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RESEARCH ARTICLE

Sensory impairment and beta-amyloid deposition in the Baltimore longitudinal study of aging

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Abstract

Introduction: Beta-amyloid (Aβ) plaque deposition is a biomarker of preclinical Alzheimer's disease (AD). Impairments in sensory function are associated with cognitive decline. We sought to investigate the relationship between PET-indicated Aβ deposition and sensory impairment.

Methods: Using data from 174 participants ≥55 years in the Baltimore Longitudinal Study of Aging, we analyzed associations between sensory impairments and Aβ deposition measured by PET and Pittsburgh Compound B (PiB) mean cortical distribution volume ratio (cDVR).

Results: The combinations of hearing and proprioceptive impairment and hearing, vision, and proprioceptive impairment, were positively correlated with cDVR ($\beta = 0.087$ and $p = 0.036$, $\beta = 0.110$ and $p = 0.018$, respectively). In stratified analyses of PiB+ participants, combinations of two, three, and four sensory impairments (all involving proprioception) were associated with higher cDVR.

Discussion: Our findings suggest a relationship between multi-sensory impairment (notably proprioceptive impairment) and Aβ deposition, which could reflect sensory impairment as an indicator or potentially a risk factor for Aβ deposition.

KEYWORDS
Alzheimer disease, beta-amyloid, hearing impairment, positron-emission tomography, proprioceptive disorders, vestibular deficiency, visual impairment

1 | BACKGROUND

Alzheimer's disease (AD) causes memory disorders, impaired reasoning, and behavioral changes.[1] A defining pathological feature of AD is beta-amyloid (Aβ) deposition, which can be measured through positron emission tomography (PET)[2] and is associated with cognitive decline and AD progression.[3–8] Aβ is of heightened importance for identifying preclinical AD, a period during which interventions/treatments are likely to be most effective before other downstream pathological sequelae emerge.[2,9,10]

The impaired sensory function has been associated with cognitive decline and dementia.[11–14] While both Aβ deposition and sensory

impairment are linked to the risk of AD,[12,13] the relationship between them is unclear. It is possible that they occur independently; alternatively, the sensory impairment may be linked to Aβ deposition as an indicator or potentially as a causal factor.

This study aims to characterize the relationship between specific sensory impairments, individually and in combination, and PET-indicated Aβ deposition. Given that multisensory cortical regions (e.g., the precuneus) are among the earliest sites of amyloid deposition,[15] we hypothesize that among cognitively normal older adults, multiple sensory impairments are associated with Aβ deposition.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using traditional (e.g., PubMed) sources and meeting abstracts and presentations. Previous studies have established that hearing, vestibular, and olfactory impairment are associated with cognitive impairment and the progression of Alzheimer's disease (AD). However, they have not established a clear relationship between sensory impairment and beta-amyloid (Aβ) burden. These relevant citations are appropriately cited.
2. **Interpretation**: Our findings suggest a relationship between sensory impairment (notably proprioceptive impairment) and Aβ deposition, although only when cortical Aβ deposition is viewed as a continuous measure.
3. **Future Directions**: Future studies can be conducted to determine the temporality of the observed relationships between sensory impairment and Aβ deposition, to elucidate whether sensory impairment and Aβ deposition independently contribute to the risk of cognitive decline and mild cognitive impairment/AD (MCI/AD), and whether there are interactions between sensory impairment and Aβ deposition (effect modification/mediation) in predicting risk of cognitive decline and MCI/AD.

2 | METHODS

2.1 | Study design and participants

Cognitively normal participants were selected from the Baltimore Longitudinal Study of Aging (BLSA). Healthy adults aged ≥20 years are eligible to enroll in the BLSA. Participants undergo a comprehensive assessment of health and functional status and are followed longitudinally. Amyloid PET scans were added in 2005 to assess BLSA participants aged 55 years and older.[16]

The most recent BLSA visit was used for the analysis of multisensory function in relation to brain amyloid. A total of 174 participants had data collected on at least one of four sensory systems (vision, hearing, proprioception, and vestibular) as well as PiB data at the most recent visit or a prior visit. Participants provided written informed consent, the BLSA study protocol was approved by the Institutional Review Board of the National Institutes of Health Intramural Research Program, and the PET studies were approved by the Johns Hopkins Medicine Institutional Review Board.

2.2 | Image acquisition and processing

Dynamic 11C-Pittsburgh compound B positron emission tomography (PiB-PET) scans were obtained using a GE Advance or a Siemens HRRT scanner in 3D mode directly after 15 mCi of [11C]-PiB was injected intravenously.[17] PiB binds to amyloid fibrils formed by Aβ proteins and thus can be used to noninvasively image amyloid deposition. Participants wore a thermoplastic head mask to decrease motion. PET scans were acquired according to the following protocol for frame duration: 4 × 0.25, 8 × 0.5, 9 × 1, 2 × 3, 10 × 5 min (70 min total, 33 frames). Magnetization prepared rapid gradient echo (MPRAGE) images were obtained using a 3T scanner [Philips Achieva, repetition time (TR) = 6.8 milliseconds (ms), echo time (TE) = 3.2 ms, flip angle 8°, image matrix = 256 × 256, 170 slices, pixel size = 1 × 1 mm, slice thickness = 1.2 mm]. For each participant, a concurrent or closest-in-time MRI scan was matched with each PiB-PET image. Anatomical labels were obtained for each MRI scan using Multi-Atlas region Segmentation using Ensembles of registration algorithms and parameters (MUSE).[18]

Each dynamic PET scan was aligned to the mean of the first 2 min of the scan to adjust for movement.[19] The average of the first 20 min of PET scans was rigidly registered onto the corresponding MRI, and the MUSE label image was transformed from MRI to PET space. Distribution volume ratio (DVR) images were computed in PET native space using a simplified reference tissue model with the cerebellar gray matter as the reference region.[20] Mean cortical β-amyloid burden was calculated as the average of the DVR values in cingulate, frontal, parietal (including precuneus), lateral temporal, and lateral occipital cortical regions, excluding the sensorimotor strip. Image processing and harmonization of DVRs between scanners are detailed in previous publications.[21,22]

2.3 | Pittsburgh compound B (PiB) status

PiB-PET imaging has been dichotomized into positive and negative status using a mean cortical distribution volume ratio (cDVR).[17,23–25] PiB+ versus PiB- status was determined using a two-class Gaussian mixture model fitted to the baseline mean cDVR data. The cDVR corresponding to the intersection of the probability density functions of the two classes (1.062 in this study) was used to categorize subjects into PiB+ and PiB−.[25,26] Villeneuve et al. validated PiB thresholds derived using various methods against post-mortem amyloid burden; they reported 1.06 as the optimal cDVR threshold compared to higher, more stringent values being used in literature, as it results in higher sensitivity (81%) and preserves specificity (95.8%).[25]

2.4 | Vision testing

The vision was assessed through visual acuity, visual fields, contrast sensitivity, and stereo acuity. The Early Treatment Diabetic Retinopathy Study (ETDRS) chart was utilized by a trained examiner to conduct visual acuity testing. Participants were seated 8 feet from the chart and a calibrated light at a constant level of 85 cd/m^2 (candela per square meter) highlighted the row participants were prompted to read. Presenting acuity in the better-seeing eye was calculated by summing the number of letters the participant could read with a score of 0.2 log units per letter. The participant was given credit for lines where they were able to read correctly at least three out of five letters. Standard visual acuity measurements of 20/10, 20/20, 20/40, and 20/200 correspond to LogMAR scores of −0.3, 0, 0.3, and 1.0.[27,28] For the sensory impairment analyses involving dichotomous measures, visual impairment was defined as any corrected LogMAR score greater than or equal to 0.3, corresponding to a 20/40 visual acuity.[29] Visual fields were measured using a Humphrey 81-point single intensity (24 dB) full field (60°) screen (Humphrey Field Analyzer, Carl Zeiss Meditec, Dublin, CA) and assessed based on the number of points missed out of a total of 96 points on the monocular visual field test. The binocular visual field was then estimated from the monocular measurement. Visual field was considered impaired if this score was >1 standard deviation away from the population mean. Contrast sensitivity was measured using a Pelli–Roboson chart, which assessed the participants' ability to discern between shades.[30] This test was administered with participants wearing habitual corrective lenses and the total number of letters read correctly was recorded from each chart. The score was calculated as logContrast units, which indicates the lowest contrast threshold discerned and ranges from 0 to 2.25 logContrast units where higher values indicate better contrast sensitivity. Contrast sensitivity was considered impaired if the score was <1.55 log contrast units.[30,31] Finally, stereo acuity was measured using the Randot stereo vision test, which assessed the minimum depth differential that the participant could see. Participants were presented with stereo images of decreasing depth differentials; stereo acuity was considered impaired if the value was >80 s of arc (arcsec).[31] Vision function was defined as impaired if any of these four factors of vision were impaired.

2.5 | Audiometric testing

Audiometric testing was performed in a sound attenuating booth using an Interacoustics AD629 audiometer with ER3A insert earphones. Audiometric thresholds were obtained at frequencies 500–8000 Hz. Pure-tone averages (PTA) were calculated as the mean thresholds in decibels hearing level (dB HL) at the frequencies of 0.5, 1, 2, 4, and 8 KHz in both ears.[32] A participant's hearing threshold was calculated by averaging the mean thresholds across all frequencies in both ears, and those with a threshold >25 dB in the better-hearing ear were considered to have impaired hearing function.

2.6 | Proprioceptive testing

Proprioception was quantified by measuring the threshold for perception of passive movement (TPPM), a reliable and sensitive measure of ankle proprioception.[33] Trained examiners used customized equipment to measure TPPM.[34] The equipment consisted of two pedals: the right pedal controlled by a motor (BALDOR, Ft. Smith, AZ, USA) and the left pedal moved freely by the participant. Both pedals measured angle deviation from a baseline using potentiometers. For testing, participants were blindfolded and had their bare or stocking feet placed on the pedals, which were set at a neutral ankle angle of 100° that would serve as the baseline for testing. The right pedal was moved by a servomotor at the angular velocity of 0.3°/s. Participants were instructed to press a switch when they perceived movement and the direction of the movement (up/down). The corresponding ankle angular rotation was recorded in degrees. A total of four trials were performed in the sequence of plantarflexion, dorsiflexion, dorsiflexion, and plantarflexion. The average of the best plantarflexion trial and best dorsiflexion trial was used as the TPPM. Proprioception was considered impaired if the TPPM was >2.2°.

2.7 | Vestibular function testing

Cervical vestibular-evoked myogenic potential (cVEMP) testing was used to assess vestibular function, specifically, the function of the saccular end-organ of the vestibular system.[35–37] Participants were asked to lie at a 30° angle from the horizontal on the testing chair and electrodes were placed at the upper sternal area and both sternocleidomastoid (SCM) muscles. A non-inverting electrode was placed at the midpoint of the SCM muscle, an inverting electrode was placed at the sternoclavicular joint, and a ground electrode was placed at the upper sternum. Participants were asked to lift their heads to provide a sample of background SCM activity. Audible stimuli were then delivered through Audiocups noise-canceling headphones from Amplivox (Eden Prairie, MN, USA). The stimulus was a 500 Hz, 125 dB sound pressure level (SPL) tone burst, with a repetition rate of 5 Hz, a 1 ms rise/fall time, and a 2 ms plateau. For a cVEMP tracing to be valid, the background electromyography (EMG) signal was required to reach at least 30 mV over 10 ms prior to the applied stimulus.

The cVEMP waveform consisted of a positive initial deflection followed by a negative deflection. The peak-to-peak amplitude was the voltage difference between the peak of the first positive deflection and the peak of the following negative deflection. The peak-to-peak cVEMP amplitude was divided by the background EMG signal to obtain the "corrected" peak-to-peak amplitude, which accounted for background level of muscle activity. Subjects with EMG recordings that lacked the initial characteristic positive deflection of the waveform were considered to have bilaterally absent cVEMP response and vestibular impairment for the purposes of this study.

Vestibular function was further assessed via semicircular canal function. This was measured as the ratio of eye velocity to head

TABLE 1 Sociodemographics and PiB-indicated Aβ status.

Characteristics-Value	All N = 174	PiB-Indicated Aβ Status (n = 174) Positive n = 51 (29.3%)	Negative n = 123 (70.7%)	*p*-Value
Age (years)	78.7 ± 9.2	81.5 ± 8.7	77.6 ± 9.2	0.011
Female	92 (52.9)	24 (47.1)	68 (55.3)	0.323
White	132 (75.9)	40 (78.4)	92 (74.8)	0.610
Education years	18.1 ± 2.5	17.8 ± 2.4	18.2 ± 2.5	0.363
BMI	27.7 ± 5.7	26.6 ± 4.0	28.2 ± 6.2	0.086

Note: Chi-squared tests for female and white; independent t-tests for age, BMI, and education years. PiB positivity is demarcated by the threshold of 1.062.
Abbreviations: Aβ, beta-amyloid; BMI, body mass index; PiB, Pittsburgh Compound B.

velocity—a quantity referred to as vestibulo-ocular reflex (VOR) gain. Vestibular function was considered impaired if the mean VOR gain <0.7.

2.8 | Statistical analysis

Sensory system data and Aβ data from the most recent visit were analyzed. For those who were missing data on sensory function at the most recent visit, impaired status was imputed if the participant was ever categorized as sensory-impaired in previous visits based on the assumption that older adults who have developed sensory impairment are unlikely to return to an unimpaired state, given that age-related losses typically reflect sensory end-organ degeneration.[38,39] Missing values from the most recent visit were retained if the participant had no prior history of sensory impairment or had missing values in all previous visits.

Demographic characteristics were summarized across PiB status (positive vs. negative) using independent t-tests for continuous variables and chi-square tests for dichotomous variables. The proportions of participants with individual sensory impairments as well as all possible combinations of ≥2, ≥3, or ≥4 sensory impairments together were compared across PiB status using chi-square tests.

Log-binomial regression models were used to estimate the prevalence ratios (PRs) of PiB positivity by individual and combined sensory impairments. We also considered PiB level as a continuous outcome measure in the form of mean cDVR. Linear regression modeling was used to examine the association between sensory impairment and mean cDVR. Linear regression models were also constructed in PiB+ and PiB− participants separately. Further, to explore whether the associations between sensory impairment and quantitative PiB deposition are modified by PiB status, linear regression models with interaction terms were developed, with sensory impairment and PiB status as independent variables and mean cDVR as the dependent variable. Multivariable models were adjusted for age, sex, race, and years of education.

All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC). The significance level α was set as 0.05.

3 | RESULTS

3.1 | Demographics of the whole cohort

The cohort consisted of 174 participants with PiB-PET scans, of whom 160 had audiometric testing results, 158 had visual acuity testing results, 106 had vestibular function testing results, and 132 had proprioceptive testing results (Table 1). Seventy-nine participants had complete sensory and PiB-PET data. Ninety-two (52.9%) participants were female and 82 (47.1%) participants were male. The average age of participants was 78.7 (SD = 9.2) years. One hundred thirty-two (75.9%) were white participants and 42 (24.1%) were non-white participants. Participants had 18.1 (SD = 2.5) years of education on average.

3.2 | Demographics stratified by PiB status

Of the 174 participants, 51 (29.3%) were classified as PiB+ while 123 (70.7%) were classified as PiB− by their mean cDVR (Table 1). The average age of PiB+ participants (81.5 ± 8.7 years) and PiB− participants (77.6 ± 9.2 years) differed significantly, with PiB+ participants being older (p = 0.011). There were no significant differences in sex (p = 0.323), racial composition (p = 0.610), or years of education (p = 0.363) between the PiB+ versus PiB− groups.

3.3 | Sensory impairment of the whole cohort

Of the 160 participants for whom audiometric testing results were available, 111 (69.4%) had hearing impairment; 100 (63.3%) of the 158 participants for whom vision testing results were available had vision impairment; 52 (49.1%) of the 106 participants for whom vestibular function testing results were available had vestibular impairment; and 45 (34.1%) of the 132 participants for whom proprioceptive testing results were available had proprioceptive impairment (Table 2). Sensory impairments were analyzed individually and also in groups of two, three, and four impairments.

TABLE 2 Sensory impairment and PiB-indicated Aβ status.

Sensory impairment	All N = 174	PiB-Indicated Aβ status (n = 174) Positive n = 51 (29.3%)	Negative n = 123 (70.7%)	*p*-value*
One or more sensory impairment				
Hearing	111 (69.4)/160	34 (73.9)	77 (67.5)	0.429
Vision	100 (63.3)/158	36 (75.0)	64 (58.2)	0.044
Vestibular function	52 (49.1)/106	13 (44.8)	39 (50.7)	0.593
Proprioception	45 (34.1)/132	16 (39.0)	29 (31.9)	0.422
Two or more sensory impairments				
H + VS	76 (52.4)/145	27 (61.4)	49 (48.5)	0.154
H + VES	40 (39.6)/101	12 (41.4)	28 (38.9)	0.817
H + P	33 (26.8)/123	14 (36.8)	19 (22.4)	0.094
VS + VES	37 (38.1)/97	10 (34.5)	27 (39.7)	0.628
VS + P	33 (28.0)/118	13 (32.5)	20 (25.6)	0.432
VES + P	20 (21.5)/93	8 (28.6)	12 (18.5)	0.276
Three or more sensory impairments				
H + VS + VES	32 (34.8)/92	10 (34.5)	22 (34.9)	0.967
H + VS + P	27 (24.6)/110	12 (31.6)	15 (20.8)	0.213
H + VES + P	18 (20.5)/88	8 (28.6)	10 (16.7)	0.197
VS + VES + P	17 (20.2)/84	6 (21.4)	11 (19.6)	0.848
Four sensory impairments				
H + VS + VES + P	15 (19.0)/79	6 (21.4)	9 (17.7)	0.682
≥ 2 sensory impairments	96 (55.2)	30 (58.8)	66 (53.7)	0.533
≥ 3 sensory impairments	49 (28.2)	18 (35.3)	31 (25.2)	0.178
No. of sensory impairments				0.716
0	26 (14.9)	6 (11.8)	20 (16.3)	
1	52 (29.9)	15 (29.4)	37 (30.1)	
≥2	96 (55.2)	30 (58.8)	66 (53.7)	

Abbreviations: Aβ, beta-amyloid; H, hearing; P, proprioception; PiB, Pittsburgh Compound B; VS, vision; VES, vestibular.
*Fisher's exact test.

3.4 | Unadjusted analyses of sensory impairment and PiB status

There was no difference in the proportion of participants with impaired hearing, vestibular function, or proprioception between the PiB+ and PiB− groups ($p = 0.429$, $p = 0.593$, and $p = 0.422$, respectively) (Table 2). There was, however, a higher proportion of vision impaired participants in the PiB+ group than in the PiB− group ($p = 0.044$); this difference in proportion was largely driven by the higher proportion of participants with impaired visual field and stereo acuity in the PiB+ group. There were no differences between PiB+ and PiB− participants among the pairings of two or more sensory impairments. There were similarly no differences in the proportions of participants with combinations of three or more sensory impairments, or all four impairments, between the PiB+ and PiB− groups.

3.5 | Adjusted analyses of sensory impairment and PiB status

Log-binomial regression models, both unadjusted and adjusted, were utilized to estimate prevalence ratios (PRs) of PiB positivity by sensory impairments; the resulting PRs are presented in Table 3. For the unadjusted log-binomial models, no significant PRs were found. However, there was a non-significant trend for participants with vision impairment to be more likely to be PiB positive than those without vision impairment (PR = 1.74, 95% confidence interval [CI]: 0.99-3.07, $p = 0.056$). There were also no significant associations between any combinations of sensory impairments and PiB status in the unadjusted models. The results for models adjusted for age, sex, race, and years of education were similar: no statistically significant PRs were found.

TABLE 3 Prevalence ratios of PiB-indicated Aβ positivity by sensory impairment.

	Model 1 (n = 174)			Model 2 (n = 174)		
	PR	95% CI	*p*-Value	PR	95% CI	*p*-Value
One or more sensory impairment						
Hearing	1.25	0.71-2.20	0.438	0.85	0.44-1.66	0.640
Vision	1.74	0.99-3.07	0.056	1.45	0.77-2.76	0.251
Vestibular function	0.84	0.45-1.58	0.594	0.64	0.33-1.24	0.184
Proprioception	1.24	0.74-2.07	0.417	1.00	0.58-1.72	0.996
Two or more sensory impairments						
H + VS	1.44	0.86-2.41	0.161	1.12	0.61-2.05	0.720
H + VES	1.08	0.58-2.01	0.816	0.83	0.40-1.72	0.619
H + P	1.59	0.94-2.69	0.083	1.22	0.67-2.25	0.516
VS + VES	0.85	0.45-1.63	0.631	0.74	0.36-1.50	0.402
VS + P	1.24	0.73-2.10	0.422	1.05	0.59-1.87	0.859
VES + P	1.46	0.76-2.81	0.257	1.29	0.59-2.80	0.521
Three or more sensory impairments						
H + VS + VES	0.99	0.52-1.86	0.967	0.88	0.44-1.77	0.719
H + VS + P	1.42	0.84-2.41	0.195	1.20	0.66-2.16	0.556
H + VES + P	1.56	0.82-2.94	0.173	1.40	0.65-3.03	0.389
VS + VES + P	1.07	0.52-2.23	0.846	1.10	0.47-2.55	0.824
Four sensory impairments						
H + VS + VES + P	1.16	0.57-2.36	0.674	1.22	0.55-2.69	0.629
No. of sensory impairments (categorical)						
0	Ref			Ref		
1	1.25	0.55-2.84	0.594	0.99	0.45-2.20	0.983
2 or more	1.35	0.63-2.90	0.435	0.76	0.33-1.73	0.509
≥2 sensory impairments	1.16	0.72-1.86	0.535	0.76	0.44-1.30	0.322
≥3 sensory impairments	1.39	0.87-2.23	0.168	1.04	0.62-1.73	0.889

Note: Log-binomial regression model 1: unadjusted model; model 2: adjusted for age, sex, race, and years of education.
Abbreviations: Aβ, beta-amyloid; CI, confidence interval; H, hearing; P, proprioception; PiB, Pittsburgh Compound B; PR, prevalence ratio VS, vision; VES, vestibular.

3.6 | Association between sensory impairment and mean cDVR

Linear regression models were constructed to evaluate the association between sensory impairment status as the independent variable of interest and mean cDVR of PiB as the outcome of interest (Table 4). In the unadjusted models, vision impairment and proprioceptive impairment were found to be positively correlated with mean cDVR ($\beta = 0.082$ and $p = 0.004$, $\beta = 0.068$ and $p = 0.035$, respectively). Hearing or vestibular impairments alone were not associated with mean cDVR.

Various combinations of two and three sensory impairments were significantly associated with mean cDVR (Table 4). The presence of all four sensory impairments in an individual was positively associated with mean cDVR as well ($\beta = 0.108$ and $p = 0.019$). Overall, when the number of sensory impairments was considered as a continuous variable, the number of sensory impairments was positively associated with mean cDVR ($\beta = 0.023$ and $p = 0.038$). In the models adjusted for age, sex, race, and education, many associations lost significance. The only significant associations with mean cDVR resulted from the pairing of hearing + proprioceptive impairments and the grouping of hearing + vision + proprioceptive impairments, with the presence of these combinations of impairments being positively associated with mean cDVR.

3.7 | Association between sensory impairment and mean cDVR by PiB status

As a sensitivity analysis, adjusted linear regression models between sensory impairment and mean cDVR stratified by PiB status were evaluated, to determine whether the relationship between sensory impairment and mean cDVR differs by PiB status. We considered both stratified analyses, and also tested interaction terms between sensory

TABLE 4 Linear regression models for sensory impairment and PiB mean cortical DVR.

	Model 1 (n = 174)			Model 2 (n = 174)		
	β	SE	*p*-Value	*β*	SE	*p*-Value
One or more sensory impairment						
Hearing	0.020	0.029	0.500	−0.030	0.033	0.374
Vision	0.082	0.028	0.004	0.054	0.034	0.109
Vestibular function	0.026	0.030	0.387	−0.017	0.034	0.617
Proprioception	0.068	0.032	0.035	0.035	0.036	0.333
Two or more sensory impairments						
H + VS	0.064	0.028	0.024	0.027	0.036	0.456
H + VES	0.049	0.032	0.129	0.002	0.039	0.962
H + P	0.114	0.034	0.001	0.087	0.041	0.036
VS + VES	0.044	0.033	0.192	0.009	0.039	0.821
VS + P	0.093	0.036	0.011	0.064	0.041	0.127
VES + P	0.095	0.038	0.014	0.066	0.044	0.141
Three or more sensory impairments						
H + VS + VES	0.059	0.035	0.096	0.023	0.044	0.594
H + VS + P	0.128	0.038	0.001	0.110	0.046	0.018
H + VES + P	0.108	0.040	0.008	0.080	0.047	0.093
VS + VES + P	0.091	0.042	0.033	0.073	0.050	0.146
Four sensory impairments						
H + VS + VES + P	0.108	0.045	0.019	0.091	0.053	0.091
No. of sensory impairments (continuous)	0.023	0.011	0.038	0.0005	0.014	0.969
No. of sensory impairments (categorical)						
0	Ref			Ref		
1	0.004	0.042	0.922	−0.030	0.042	0.479
2 or more	0.029	0.039	0.454	−0.052	0.045	0.247
≥2 sensory impairments	0.026	0.026	0.324	−0.029	0.031	0.349
≥3 sensory impairments	0.075	0.029	0.010	0.035	0.033	0.283

Note: Linear regression model 1: unadjusted model; model 2: adjusted for age, sex, race, and years of education.
Abbreviations: DVR, distribution volume ratio; H, hearing; P, proprioception; PiB, Pittsburgh Compound B; SE, standard error; VES, vestibular; VS, vision.

impairment and PiB status (Table 5). We noted in the stratified analysis that amongst PiB+ participants, various combinations of sensory impairments all involving proprioception were significantly associated with higher mean cDVR, and the magnitude of the beta-coefficients increased with the number of sensory impairments. Notably, a similar finding was observed in PiB- participants, although the magnitudes of the beta-coefficients were lower. Additionally, we observed that most interaction terms for one (with the exception of hearing), two, three, and four sensory impairments were significant, such that the magnitude of the association between sensory impairment and mean cDVR differed by PiB status.

4 | DISCUSSION

Taken together, the results from the multiple analyses conducted suggest at best a weak overall relationship between multiple sensory impairments and Aβ deposition, that approaches a meaningful magnitude among PiB+ adults. Importantly, proprioceptive impairment appears to drive the relationship between multiple sensory impairment and cortical Aβ deposition. As proprioception is not widely assessed in research or clinical settings and may be related to the accumulation of Aβ pathology, increased attention to the evaluation of proprioception appears warranted.

Various mechanisms may explain the association between sensory impairment and Aβ deposition, such as the early occurrence of Aβ deposition in the multi-sensory precuneus.[2,3] The precuneus includes proprioceptive, general sensory-motor, cognitive, and vision-related areas.[40] It is possible that early Aβ plaques in the precuneus may contribute to both sensory and cognitive impairment. Moreover, there may be overlap between the cortical centers that receive proprioceptive input (precuneus and parietal lobe) and areas of early Aβ deposition, given the consistent relationships observed between Aβ deposition and proprioceptive

TABLE 5 Linear regressions stratified by PiB-indicated Aβ status and corresponding interaction terms* for sensory impairment and mean cDVR.

	PiB-Indicated Aβ positive			PiB-Indicated Aβ negative			Interaction Term with PiB		
	β	SE	p-Value	β	SE	p-Value	β	SE	p-Value
One or more sensory impairment									
Hearing	−0.067	0.066	0.317	0.005	0.006	0.449	−0.001	0.038	0.977
Vision	0.114	0.078	0.154	0.0002	0.006	0.977	0.150	0.038	<0.001
Vestibular function	0.050	0.086	0.569	−0.004	0.023	0.855	0.100	0.041	0.016
Proprioception	0.093	0.069	0.184	0.013	0.006	0.053	0.111	0.039	0.005
Two or more sensory impairments									
H + VS	0.045	0.079	0.575	0.005	0.006	0.401	0.102	0.037	0.007
H + VES	0.095	0.095	0.329	0.012	0.008	0.131	0.126	0.042	0.004
H + P	0.140	0.074	0.069	0.026	0.007	<0.001	0.138	0.041	0.001
VS + VES	0.179	0.095	0.074	0.013	0.008	0.103	0.176	0.042	<0.001
VS + P	0.144	0.066	0.035	0.012	0.008	0.145	0.169	0.042	<0.001
VES + P	0.112	0.085	0.199	0.028	0.010	0.004	0.124	0.049	0.013
Three or more sensory impairments									
H + VS + VES	0.179	0.095	0.074	0.015	0.009	0.096	0.176	0.044	<0.001
H + VS + P	0.200	0.074	0.010	0.023	0.009	0.010	0.185	0.043	<0.001
H + VES + P	0.112	0.085	0.199	0.030	0.010	0.005	0.123	0.051	0.019
VS + VES + P	0.202	0.090	0.035	0.032	0.011	0.004	0.203	0.052	<0.001
Four sensory impairments									
H + VS + VES + P	0.202	0.090	0.035	0.034	0.011	0.005	0.201	0.055	<0.001

Note. Adjusted for age, sex, race, and years of education.
Abbreviations: Aβ, beta-amyloid; cDVR, cortical distribution volume ratio; H, hearing; P, proprioception; PiB, Pittsburgh Compound B; SE, standard error; VES, vestibular; VS, vision.
*Interaction terms derived from separate, unstratified linear regression models.

impairment, independently and in combination with other sensory impairments.

Sensory impairment and Aβ deposition may also be causally related, whereby peripheral sensory impairment causes central Aβ deposition through sensory deafferentation and resulting cortical neuronal dysfunction. In cognitively normal older adults, depletion of cortical cholinergic markers due to deafferentation has been associated with increased Aβ deposition.[41,42] Sensory impairment resulting from deafferentation may be causally linked to Aβ plaque deposition. Finally, there may be a common cause underlying both sensory impairment and amyloid deposition, such as metabolic exposure, infectious exposure and inflammation, toxic exposure, or ischemic exposure.

Previous studies of hearing, vestibular, and olfactory impairment have not established a clear relationship between sensory impairment and Aβ burden.[11–13] A notable difference between prior literature and the present study is that prior studies only considered Aβ deposition as a dichotomous variable of positive or negative status. Our results suggest a relationship between sensory impairment and Aβ deposition, although only when cortical Aβ deposition is viewed as a continuous measure, and of greater magnitude in PiB+. There are several possible explanations for the different results we observed when considering PiB status as a dichotomous versus continuous measure. First, although dichotomizing Aβ deposition allows for simplicity in interpretation and statistical analysis, this results in a loss of information and statistical power. Second, dichotomizing this continuous measure ignores the level of variation within each group, and participants close to the AB/PiB positivity threshold (i.e., DVR of 1.062) may be characterized as being either "positive" or "negative" despite close proximity to the opposite status.[43] Further, most information regarding variation in Aβ deposition in relation to sensory impairment is found in the PiB+ group in part due to the fact that a large proportion of variation in the PiB- group reflects measurement error.[25]

There are several limitations in this study. The cross-sectional measurement of sensory function and Aβ deposition preclude making causal inferences. Moreover, the prevalence of sensory deficits is greater than the prevalence of PiB positivity, making a strong causal relationship less likely. However, to our knowledge, this is the first study examining multiple sensory systems in relation to PiB-indicated Aβ deposition, as prior studies have considered only single sensory systems.[11–13] A recent study showed that dual impairment in both hearing and vision significantly increased the risk for AD[44]; thus, consideration of multiple sensory systems in relation to Aβ deposition is particularly important for a more complete understanding of AD onset.[44] Additionally, the different senses were ascertained on slightly

different schedules resulting in visit-specific missingness. Since sensory impairments generally remain the same or worsen, but do not improve, we feel confident that carrying forward sensory impairment status for missing observations was valid and preserved our already-limited study power. While this assumption may have exceptions (e.g., cataract surgery to improve vision), on a population level it is likely reasonable. Further, the participants in this study may not be representative of the general population, as suggested by their relatively high average number of years of education. As such, the study may have limited generalizability. Finally, for this introductory analysis, we conducted multivariate analyses with the goal of identifying any broad, consistent trends related to sensory function and beta-amyloid deposition, and as such did not adjust for multiple comparisons. Future studies could adjust for multiple combinations of sensory impairments in the analysis.

Multiple sensory impairment, notably involving proprioceptive impairment, holds potential as a pre-clinical indicator of Aβ progression, as well as MCI/AD risk given its relationship with Aβ deposition as a continuous measure in PiB+ participants. Future studies need to determine the temporality of the observed relationships between sensory impairment and Aβ deposition, to elucidate whether sensory impairment and Aβ deposition independently contribute to risk of cognitive decline and MCI/AD, and whether there are interactions between sensory impairment and Aβ deposition (effect modification/mediation) in predicting risk of cognitive decline and MCI/AD.

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CONFLICT OF INTEREST STATEMENT

The authors have no disclosures. Author disclosures are available in the supporting information.

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