment impacting cognitive performance, it is unknown whether cognitive ability is differentially affected according to type of vestibular impairment (semicircular canal (SCC) vs. saccule) among patients with diagnosed vestibular disease.

Design—54 patients who presented to an academic Neurotologic clinic were recruited into the study. All patients received a specific vestibular diagnosis. Forty-one patients had saccule function measured with the cervical vestibular-evoked myogenic potential (cVEMP), and 43 had SCC function measured using caloric irrigation. Cognitive tests were administered to assess cognitive performance among patients. 125 matched controls were recruited from the Baltimore Longitudinal Study of Aging (BLSA) to compare cognitive performance in patients relative to age-matched healthy controls.

Results—Using multivariate linear regression analyses, patients with bilaterally absent cVEMP responses (i.e. bilateral saccular impairments) were found to take longer in completing the Trail Making Test (TMT) (β=25.7 seconds, 95% CI −0.3, 51.6) and to make significantly more errors on the Benton Visual Retention Test Part-C (BVRT-C) (β=4.5 errors, 95% CI 1.2, 7.8). Patients with bilateral SCC impairment were found to make significantly more errors on the BVRT-C (β=9.8 errors, 95% CI 0.2, 19.4). From case control analysis, for each standard deviation difference in TMT-B time, there was a corresponding 142% increase in odds of having vestibular impairment (OR 2.42, 95% CI 1.44, 4.07).

Conclusions—These data suggest that bilateral saccule and SCC vestibular impairments may significantly affect various domains of cognitive performance. Notably, the cognitive performance in patients in this study was significantly poorer relative to age-matched healthy adults. Cognitive assessment may be considered in patients with saccule and/or SCC impairments, and cognitive deficits in vestibular patients may represent an important target for intervention.

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Introduction

Recent studies have shown that vestibular function is associated not only with maintaining balance and postural control, but also with various cognitive processes (Agrawal et al. 2013; Brandt et al. 2005; Hansson & Magnusson 2013; Grimm, Hemenway et al. 1989; Guidetti et al. 2008; Kremmyda et al. 2016; Liston et al. 2014; Popp et al. 2017; Risey & Briner 1991). Vestibular impairment has been associated with decreased performance on neurocognitive tests of executive function and visuospatial ability (Bigelow et al. 2015; Popp et al. 2017). Moreover, evidence from both animal and human investigations have demonstrated detrimental behavioral impacts of vestibular impairment on spatial orientation, memory and navigation (Brandt et al. 2005; Guidetti et al. 2008; Yoder & Taube 2014; Zheng, Goddard et al. 2007). In older adults, studies suggest that age-related vestibular impairment may contribute to the known decline in navigational ability (e.g. manifested as an increase in driving difficulty) that occurs with age (Adamo et al. 2012; Baccini et al. 2014; Moffat et al. 2001; Moffat & Resnick 2002; Moffat et al. 2006; Popp et al., 2017).

Despite the recent body of evidence demonstrating that vestibular impairment impacts cognitive performance (i.e. executive function and visuospatial ability) in healthy older adults, only a few studies have examined how severity (i.e. unilateral versus bilateral involvement) and organ-specific (e.g. saccule versus semicircular canal (SCC)) impairments in vestibular function affect cognitive performance among patients with diagnosed vestibular disease. Kremmyda et al. assessed patients with partial bilateral vestibulopathy, determined based on head-impulse and caloric irrigation (i.e. semicircular canal (SCC)) testing, and revealed impairments in spatial memory and navigation, associated with increased spatial anxiety and mid-hippocampal atrophy (Kremmyda et al. 2016). Popp et al. further demonstrated greater deficits in cognitive domains tested among patients with bilateral vestibular (specifically SCC) failure compared to those with unilateral involvement (Popp et al. 2017). However, more detailed investigation into how unilateral or bilateral SCC and saccule impairments is needed to advance rehabilitation among patients with diagnosed vestibular diseases. In this study, we evaluated 54 patients who presented with dizziness and vertigo to the Johns Hopkins Neurotology Clinic and were subsequently diagnosed with a vestibular disease. We investigated the relationship between physiologic tests of SCC and saccule, function and multiple domains of cognitive function among patients, and also compared cognitive performance between patients and matched controls, to assess whether cognitive performance in the patients differed from expected performance levels. These data further underscore the significant link between vestibular and cognitive, notably spatial cognitive, function.

Materials and Methods

Clinic patients

Patients who presented to the Johns Hopkins Neurotology Clinic for dizziness and vertigo between August 2017 and March 2018 were recruited to participate in the study. All patients underwent vestibular physiologic testing as part of their routine evaluation, which included caloric testing and cervical vestibular-evoked myogenic potential (cVEMP) testing. Patients were assigned specific vestibular diagnoses following their clinical visit, which including the

following primary diagnoses: active (i.e. nystagmus on Dix-Hallpike maneuver) benign paroxysmal positional vertigo (BPPV), vestibular neuritis, Meniere's disease, post-stroke, vestibular migraine, concussion, functional dizziness, Mal de Debarquement syndrome (MDD), and idiopathic intracranial hypertension (IIH). All patients with a diagnosed vestibular disease were only included if vestibular disease was active at time of cognitive testing. Patient characteristics including age, gender, education, and history of hearing loss were obtained from the patients' charts. Potential patients were excluded if they were unable to understand and participate in the vestibular or cognitive testing. Patients with diagnosed mental health disorders (e.g. anxiety and depression), known cognitive disorders (e.g. dementia), and primary vestibular disorders of superior canal dehiscence and normal pressure hydrocephalous were also excluded. The study was approved by the Johns Hopkins Hospital Institutional Review Board and all patients provided written informed consent.

Control participants were recruited from the Baltimore Longitudinal Study of Aging (BLSA), a prospective cohort study of normal aging at the National Institute on Aging (NIA) Clinical Research Unit at Harbor Hospital in Baltimore, Maryland. The BLSA is supported by the Intramural Research Program of the NIA. Individuals with a diagnosis of mild cognitive impairment or dementia were excluded. The BLSA protocol was approved by the Institutional Review Board of the National Institute of Environmental Health Sciences in Research Triangle Park, NC, USA.

Vestibular Function Tests

Cervical vestibular-evoked myogenic potential (cVEMP) responses were used as the main determinant of saccule function in patients (Li et al. 2014; Nguyen et al. 2010). VEMPs were acquired with established standards (Rosengren et al. 2009; Rosengren et al. 2014). Patients sat on a chair inclined at 30° from the horizontal. Trained examiners placed recording electromyographic (EMG) electrodes on the sternocleidomastoid (SCM) muscles and at the sternoclavicular junction bilaterally. A ground electrode was placed on the manubrium sterni. While patients kept their heads turned against resistance to activate the SCM muscle, sound stimuli consisting auditory tone bursts (500 Hertz, 125 dB sound pressure level (SPL)) were delivered monaurally through headphones (Viasys Healthcare, Madison, WI, USA) and inhibitory potentials were recorded from the ipsilateral SCM muscle. cVEMP responses were normalized for background EMG activity during the 10 ms recorded before stimulus onset. Lower level cut-off for EMG was 30 microvolts of background EMG activity. The presence or absence of a cVEMP response was recorded for each ear, indicating normal or impaired saccular function, respectively, as described in published guidelines (Li et al. 2014; Nguyen et al. 2010). Overall, patients were categorized based on cVEMP responses as bilaterally present, unilaterally absent, or bilaterally absent based on previously described definitions of abnormal cVEMP testing (Li et al. 2014; Nguyen et al. 2010).

SCC function was also assessed in patients using caloric testing. Caloric tests were performed with temperature-switch irrigation at water temperatures of 30.5°C and 43.5°C (Proctor et al. 1975). Video oculography was used to record horizontal eye movements with the eyes open under vision-denied conditions. Calibration of eye movements was performed

per the system's operating procedures. Based on convention, maximum velocity of the slow-phase component of nystagmus was analyzed for unilateral weakness (UW). The maximum slow component velocity was identified within a time window of 120 seconds, typically at 60–90 seconds following stimulus onset. UW was computed using the Jongkees formula and represents the difference between the sum of the response magnitudes between the right and left ear stimulation, normalized by the sum of response magnitudes for all four irrigations. An ice-water caloric test was done if there was no response to warm or cold irrigation (100% UW). If nystagmus was observed with ice-water testing, the patient was turned from a supine to prone position to see if nystagmus reversed direction, which is expected based on convection (Minor & Goldberg 1990). An asymmetric caloric response of UW >25% or more was categorized as unilateral SCC impairment (Halmagyi et al. 1997). Bilateral SCC impairment was determined by a combined mean peak slow-phase velocity of <6°/second for cold and warm water irrigation on both sides (Strupp et al. 2016). Of the 54 patients who underwent cognitive testing, 41 and 43 patients underwent cVEMP and caloric irrigation testing in our Neurotology clinic. The reasons for missing vestibular testing data included lack of time for full vestibular physiologic assessment or equipment unavailability. All patients received a vestibular diagnosis following their clinical visit.

Cognitive Tests

Given prior data showing a relationship between vestibular function and spatial cognitive ability, we focused our analysis on measures of spatial cognition including the Benton Visual Retention Test (BVRT), the Trail-Making Test Part B (TMT-B), and the Money Road Map Test (MRMT). Notably, cognitive tests were administered on the same day as patients' vestibular tests for patient convenience, however, patients were given at least thirty minutes of rest post-vestibular testing prior to cognitive testing if vestibular testing was done before cognitive testing.

Benton Visual Retention Test Form C—The BVRT is used to assess nonverbal memory and visuoconstructional skill. For form C of the BVRT (BVRT-C), participants are shown 10 cards, each containing geometric shapes for 10 seconds each, and are then asked to re-draw the shapes on a blank piece of paper as accurately as possible after the original image is removed from sight. The total number of errors (error score) across the 10 cards was the outcome measure in our analysis as described previously (Benton 1963). The BVRT-C was administered in both clinic patients and in the BLSA.

Trail-Making Test Part B—The TMT-B assesses executive function, set-shifting, attention, processing speed and visual scanning ability. In the TMT-B, participants are asked to connect a series of letters and numbers in alternating consecutive order (1, A, 2, B, 3, C, etc.). The time in seconds to complete the task is recorded (Reitan 1992). The TMT-B was administered in both clinic patients and in the BLSA.

Money Road Map Test—The MRMT measures visuospatial ability by showing patients a 2D representation of a small city map on paper in a fixed orientation (Money et al. 1965; Rainville et al. 2002). Buildings are shown as squares to represent a "bird's eye view" of the city. The city map contains a walking path with 32 turns, which is designated with a dotted

line between the buildings. Participants are instructed to imagine they were traveling along the path in the city, either by vehicle or walking, to establish the perspective of being on the path approaching each turn from “street”-level. As the examiner traced the path, the participant stated at each turn whether a right or left turn would be required to continue along the path. The participants’ responses were recorded at each turn by the examiner. The main outcomes of interest were number of errors (i.e. incorrect or missing responses) out of 32 turns (MRMT errors) and total time taken to complete the path (MRMT time). All 54 participants had MRMT time and MRMT errors recorded, however the MRMT was not administered for the BLSA.

Statistical Analysis

Multivariate linear regression modeling was used to evaluate the association between vestibular function (including both saccule and SCC function) and cognitive performance, after adjusting for demographic characteristics (age, gender, and education). Age, gender, and level of education in addition to history of hearing loss were added to regression models as covariates to account for potential influence on cognitive performance. In addition to the influences of other covariates such as age described above, history of hearing loss has been independently associated with accelerated cognitive decline in old adults, which can remain affected even after treatment of hearing impairments (Lin et al. 2013; Taljaard et al. 2016). Furthermore, cognitive function between patients from the Neurotology clinic and matched controls from the BLSA were compared. The TMT-B and BVRT-C were administered to participants at the BLSA. Time taken to complete the TMT-B and BVRT-C error score standardized variables were generated for case-control analyses to evaluate the odds of being a case associated with significant differences in cognitive performance. Cases (clinic patients) were matched 1:4 to controls from the BLSA without replacement based on age (within ± 3 years), sex, and education. Matched BLSA controls were also excluded if they had abnormal cVEMP testing (i.e. unilaterally or bilaterally absent cVEMP responses). Of the 54 cases, 38 cases were successfully matched to 125 controls based on this criteria. Conditional logistic regression analyses adjusting for age, sex, and education were conducted to evaluate the association between cognitive function and vestibular impairment. A p-value of less than 0.05 was considered statistically significant. STATA 14 statistical software was used for all analyses (StataCorp, College Station, TX, USA).

Results

Fifty-four patients presenting to the Johns Hopkins Neurotology Clinic between August 2017 and March 2018 were enrolled in the study (Table 1). The patients were 59.3% female, with a mean age of 55.9±15.6 years. Among 40 patients with cVEMP testing, 31.7%, 14.6%, and 55.8% of patients had bilaterally present, unilaterally absent, and bilaterally absent cVEMP responses, respectively. Among 43 patients with caloric irrigation testing, 55.8%, 32.6%, and 11.6% had normal SCC function, unilateral SCC impairment, and bilateral SCC impairment, respectively.

Multiple linear regression analyses were conducted to assess the association between saccule and SCC function and each cognitive performance measure among patients (Tables 2 and 3).

Compared to patients with bilaterally present cVEMP responses (i.e. reference for comparison in the regression analyses), patients with bilaterally absent cVEMP responses made significantly more errors on the BVRT-C (β=4.5 errors, 95% CI 1.2, 7.8). Additionally, multiple linear regression analyses were conducted to assess the association between SCC function and cognitive performance among patients (Table 3). Interestingly, patients with bilateral SCC impairment made significantly more errors on the BVRT-C (β=9.8 errors, 95% CI 0.2, 19.4). Further linear regression analyses revealed no significant differences in cognitive performance among patients with combined unilateral or bilateral SCC and saccule impairment, although only 11 patients had combined SCC and saccule impairment which limited the power of this analysis (Table 4).

Case-control analyses were conducted using conditional logistic regressions to compare cognitive performance (i.e. standardized values of TMT-B time and BVRT-C error score) between 38 patients (cases) and 125 matched BLSA controls, while controlling for demographic factors (Table 5). The 25th, 50th, 75th, and 99th percentiles for standardized values of TMT-B time were determined to be −0.69, −0.25, 0.41, and 3.89. Based on adjusted analyses, for each standard deviation difference in TMT-B time, there was a corresponding significant 142% increase in odds of having vestibular impairment (OR 2.42, 95% CI 1.44, 4.07). Additionally, the percentiles for standardized values of BVRT-C error score were −0.72, −0.14, 0.63, and 2.55, and there was no significant increase in odds of having vestibular impairment based on BVRT-C error score.

Discussion

This study further demonstrates the associations between severity (i.e. bilateral and unilateral) and organ-specific (e.g. saccule and SCC) impairments among patients with vestibular disease and cognitive performance. Among patients presenting with dizziness and vertigo to a tertiary care Neurotology clinic, bilateral saccule impairment, determined by bilaterally absent responses on cVEMP testing, was associated with significantly higher number of errors made on the BVRT-C. Furthermore, bilateral SCC impairment was significantly associated with more errors made on the BVRT-C. Importantly, case-control analyses showed that patients had significantly poorer cognitive performance compared to controls, notably on the TMT-B test.

Our study's findings are consistent with recent investigations that have shown associations between saccular function and cognitive domains of executive function, attention, nonverbal memory and visuoconstructional skill (Schlindwein et al. 2008; Stiles & Smith 2015; Yoder & Taube 2014). Bigelow et al (2015) reported associations between saccular impairment and decreased performance on the same cognitive tests, BVRT-C and TMT-B in healthy older adults (Bigelow et al. 2015). Xie et al. (2017) also demonstrated deficits in spatial navigation with a triangle completion task among patients with abnormal cVEMP responses (includes both unilateral and bilateral impairments) (Xie et al. 2017). Similarly, we found that only patients with bilateral saccular impairment had the poorest cognitive performance on the BVRT-C. Unlike prior studies, we did not find a significant difference in cognitive performance among unilaterally affected patients, potentially supporting the importance of intact unilateral vestibular function in order to maintain vestibular input into higher cognitive

processing (Popp et al. 2017). Although Popp et al. made this statement in the setting of SCC function, we believe our data similarly shows evidence of the importance of intact unilateral saccular functioning in maintaining cognitive performance.

Similar to recent investigation, our study determined an association between bilateral SCC function and worsened nonverbal memory and visuoconstructional skill with the BVRT-C test (Kremmyda et al. 2016; Popp et al. 2017). Prior work has shown associations of bilateral SCC impairment negatively affecting cognitive domains of visuospatial ability, processing speed, short-term memory and executive function compared to unilateral SCC impairment affecting only visuospatial ability and processing speed (Popp et al. 2017). Our data reveals comparable results in regards to effects of bilateral vs. unilateral SCC impairment in a population of patients with diagnosed vestibular disease. It is possible that in the case of unilateral SCC impairment, contralateral SCC function and central compensation mitigate functional loss and impacts on cognitive function.

We observed that bilateral saccular and bilateral SCC impairment among patients were each associated with poorer BVRT-C performance, though in the comparison of patients and controls in the case-control analysis there was a significant difference in TMT-B score. The reason for this discrepancy may be that a slightly different sample of patients was selected for the case-control analysis given that only patients with a suitably matched control were entered into the analysis. The difference in TMT-B scores which was borderline significant among patients may have become significant in the case-control analysis. Further studies with more robust sample sizes will be required to clarify which cognitive skills and tests are most sensitive to differences in vestibular function both among patients and in case-control comparisons.

Although an explanation is not explicitly clear from literature, studies suggest that bilateral vestibular impairment is associated with anatomical changes in important neurological pathways associated with cognition. Significant hippocampal atrophy and associated impairments in visuospatial tasks such as navigation in a virtual maze were discovered in a small group of patients with bilateral vestibular failure due to vestibular nerve sectioning (Brandt et al. 2005). Additional studies examining patients with bilateral SCC impairment demonstrated both high spatial anxiety and delayed spatial learning in addition to decreases in mid-hippocampal and posterior parahippocampal volume (Kremmyda et al. 2016). The hippocampus and basal ganglia also contain important spatial working memory centers that may be affected in these patients (Stiles & Smith 2015). These anatomic changes in the hippocampus and basal ganglia with memory centers seen among patients previously with bilateral vestibular impairment supports our determined associations between bilateral saccule and bilateral SCC impairments and the BVRT-C, a test of visual perception and visual memory. Interestingly, prior work has shown deficits in spatial memory without accompanied hippocampal atrophy for patients with unilateral vestibular loss, which suggests potential for rehabilitative intervention and vestibular compensation as seen in among our patients with unilateral SCC impairment without more permanent anatomic hippocampal alternations (Hüfner et al. 2007; Jahn et al. 2009). In addition to effects on the hippocampus, bilateral vestibular impairment is also associated with decreases in functional connectivity of temporoparietal junction structures critical for visuospatial processing

(Göttlich et al. 2014). These patients also demonstrated enduring changes in the resting-state connectivity of the brain, which were hypothesized to partially describe persistent deficits in visuospatial attention and spatial orientation (Göttlich et al. 2014). Further work has demonstrated that decreased peripheral vestibular input leading to atrophy of the cortical vestibular network, which includes not only the temporoparietal junction and hippocampus but also the dorsal thalamus, results in visuospatial memory and perception deficits (Dieterich & Brandt 2008). Therefore, the effects of bilateral saccule impairment as seen in our study, in respect to errors made on the BVRT-C and time taken on the TMT-B compared to healthy controls, may be explained by enduring decreases in connectivity between cortical brains structures critical to higher order visuospatial processing and scanning, attention, and executive function.

The limitations of this study include the cross-sectional analysis conducted which cannot support causal inferences between saccule and SCC impairments and cognitive performance. Future longitudinal studies will be needed to determine the causal nature of this association. As described above, the association between bilateral saccule impairment and TMT-B was not significant, while TMT-B time was significantly different between patients and BLSA controls. Although bilateral saccule impairment causes enduring cognitive deficits on the TMT-B test among patients with vestibular disease compared to controls, this specific association similarly needs to be further explored with a larger sample of patients and other tests of vestibular function. Additional cognitive tests should also be similarly assessed to explore effects of saccule and SCC impairments on other domains of cognitive function. Moreover, other factors such as hypertension, diabetes mellitus, cardiovascular disease, and/or traumatic brain injury may confound the association between saccule and SCC impairments and cognitive decline (Previc 2013). We also recognize post-stroke disturbances in vestibular function can vary between supra and infra-tentorial locations for which we did not account for among the three clinic patients included with this vestibular disease etiology. The effects of confounding were minimized by adjusting for potential predictors of cognitive dysfunction including age, sex, level of education, and history of hearing loss. Almost one quarter of the patients did not have cVEMP and caloric testing completed and were not included in analyses, decreasing our sample size and ability to associate vestibular dysfunction with cognitive performance. Although 30 minutes of rest was given to patients taking cognitive tests after vestibular testing, we recognize the impact of vestibular testing on eliciting symptoms of vestibular disorders and therefore possibly making cognitive testing more difficult for select patients. Although patients' subjective cognitive deficits in daily tasks were not assessed during cognitive testing through survey or tools such as the MMSE or MOCA, we excluded all patients unable to understand, follow directions, and participate in the vestibular or cognitive testing. Although patients were excluded with cognitive disorders or diagnosed underlying cognitive deficits, assessing patient subjective function and cognition is important account for undiagnosed and undetected cognitive impairment. UW >25% was considered abnormal, but only indicates relative weakness (i.e. asymmetry) and can occur when the weaker ear is in normal range. Furthermore, only 38 of the 54 patients could be matched to 125 BLSA controls for case control analysis due to the inclusion criteria specifically for age (within ± 3 years) and normal BLSA cVEMP testing because these patients did not match to the older population of patients that were followed

by the BLSA. Although we were able to exclude controls with abnormal cVEMP testing, caloric testing was not conducted on subjects in the BLSA, and therefore, we were unable to exclude controls with abnormal caloric testing in our case-control analyses. Significant findings from case-control analyses may be influenced by undetermined SCC impairment among controls. We also note the non-significant associations of combined SCC and saccule impairments and cognitive performance likely arise from a small sample size of only 11 patients with combined impairments, leading to an under-powered analysis. We also recognize the limited generalizability of caloric testing data given our small population of bilateral and unilateral SCC impaired patients. Although only cVEMP testing was utilized to characterize saccule function in this study, we recognize oVEMP (i.e. utricle) testing can also be done as well. Data not included was non-significant and not worth describing because only 26 patients had oVEMP testing done and among these patients, 25 were normal, which was not adequate for analysis. Further longitudinal studies in larger patient cohorts will be needed to mitigate these limitations.

Conclusion

This investigation of patients diagnosed with vestibular disease determined that bilateral saccule and bilateral SCC impairments significantly affect cognitive performance. These data have potential clinical relevance: knowing that a patient has bilateral saccule or bilateral SCC impairment could be useful in guiding clinicians to assess cognition and modify and/or prescribe interventions accordingly. Moreover, this study has implications with respect to vestibular rehabilitation, and whether conventional methods address the cognitive deficits or whether additional intervention is required in some vestibular patients who exhibit concomitant cognitive difficulties.

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K.P. interviewed clinic patients, collected data, assisted in analysis, and wrote the paper. D.P. recruited and interviewed clinic patients and collected data. E.W., R.K., and B.K. assisted in editing the paper. E.W. performed most of the analyses. Y.A. designed the project and edited the entire paper.

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Table 1

Demographic characteristics of clinic patients and matched BLSA controls, vestibular function, and cognitive performance

	Clinic patients N=54		Controls N=125	
	Mean (SD)	**N (%)**	**Mean (SD)**	**N (%)**
Sex				
Male		22 (40.7%)		50 (40.0%)
Female		32 (59.3%)		75 (60.0%)
Mean age (SD)	55.9 (15.6)		62.0 (12.7)	
Education				
Less than college		24 (44.4%)		31 (24.8%)
College		13 (24.1%)		28 (22.4%)
Greater than college		17 (31.5%)		66 (52.8%)
cVEMP responses				
Bilaterally present		13 (31.7%)		125 (100%)
Unilaterally absent		6 (14.6%)		0 (0%)
Bilaterally absent		22 (53.7%)		0 (0%)
Bithermal Caloric irrigation				
Bilaterally present		24 (55.8%)	-	
Unilateral impairment		18 (41.9%)	-	
Bilateral impairment		1 (2.3%)	-	
Cognitive performance				
MRMT time	116.6 (71.2)		-	
MRMT errors	3.0 (3.4)		-	
TMT-B time	78.6 (33.5)		67.0 (36.7)	
BVRT-C error score	7.2 (4.6)		8.0 (5.3)	

Abbreviations: cVEMP = Cervical vestibular-evoked myogenic potential, SD = standard deviation, "-" = studies not conducted with BLSA participants

Table 2

Saccule function and cognitive performance

	MRMT Time		MRMT Errors		TMT-B Time		BVRT-C Error Score	
	β (95% CI)	*P*	β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*
Saccule function								
Bilaterally present	Reference		Reference		Reference		Reference	
Unilaterally absent	15.7 (−45.5, 76.9)	0.605	−2.4 (−5.2, 0.4)	0.089	18.9 (−9.6, 47.4)	0.186	−0.6 (−4.2, 3.0)	0.734
Bilaterally absent	29.1 (−26.8, 84.9)	0.298	−0.4 (−3.0, 2.1)	0.754	25.7 (−0.3, 51.6)	0.053	**4.5 (1.2, 7.8)**	**0.009**
Age	0.7 (−0.7, 2.1)	0.308	0.04 (−0.02, 0.1)	0.181	0.6 (−0.1, 1.2)	0.104	0.07 (−0.01, 0.2)	0.097
Sex								
Male	Reference		Reference		Reference		Reference	
Female	**72.4 (33.0, 111.9)**	**0.001**	1.8 (−0.01, 3.6)	0.052	**28.3 (9.4, 47.3)**	**0.005**	1.8 (−0.6, 4.2)	0.141
Education								
Less than college	Reference		Reference		Reference		Reference	
College	13.7 (−37.5, 64.8)	0.590	−1.9 (−4.3, 0.4)	0.098	−2.5 (−26.5, 21.5)	0.835	−1.9 (−4.9, 1.2)	0.219
Greater than college	−21.8 (−66.9, 23.3)	0.333	−1.9 (−4.0, 0.2)	0.069	−5.3 (−26.8, 16.2)	0.617	−2.7 (−5.4, 0.05)	0.054
History of hearing loss	−8.8 (−29.4, 46.9)	0.643	1.1 (−0.7, 2.8)	0.216	8.0 (−9.8, 25.7)	0.368	−0.9 (−3.1, 1.4)	0.431

Abbreviations: MRMT = Money Road Map Test, TMT-B = Trail-Making Part B, BVRT-C = Benton Visual Retention Test Form C, CI = Confidence Interval, *p* = p-value

Table 3:

SCC function and cognitive performance

	MRMT Time		MRMT Errors		TMT-B Time		BVRT-C Error Score	
	β (95% CI)	***p***	**β (95% CI)**	***p***	**β (95% CI)**	***p***	**β (95% CI)**	***p***
SCC function								
Bilaterally present	Reference		Reference		Reference		Reference	
Unilateral impairment	−20.2 (−69.7, 29.3)	0.413	2.0 (−0.3, 4.3)	0.084	−13.5 (−34.8, 7.8)	0.208	1.0 (−1.9, 3.8)	0.503
Bilateral impairment	26.8 (−138.2, 191.9)	0.743	4.5 (−3.2, 12.1)	0.243	−17.0 (−88.0, 54.1)	0.630	**9.8 (0.2, 19.4)**	**0.045**
Age	1.9 (−0.005, 3.7)	0.051	0.0004 (−0.09, 0.09)	0.992	**1.6 (0.7, 2.4)**	**0.001**	0.1 (−0.02, 0.2)	0.114
Sex								
Male	Reference		Reference		Reference		Reference	
Female	**76.7 (30.0, 123.3)**	**0.002**	**2.4 (0.2, 4.5)**	**0.033**	**38.6 (18.0, 59.2)**	**0.001**	1.8 (−1.0, 4.5)	0.205
Education								
Less than college	Reference		Reference		Reference		Reference	
College	−23.4 (−83.1, 36.4)	0.432	**−3.2 (−5.9, −0.4)**	**0.026**	−11.2 (−37.0, 14.5)	0.381	**−4.9 (−8.3, −1.4)**	**0.008**
Greater than college	−39.2 (−89.6, 11.3)	0.124	**−2.9 (−5.3, −0.6)**	**0.015**	−9.7 (−31.9, 12.4)	0.378	**−3.5 (−6.5, −0.5)**	**0.024**
History of hearing loss	24.7 (−19.6, 69.0)	0.265	0.4 (−1.7, 2.4)	0.728	14.5 (−4.7, 33.7)	0.133	0.4 (−2.2, 3.0)	0.738

Abbreviations: MRMT = Money Road Map Test, TMT-B = Trail-Making Part B, BVRT-C = Benton Visual Retention Test Form C, CI = Confidence Interval, *p* = p-value

Table 4

Combined saccule and SCC function with cognitive performance

	MRMT Time		MRMT Errors		TMT-B Time		BVRT-C Error Score	
	β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*
Combined saccule and SCC function								
Normal	Reference		Reference		Reference		Reference	
Abnormal	−26.7 (−172.5, 119.0)	0.691	−0.06 (−6.2, 6.0)	0.982	−4.4 (−42.9, 34.1)	0.801	5.0 (−2.9, 12.8)	0.186
Age	2.8 (−0.7, 6.3)	0.108	0.09 (−0.06, 0.2)	0.208	**1.1 (0.1, 2.1)**	**0.032**	0.05 (−0.2, 0.3)	0.596
Sex								
Male	Reference		Reference		Reference		Reference	
Female	**98.6 (6.6, 190.6)**	**0.038**	2.6 (−1.2, 6.5)	0.163	**15.8 (−10.9, 42.4)**	**0.214**	2.7 (−2.7, 8.1)	0.292
Education								
Less than college	Reference		Reference		Reference		Reference	
College	23.3 (−75.1, 121.8)	0.609	−0.3 (−4.4, 3.9)	0.890	−9.9 (−35.9, 16.2)	0.415	−0.4 (−5.6, 4.9)	0.884
Greater than college	−31.4 (−139.8, 76.9)	0.532	−1.7 (−6.2, 2.9)	0.431	20.6 (−10.1, 51.3)	0.163	−1.1 (−7.3, 5.2)	0.709
History of hearing loss	2.3 (−83.2, 87.8)	0.953	−0.1 (−3.7, 3.5)	0.953	4.7 (−18.0, 27.5)	0.648	−0.5 (−5.2, 4.1)	0.797

Abbreviations: MRMT = Money Road Map Test, TMT-B = Trail-Making Part B, BVRT-C = Benton Visual Retention Test Form C, CI = Confidence Interval, *p* = p-value

Table 5

Case-control analysis using standardized values for cognitive performance

	Case: TMT-B time			Case: BVRT-C error score	
	OR (95% CI)	***p***		**OR (95% CI)**	***p***
Cognitive assessment			Cognitive assessment		
TMT-B time	**2.42 (1.44, 4.07)**	**0.001**	BVRT-C error score	0.84 (0.57, 1.24)	0.375
Age	0.80 (0.59, 1.10)	0.168	Age	0.88 (0.66, 1.16)	0.353

Abbreviations: TMT-B = Trail-Making Part B, BVRT-C = Benton Visual Retention Test Form C, CI = Confidence Interval, *p* = p-value