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Original Research Articles

Vestibular Function is Associated with Prefrontal and Sensorimotor Cortical Gray Matter Volumes in a Cross-Sectional Study of Healthy, Older Adults

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Background

The vestibular system is associated with alterations in the structure and function of the central nervous system. Yet, whether age-related vestibular loss is related to volume loss in the cerebral cortical areas that have been reported to receive vestibular input remains unknown. In this cross-sectional study of 117 healthy, older adults from the Baltimore Longitudinal Study of Aging, we examine the relationships between age-related vestibular functions and the gray matter volumes of the prefrontal cortex and its subregions and of the sensorimotor cortex—regions known to process vestibular information.

Methods

T1-weighted MRI scans were automatically segmented using MRICloud. Log-linear multiple regression was used to investigate the relationships between average regional volume and vestibular function, adjusting for age, sex, and intracranial volume. Permutation testing was used for hypothesis testing, and bootstrapping was used to estimate confidence intervals.

Results

We found that age-related changes in vestibular end-organ function are associated with differentially altered gray matter volumes in the prefrontal and sensorimotor cortices, with many findings persisting when considering left (or right) side only. Concomitant with age-related, global brain atrophy, lower canal and utricular function were associated with additional volume atrophy of the prefrontal cortex and middle frontal gyrus, respectively. Lower saccular and utricular function were associated with the preservation of the volumes of the sensorimotor cortex and the pole of the superior frontal gyrus, respectively, against age-related, global brain atrophy. Canal and utricular function were not associated with the volumes of the sensorimotor cortex, and saccular function was not associated with the relative volumes of the prefrontal cortex.

Conclusion

Together, these findings of relative volume preservation or additional atrophy suggest that vestibular function may play a role in the resilience to or magnification of global age effects on cerebral cortical structure.

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KEY POINTS

- Age-related vestibular function is significantly associated with gray matter volumes in the prefrontal and sensorimotor cortices in adults.
- Lower canal function showed an association with additional atrophy of the prefrontal cortex in addition to age-related brain atrophy. Lower saccular function had an association with a protective effect against age-related atrophy on sensorimotor cortical volume. Lower utricular function showed an association with additional relative volume atrophy of the middle frontal gyrus and a protective effect on the relative volume of the pole of the superior frontal gyrus. Canal and utricular function were not associated with the relative volumes of the sensorimotor cortex, and saccular function was not associated with the relative volumes of the prefrontal cortex.
- Lower canal and utricular function may play an important role in magnifying age-related brain atrophy in the prefrontal cortex and in the middle frontal gyrus, respectively. An association between central sensitization to otolith inputs with age and lower utricular function may be related to structural adaptations observed as resilience to age-related atrophy in the pole of the superior frontal gyrus.

1. INTRODUCTION

The vestibular, or inner ear balance, system is comprised of five organs: three semi-circular canals which detect rotational accelerations of the head in three dimensions, and two otolith organs, the utricle and saccule, which detect linear head accelerations in three dimensions and the orientation of the head with respect to gravity.[1] Peripheral vestibular information is sent widely throughout the brain[2-6] and helps to maintain stable balance and gaze control during movement.[7] Notably, evidence is mounting that the vestibular system contributes to higher-order cognitive functions, such as visuospatial cognitive function,[1,8-11] attention, executive function, memory function,[8] self-motion perception,[12] and motor planning and execution.[13] Vestibular structure[14,15] and function[16-18] decline with normal aging, and vestibular loss is associated with cognitive declines in older adults.[8,19-22] Importantly, the age-related vestibular associations with self-motion perception, motor planning, and executive function imply the roles of the structure and function of the sensorimotor and prefrontal cortices, each of which receive vestibular information via multiple pathways.[2,4,6] However, the exact vestibular pathways and the age-related function of vestibular end-organ inputs to the somatosensory, motor, and prefrontal cortices are not well-defined in humans.

Brain imaging studies have revealed that vestibular stimulation, such as caloric, single-shock, galvanic, and electrical stimulations, activates the postcentral gyrus, precentral gyrus, and prefrontal cortex, among other regions.[4,23-30] Primate studies have shown the vestibular responses in the periarcuate cortex near the frontal eye fields.[2,31] Additionally, a recent study in rats has shown projections from the vestibular nuclei to the supplementary motor area.[32] Yet, clinical voxel-based morphometry studies have presented equivocal findings regarding the relationships between gray matter volumes in the somatosensory, motor, and prefrontal cortices and peripheral vestibular function. Some studies have indicated null or inconsistent associations.[33-39] However, despite these disparities, several studies have identified connections with the somatosensory,[33] motor,[38] and prefrontal cortices.[36,38] Additionally, of the neuroimaging studies demonstrating positive relationships between age-related, subclinical loss of vestibular end-organ functions and brain structure, none examined the sensorimotor and prefrontal cortices.[40-42] Because the somatosensory, motor, and frontal cortices are not the most commonly reported brain areas in vestibular neuroimaging studies yet are hypothesized to play a role in vestibular-modulated self-motion perception, motor planning, and executive function, we have chosen to focus on these regions. The overarching question that emerges from this body of work is: is age-related, subclinical vestibular end-organ function associated with the structure of the somatosensory, motor, and prefrontal cortices?

Considering the gaps and inconsistencies in the literature, the primary goal of this cross-sectional study is to determine the associations between age-related, subclinical vestibular end-organ function and gray matter volumes of the somatosensory, motor, and prefrontal cortices. Multiple log-linear regression adjusted for age, intracranial volume, and sex is used to investigate the relationships between saccular, utricular, and horizontal semi-circular canal functions and MRI-based volumes of 117 healthy, older participants aged 60 years and older from the Baltimore Longitudinal Study of Aging between 2013 and 2015. This cohort and its measurements were used in previous studies by our group[40,41] that explored distinct research questions involving a different cognitive network. We hypothesized that higher functioning in the better ear of the saccule, utricle, and horizontal semi-circular canal is related to significantly higher gray matter volumes in the regions of interest, providing new insights into the neuroanatomical connections and potential functional significance of the vestibular system in the human brain.

2. MATERIALS AND METHODS

2.1. DATA

The data is a subset from the Baltimore Longitudinal Study of Aging (BLSA)[43] involving 117 participants ⩾ 60 years old who had MRI brain scans and vestibular testing in the same visit between 2013 and 2015. All participants gave written informed consent, and none had any history of psychiatric disorders or were diagnosed with a vestibular, ophthalmological, microvascular, or neurodegenerative disease. Hearing loss was measured as the speech-frequency pure tone average of air-conduction thresholds at 0.5, 1, 2, and 4 kHz from the better ear and was included as a confounding variable in the supplemental analysis.

2.2. VESTIBULAR PHYSIOLOGIC TESTING

Vestibular function testing included measurement of saccular function using the cervical vestibular-evoked myogenic potential (cVEMP) test, of utricular function using the ocular VEMP (oVEMP) test, and of horizontal semicircular canal function using the video head-impulse test (vHIT). cVEMP and oVEMP signals were recorded using a commercial electromyographic system (software version 14.1, Carefusion Synergy, Dublin, OH)[44,45] and were amplified × 2500 and band-pass filtered for the 20-2000 Hz and 3-500 Hz frequency intervals, respectively. Electromyograms (EMG) were recorded by disposable, pre-gelled Ag/AgCl electrodes set with 40-inch safety lead wires from GN Otometrics (Schaumburg, IL).

2.2.1. CERVICAL VESTIBULAR-EVOKED MYOGENIC POTENTIAL (CVEMP)

The cVEMP test measures the function of the saccule (and inferior vestibular nerve), following published procedures.[44-47] Participants sat on a chair inclined at 30° above the horizontal plane. Trained examiners placed EMG electrodes bilaterally on the sternocleidomastoid and sternoclavicular junction. A ground electrode was positioned on the manubrium sterni. The examiners instructed participants to turn their heads to generate at least a 30 μV background response prior to delivering sound stimuli. Auditory stimuli of 500 Hz and 125 dB were administered in bursts of 100 stimuli monoaurally through headphones (VIASYS Healthcare, Madison, WI). cVEMPs were recorded as short-latency EMGs of the inhibitory response of the ipsilateral sternocleidomastoid muscle. Corrected cVEMP amplitudes were calculated by removing nuisance background EMG activity collected 10 ms prior to the onset of the auditory stimulus. The presence or absence of a cVEMP response, respectively indicating normal or impaired saccular function, was defined per established amplitude and latency thresholds.[44,45] The higher corrected cVEMP amplitude (unitless) from the left and right sides was used as a continuous measure of saccular function. A difference of 0.5 in corrected cVEMP was considered clinically relevant, in accordance with the literature.[44]

2.2.2. OCULAR VESTIBULAR-EVOKED MYOGENIC POTENTIAL (OVEMP)

The oVEMP test measures the function of the utricle (and superior vestibular nerve), following established procedures.[44-47] Participants sat on a chair inclined at 30° above the horizontal plane. Trained examiners placed a noninverting electrode ≈3 mm below the eye centered below the pupil and an inverting electrode 2 cm below the noninverting electrode. A ground electrode was placed on the manubrium sterni. Before stimulation, participants were instructed to perform multiple 20° vertical saccades to ensure that symmetric signals are recorded from both eyes. Participants were asked to maintain an up-gaze of 20° during oVEMP testing and recording. Vibration stimuli included head taps applied to the midline of the face at the hairline and ≈30% of the distance between the inion and nasion using a reflex hammer (Aesculap model ACO12C, Center Valley, PA). oVEMPs were recorded as short-latency EMGs of the excitation response of the contralateral external oblique muscle of the eye. The presence or absence of an oVEMP response, respectively indicating normal or impaired utricular function, was defined per established amplitude and latency thresholds.[44,45] The higher oVEMP amplitude (μV) from the left and right sides was used as a continuous measure of utricular function. A difference of 5 μV in oVEMP was considered clinically relevant, in accordance with the literature.[44]

2.2.3. VIDEO HEAD IMPULSE TEST (VHIT)

The vHIT measures the horizontal vestibular-ocular reflex (VOR),[46,48,49] and was performed using the EyeSeeCam system (Interacoustics, Eden Prarie, MN) in the same plane as the right and left horizontal semicircular canals.[49,50] To position the horizontal canals in the plane of stimulation, trained examiners tilted the participant's head downward 30° below the horizontal plane. Participants were asked to maintain their gaze on a wall target ≈1.5 m away. A trained examiner delivers rotations of 5-10° (≈150-250° per second) to the participant's head. The head impulses are performed at least 10 times parallel to the ground toward the right and left, chosen randomly for unpredictability. The EyeSeeCam system quantified eye and head velocity. VOR gain was calculated as the unitless ratio of the eye velocity to the head velocity. A normal VOR gain is equal to 1.0, indicating equal eye and head velocities. Hypofunction of the semi-circular canals is indicated by a VOR gain <0.8 accompanied by refixation saccades.[47,48,51] The mean VOR gain from the left and right sides was used as a continuous variable. A difference of 0.1 in VOR gain was considered clinically relevant, in accordance with the literature.[44,46]

2.3. STRUCTURAL MRI ACQUISITION, PROCESSING, AND QUALITY CONTROL

T1-weighted volumetric MRI scans were acquired in the sagittal plane using a 3T Philips Achieva scanner at the National Institute on Aging Clinical Research Unit. The sequence used was a T1-weighted image (WI) (magnetization prepared rapid acquisition with gradient echo (MPRAGE); repetition time (TR)=6.5 ms, echo time (TE)=3.1 ms, flip angle=8°, image matrix=256× 256, 170 slices, voxel area=1.0× 1.0 mm, 1.2 mm slice thickness, FOV=256× 240 mm, sagittal acquisition). Scans were automatically segmented using MRICloud (https://www.mricloud.org/) and the T1 multi-atlas set "BIOCARD3T_297labels_10atlases_am_hi_erc_M2_252_V1". A semi-automated quality control pipeline was used to automatically identify and manually exclude scans and segmentations of poor quality. The general quality of the scans and segmentations were evaluated by three trained raters (D.P., R.O., and S.Z.). One scan was removed due to motion artefacts. To identify possible regionally specific errors left- and right-side volumes for each region of interest (ROI) in MNI space were residualized with respect to intracranial volume[52] and converted

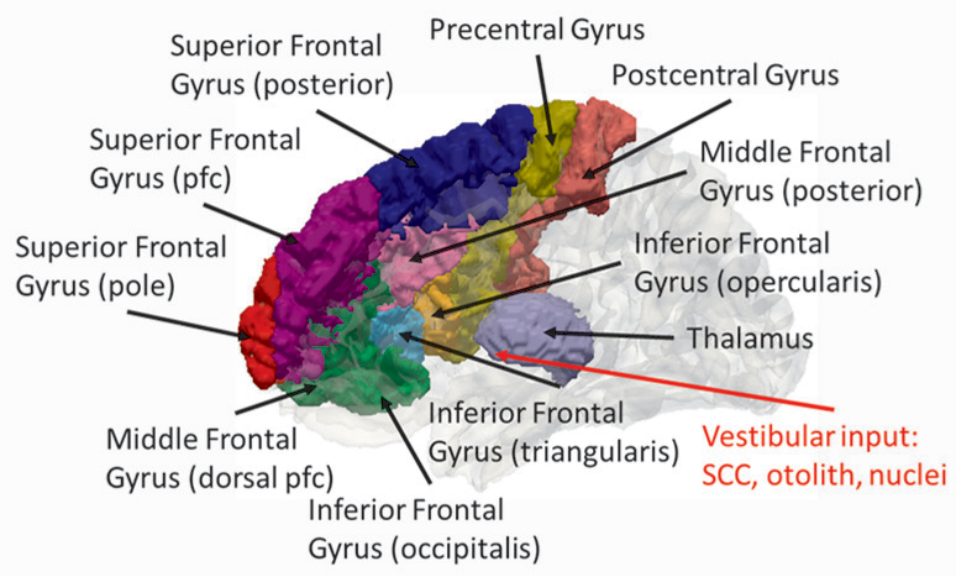

Figure 1. Cortical targets of the vestibular-thalamus-sensorimotor and vestibular-thalamus-prefrontal cortical circuits. Vestibular information from the semicircular canals, otoliths, and nuclei is thought to be relayed through the thalamus (not investigated here) to the sensorimotor cortex (pre and postcentral gyrus) and to the prefrontal cortex (frontal gyrus). The red arrow points toward the ventral lateral nucleus, a putative subfield of the thalamus that receives vestibular input.[41] CAWorks (www.cis.jhu.edu/software/caworks) was used for visualization. Key: pfc: prefrontal cortex; SCC: semicircular canals.

to z-scores. Absolute z-score distances greater than the threshold of 3 standard deviations were flagged for manual verification. One hemispheric region of interest from three participants (left posterior superior frontal gyrus, right opercularis, and left orbitalis) were flagged and verified by visual inspection as having segmentation errors. These three segmentations were subsequently removed rather than fixed because there are no consistent landmarks to guide the manual correction of these ROIs. Volumes were calculated by the number of voxels in each ROI multiplied by the size of a voxel in mm^3. Intracranial volume was comprised of bilateral cerebral volumes, cerebellum, brainstem, and cerebrospinal fluid. Our analysis focuses on the ROIs relevant to our hypothesis, according to the hierarchy defined in JHU-MNI-SS brain[53] and shown in Figure 1:

1) Prefrontal cortex, composed of

1a) Superior frontal gyrus: defined as the sum of middle-superior part of the prefrontal cortex, frontal pole, and posterior pars of superior frontal

1b) Middle Frontal gyrus: defined by the sum of dorsal prefrontal cortex and posterior pars of middle frontal

1c) Inferior frontal gyrus: defined as the sum of pars opercularis, triangularis, and orbitalis of inferior frontal.

2) Sensorimotor cortex, composed of

2a) Precentral Gyrus

2b) Postcentral Gyrus

2.4. STATISTICAL MODELING

For participants with missing vestibular data, we carried over data from an adjacent prior or subsequent visit using an external longitudinal dataset comprised of the same participants.[54] Whereas our original dataset had 58, 64, and 91 observations for cVEMP, oVEMP, and VOR, respectively, the imputed dataset had 95, 100, 107 observations for cVEMP, oVEMP, and VOR, respectively. Using this imputed dataset, multiple generalized linear regression adjusted for age, intracranial volume, and sex was used to investigate the relationship between regional volume and vestibular function. The null hypothesis in Eq. (1) predicts the natural logarithm of regional volume vol_i, for participant i, $i = 1, \ldots, N$. The alternate hypothesis predicts the natural logarithm of regional volume using a vestibular variable, $vest_i$ in Eq. (2), such as best corrected cVEMP, best oVEMP, and mean VOR gain as continuous independent variables,

$$H_0 : \ln(vol_i) = c_0 + c_2 age_i + c_3 isFemale_i + c_4 icv_i + \epsilon_i \quad (1)$$

$$H_1 : \ln(vol_i) = c_0 + c_1 vest_i + c_2 age_i + c_3 isFemale_i + c_4 icv_i + \epsilon_i \quad (2)$$

where c_0 corresponds to the global average, $age_{i,j}$ of subject i, $isFemale_i$ is a binary indicator variable for the sex of subject i (1=female, 0=male), and icv_i denotes the intracranial volume of subject i. We assumed that the natural logarithm of regional volume depends linearly on age. We also assumed that the measurement noise ϵ_i is independently and identically distributed zero-mean Gaussian with unknown, common variance. The unknown effects $\{c_0, c_1, c_2, c_3, c_4\}$ were estimated via maximum likelihood. The vestibular effects on the linear scale were multiplied by their respective relevant clinical effect size (corrected cVEMP: 0.5, oVEMP: 5 μV, VOR: 0.1). In turn, the effects are interpreted as the relative regional volume change resulting from a 1-clinically-relevant-unit change in vestibular variable. All effects reported have been transformed according to $\beta_k = 100(\exp(c_k) - 1)$, $k = 0, \ldots, 4$.

Table 1. Characteristics of the study sample (n = 117). Key: PTA: four-frequency (0.5, 1, 2, 4 kHz) pure tone average from the better ear; N: the number of participants with a visit where both the characteristic and MRI data were available; %: 100(N/n) percent; SD: standard deviation.

Characteristic	Mean (SD)	N (%)
Age (years)	77 (8.7)	
Sex		
Male		79 (67.5)
Female		38 (32.5)
Corrected cVEMP Amplitude	1.2 (0.749)	
oVEMP Amplitude (μV)	13.6 (10.1)	
Mean VOR Gain	0.997 (0.163)	
Four Frequency PTA (dB)	32 (14.9)	

To determine whether the study sample is stable and that our individual results are not driven by outliers or extreme values, we performed a permutation likelihood ratio test (LRT) by permuting model residuals under the null hypothesis, H_0. The permuted p-value, p_{perm}, was calculated as the proportion of simulated LRTs, termed LRT_{sim}, greater than the observed LRTs, termed LRT_{obs}, ($n_{perm} = 5000$ simulations),

$$p_{perm} = \frac{\sum_{i=1,\ldots,n_{perm}} \mathbb{1}\left(LRT_{sim_i} \geq LRT_{obs}\right) + 1}{n_{perm} + 1} \quad (3)$$

where $\mathbb{1}(x)$ is the indicator function that yields 1 when the argument x is true and 0 otherwise. We reject the null hypothesis if $p_{perm} < 0.05$. For models which rejected the null hypothesis, 95% confidence intervals were calculated by bootstrapping model residuals under the alternative hypothesis, H_1, (10k simulations) to mitigate the effects of outliers. A Benjamini-Hotchberg procedure was used to control the false discovery rate (FDR) of the comparisons made in this study.[55] FDR q-values indicate the expected proportion of rejected null hypotheses that are false. To avoid being overly conservative in our adjustment for multiple comparisons, we chose to adjust FDR for each side of the brain and for each level of granularity separately. For these exploratory analyses, we considered an FDR threshold of 0.10. All effects were considered significant at the $q < 0.1$ levels. These analyses were implemented in *RStudio*.[56] Bootstrapped confidence intervals were computed with 10,000 simulations using the *np.boot* function of the nptest R package.[57]

3. RESULTS

3.1. STUDY SAMPLE CHARACTERISTICS

Table 1 shows the characteristics for the study sample from the Baltimore Longitudinal Study of Aging. Summary statistics for the ICV and regional volumes can be found in Supplementary Table S1.

3.2. ASSOCIATION BETWEEN VESTIBULAR FUNCTION AND REGIONAL CORTICAL VOLUMES BASED IN GENERALIZED LINEAR REGRESSION

Figure 2A summarizes the relationships between the definitions of the anatomical regions of interest, where the child nodes are a part of the parent nodes, as illustrated in Figure 1. Figure 2B depicts the associations between vestibular functions and regional brain volumes for models which rejected the null hypothesis according to permutation testing. The permutation testing results show that our sample is stable: our individual results are not driven by outliers or extreme values. Because age and intracranial volume are included as covariates, the vestibular effects on regional volume may be interpreted as percent volume preservation in the face of global, age-related volume reductions for each 1-clinical-unit increase in the vestibular variable. This means that regions that exhibit a higher relative volume do not actually have a higher volume; rather, they have less age-related atrophy than the whole brain, meaning they are relatively spared. Figure 2C summarizes the raw p-values calculated from the observed (not permuted) data and corresponding FDR-corrected q-values for each vestibular-volume comparison for each side at each level of granularity for the prefrontal cortex and the sensorimotor cortex. A total of 42 regression models were assessed and 18 regression models rejected the null hypothesis at the 0.05 level according to permutation testing (See Figure 2B). To correct for multiple independent comparisons across regions of interest, we performed an additional analysis of the raw p-values estimated from the 42 observed data models: seven relationships were significant (i.e. remained significant after FDR-correction) at the 0.1 level (See Figure 2C). In this additional analysis, three relationships at the coarsest level of granularity were significant at the q < 0.05 level: poorer canal function and lower relative volumes of the bilateral (% smaller ≈ 1.12, q-value ≈ 0.04), left (% smaller ≈ 1.13, q-value ≈ 0.045), and right (% smaller ≈ 1.11, q-value ≈ 0.048) prefrontal cortex. At the coarse-fine granularity, the relationship between poorer canal function and smaller relative volume of the left superior frontal gyrus was significant at the 0.05 level (% smaller ≈ 1.55, q-value ≈ 0.046) and relationship between poorer utricular function and lower relative volume of the right middle frontal gyrus (% smaller ≈ 1.16, q-value ≈ 0.086) was significant at the 0.1 level. Two relationships at the finest granularity were significant at the 0.1 level: the poorer saccular function and higher relative volume of the left postcentral gyrus (% greater ≈ -2.22, q-value ≈ 0.086) and poorer utricular function and higher relative volume of the pole of the left superior frontal gyrus model (% greater ≈ -2.01, q-value ≈ 0.084). Supplementary Table S2 details the numerical values of the vestibular relationships with relative regional volume, including the numerical values corresponding to Figures 2B and 2C. Figure 3 shows the spatial arrangement of the average estimated vestibular effects for models which remained significant after FDR-control at the 0.05 and 0.01 levels. For each hypothesis test, χ^2 tests agreed with the outcome of the permutation tests to either reject or accept the null hypothesis (results not shown).

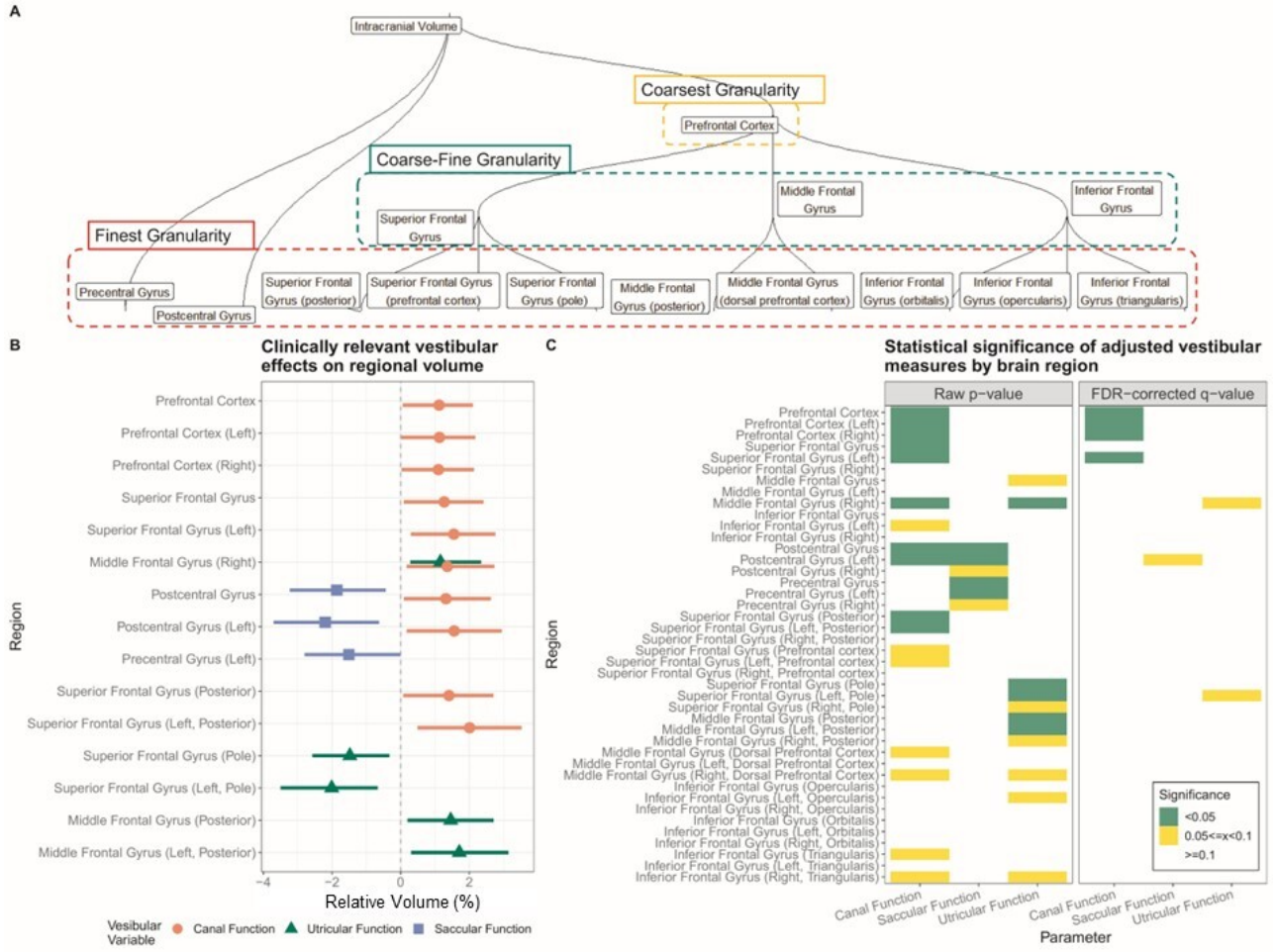

Figure 2. (A) A dendrogram showing the hierarchical relationships between the labels in which the brains were segmented. (B) A dot and whisker plot of the vestibular effects (estimated average volume preservation in percent) on regional gray matter volumes with respect to a 1-clinically-relevant-unit increase in vestibular function for models which rejected the null hypothesis according to permutation testing. The point-shapes correspond to the average effect and the extent of the whiskers corresponds to the 95% confidence intervals. Notably, regions that exhibit a higher relative volume do not actually have a higher volume; rather, they have less age-related atrophy than the whole brain—they are relatively spared. (C) Heat maps of the raw p-values (left) calculated from the observed data models and the FDR-corrected q-values (right) for all granularities of structure models by region. FDR-correction was performed independently for each side (bilateral-mean, left, right) and level of granularity. All models were adjusted for age, sex, and intracranial volume (n=117).

To examine whether the addition of hearing function can account for the potential relationships between vestibular function and cortical volumes, we performed our analysis pipeline additionally adjusting for hearing function. The addition of hearing function to the models reduced the sample size from 117 to 115 participants and resulted in the same significant associations previously observed with similar effect sizes (See Supplementary Table S3). Furthermore, similar results were attained when comparing participants with bilaterally absent saccular or utricular function and those with residual function (results not shown). Supplementary Table S4 summarizes the age effects on regional volume.

4. DISCUSSION

In this study, we investigated the relationship between vestibular function and cortical gray matter volume (GMV) in older adults. We examined key cortical regions that are thought to be involved in vestibular processing but are not commonly reported in the vestibular neuroimaging literature: the prefrontal cortex, made up of the superior, middle, and inferior frontal gyri, the precentral gyrus in the motor cortex, and the postcentral gyrus in the somatosensory cortex.[2,4,6] We found significant relationships between vestibular function and the volumes of these cortical areas. To our knowledge, these findings provide some of the first demonstrations that age-related loss of vestibular end-organ functions in older adults is associated with GMV changes in several prefrontal and sensorimotor cortical regions that have been reported to receive vestibular inputs.

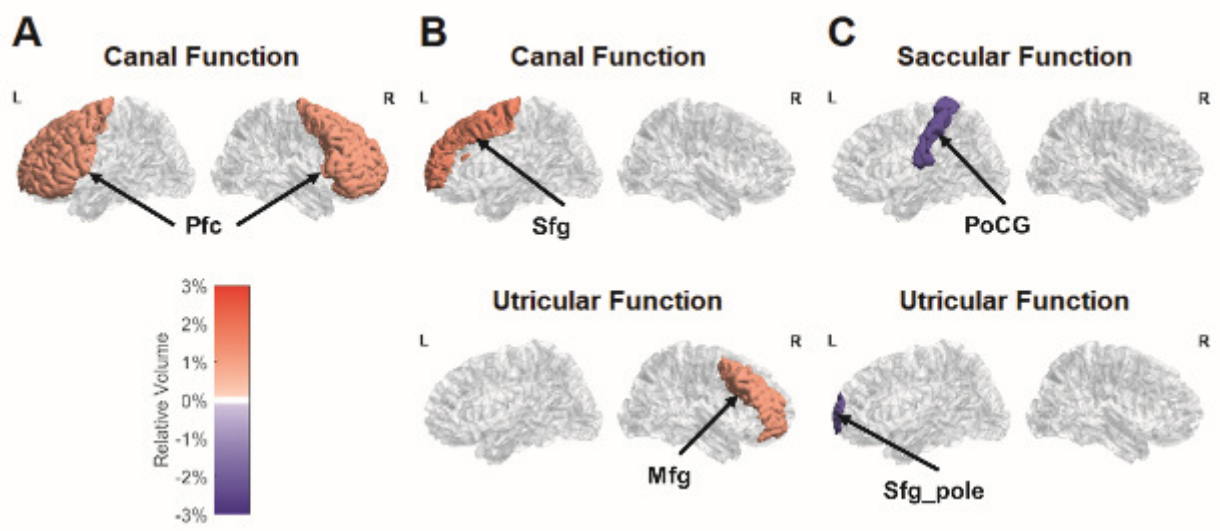

Figure 3. Spatial distribution of average vestibular effects on regional gray matter volumes at three levels of granularity with respect to a 1-clinically-relevant-unit increase in vestibular function for models which survived FDR-control at the 0.05 and 0.1 levels. (A) coarse granularity: from the top row downwards, the prefrontal cortex (Pfc) and color bar. (B) coarse-fine granularity: left superior frontal gyrus (Sfg) (top row) and right middle frontal gyrus (Mfg) (middle row). (C) fine granularity: left postcentral gyrus (PoCG) (top row), left pole of the superior frontal gyrus (Sfg_pole) (bottom row). Whereas red color indicates percent volume expansion in the face of age-related global brain size reduction, blue color indicates relative volume reduction. Notably, regions that exhibit a higher relative volume do not actually have a higher volume; rather, they have less age-related atrophy than the whole brain—they are relatively spared. The L and R labels indicate the lateral views of the left and right hemispheres, respectively. This figure was visualized with the BrainNet Viewer[58] (http://www.nitrc.org/projects/bnv/).

Notably, we found in this cohort of healthy older adults that vestibular impairment (both canal and otolith) was associated with reduced GMV in the prefrontal cortex, and specifically the superior and middle frontal gyri. These findings are compatible with clinical studies that demonstrated that patients with vestibular impairment had reductions in GMV in the right superior frontal gyri[36] and in the left dorsolateral prefrontal cortex compared to controls.[38] While our study focuses on specific clinical assessments of vestibular function, it complements previous structural neuroimaging studies that have explored associations between vestibular function and brain structure in regions involved in balance and sensory integration.[59-61] Additionally, neuroimaging during vestibular stimulation studies in humans have shown activations in regions of the prefrontal and sensorimotor cortices[2] in which we observed GMV alterations.

4.1. CORTICAL AREAS OF VESTIBULAR-MODIFIED GRAY MATTER VOLUME ALTERATIONS

4.1.1. PREFRONTAL CORTEX

The prefrontal cortex showed a lower GMV with poorer canal function. The prefrontal cortex is thought to be involved in executive function,[62] which encompasses planning, decision-making, working memory, inhibitory control, and abstract rule-learning. Peripheral vestibular information is transmitted to the brainstem which sends this information to the prefrontal cortex via thalamic-limbic-striatal-frontal circuits. Functional neuroimaging has revealed vestibular activations within the prefrontal cortex.[23-27] Various stimulation techniques, including electrical, caloric, galvanic, and single-shock, activate distinct regions such as the superior and medial frontal gyrus (Brodmann Area (BA) 10), inferior frontal gyrus (BA 46), and premotor cortex (BA 44/6).[23,24,26,27] Saccular stimulation, through methods like high-intensity clicks, consistently targets the supplementary motor area and superior frontal gyrus (BA 10).[27] Primate research highlights vestibular connections to the periarcuate cortex near the frontal eye fields,[2,31] and rat studies indicate vestibular projections to the supplementary motor area, a finding not replicated in human tractography.[32] Although the exact functions of the circuits are poorly defined, vestibular function has been shown to be associated with working memory in older adults[8] and to mental number ordering and manipulation ability.[63-65]

We observed a lower GMV of the superior frontal gyrus with poorer canal function, as well as lower GMV of the middle frontal gyrus with poorer utricular function. Each of these impacted areas serves potentially many important roles in a person's ability to interact with the world. Toward the posterior end, the superior frontal gyrus contains portions of the supplementary motor area and of the frontal eye field and is responsible in part for initiating complex movements. Owing to its circuitry and to containing portions of the premotor cortex, the middle frontal gyrus engages in aspects of motor control and planning. Interest-

ingly, looking at a finer level of granularity, the anterior pole of the superior frontal gyrus, which for brevity we term the frontal pole hereafter, showed a higher GMV with poorer utricular function. One possible explanation for this differential result is that reduced utricular inputs are modified by multisensory gain reweighting and compensation mechanisms upstream in the brainstem, cerebellum, or thalamus before reaching the frontal pole. Another explanation is that the frontal pole, or even the prefrontal cortex at large, could develop a sensitization to otolith inputs with age.[66] Because the frontal pole is thought to play a role in cognitive switching between spatial tasks and has connections with prefrontal cortex (involved in working memory and executive function), orbitofrontal cortex, cingulate cortex, temporal lobe, and inferior parietal regions and the thalamus,[67,68] such an effect could influence deficits in cognitive-motor dual tasking observed in vestibular patients.[69] We speculate that information about linear acceleration of the head in the horizontal plane transduced by the utricle may be used by the frontal pole to plan and execute actions, including body and visuomotor actions, such as locomotion during navigation, reaching, and grasping, while balancing other cognitive, interoceptive, and emotional factors. Why an association of saccular or horizontal semi-circular canal function with the frontal pole was not found is unclear. Moreover, whether the frontal pole may use information about linear acceleration of the head in the vertical plane transduced by the saccule or about angular acceleration of the head in the horizontal plane (yaw) transduced by the horizontal semi-circular canal remains a mystery. This more focal association with the frontal pole was attenuated, however, when considering the whole prefrontal cortex as well as the whole superior frontal gyrus, possibly due to relationships in the opposite direction involving the rest of those structures. Taken together, these results suggest that vestibular loss is related to relative atrophy of prefrontal cortical structures that subserve executive function and motor planning.

4.1.2. SOMATOSENSORY AND MOTOR CORTICES

We observed an association between vestibular function and GMV of somatosensory cortex at the finest level of granularity. Specifically, the left postcentral gyrus showed a higher GMV with poorer saccular function. We observed no relationships after FDR-control between GMV in the precentral gyrus and vestibular function. Why an association of utricular or horizontal semi-circular canal function with the postcentral gyrus was not found is unclear. Whether the postcentral gyrus may use information about linear acceleration of the head in the horizontal plane transduced by the utricle or about angular acceleration of the head in the horizontal plane (yaw) transduced by the horizontal semicircular canal must be elucidated. The postcentral gyrus, a part of the somatosensory cortex within the parietal cortex, is topographically organized into maps of body parts (e.g., head, trunk) and receives projections from the thalamus which carry vestibular information. Vestibular nerve stimulation-evoked potential studies in rats have demonstrated the greatest neural responses in the primary somatosensory cortex, with robust responses also observed in the primary and secondary motor cortex.[70] Functional neuroimaging studies of caloric and galvanic vestibular stimulation in humans have shown activation of the somatosensory cortex and several frontal regions including primary motor cortex and premotor cortex.[24,27,30] The postcentral gyrus is responsible somatosensation, the postural control/representation of the body, and for self-motion perception which contributes to motor planning.[12,24,71-73]

One explanation of this differential result could be that loss of saccular inputs results in reweighting by multisensory (e.g., visual, auditory, autonomic, proprioceptive) regions, like the vestibular nuclei, cerebellum, hypothalamus, and thalamus,[74,75] before sending these reweighted inputs back to the postcentral gyrus. Such saccular modulation could suppress vestibular-mediated structural changes in the postcentral gyrus. Sensory substitution as a compensatory mechanism has been suggested to explain GMV increases.[35,36] Additionally, the results indicating vestibular effects in opposing directions may be a product of different emphasis on the afferent and efferent projections that transmit vestibular information. For instance, the age-related loss of vestibular function associated with lower relative GMV may suggest a dominance of afferent connections receiving peripheral vestibular inputs, highlighting bottom-up processing. On the other hand, the age-related loss of vestibular function associated with higher relative GMV may suggest a dominance of efferent projections which modify remaining peripheral vestibular inputs that have declined due to aging. However, teasing out these bottom-up and top-down processes is a challenge that would require addressing the structural effects of compensatory and sensory substitution processes in brain regions that process vestibular and extra-vestibular information. Overall, these findings suggest differing roles of age-related vestibular end-organ functions in the morphological alterations in the cortex.

4.1.3. INTERPRETATIONS OF GRAY MATTER ALTERATIONS

We note that the GMV changes can be interpreted as regional volume preservation, or resilience to structural aging, effects. This connotation arises because vestibular associations must be interpreted concurrently with the age and intracranial volume associations, which account for linear slope trends in regional volume due to aging and global brain volume differences. With this in mind, we can conceptualize resilience to structural aging to be a cross-sectional association of two components: adversity and positive adaptation. Because the brain is known to atrophy with aging, we define a negative age association with regional volume to be the "adversity" component of resilience, and we define a positive vestibular association with regional volume to be the "positive adaptation" component of resilience. This means a concurrent negative and positive age and vestibular association, respectively, indicates an association with preservation of relative volume or resilience to lower age-related volume. In other words, regions that exhibit a higher relative volume do not actually

have a higher volume; rather, they have less age-related atrophy than the whole brain. On the other hand, concurrent negative age and vestibular associations indicate a magnification of the association with lower age-related volume, or additional atrophy. We found that the age effects on regional volume were in fact negative (see Supplementary Table S4), and the vestibular effects varied in magnitude and direction (Figure 2b), indicating associations with resilience to and exacerbation of lower relative (global, age-related) volume. Our choice to interpret our cross-sectional associations as relative volume preservation, or resilience to structural aging, follows the trend in resilience research, which has been by and large based on cross-sectional studies in which the contextual definition of resilience is specified by the researcher.[76,77] Nevertheless, a longitudinal or causal study would provide deeper insight into possible vestibular involvement in the process of resilience to structural aging. Further interpretation of the nature of the effects is limited by the fact that the exact neural substrates underlying these GMV changes remains obscure. To uncover whether the vestibular effects reflect changes in neuronal density, supplemental histological and physiological studies would be needed. Moreover, the magnitudes of structural alterations must be understood with respect to a clinically relevant magnitude of vestibular function. In this study, clinically meaningful changes in saccular, utricular, and canal function measures are 0.5, $5\mu V$, and 0.1, respectively. By multiplying the vestibular effects on the linear scale by their clinically relevant changes in value, each vestibular effect can be understood as the preservation or atrophy of GMV relative to ongoing age-related degeneration associated with a 1-clinical-unit change in vestibular function, or alternatively resilience to or acceleration of global age effects. Taken together, our findings suggest that lower vestibular function is primarily associated with additional atrophy overall in the prefrontal cortex and with preservation against, or resilience to, regional brain atrophy in the postcentral gyrus of the sensorimotor cortex.

4.2. STRENGTHS AND LIMITATIONS

We report several strengths of this study. One such strength is that the relationships examined were hypotheses-driven based on prior work, such as functional neuroimaging during vestibular stimulation and clinical studies in humans. A second strength is that we use a multi-atlas and LDDMM, which is regarded as the holy grail of non-linear image registration techniques,[78] for diffeomorphometry which overcomes the limitations of voxel-based morphometry faced by other vestibular neuroimaging studies, such as the tendency to find focal changes, rather than more spatially distributed changes.[79] A third strength is that our quality control pipeline involved manual inspections of the data at each step of processing. Fourth, our statistical testing pipeline accounts for multiple dependent and independent comparisons using permutation testing and FDR correction, respectively, as well as for outliers using bootstrapping.

Still, there are limitations to this study. Because volumes are coarse measures of structure, it is possible that we did not detect true effects if they were nonuniformly distributed across or within the region of interest. Cortical thickness and surface shape may provide more sensitive measures of variation in the structure of the region of interest. This sensitivity becomes especially advantageous if the region of interest is convoluted and difficult to segment. Additionally, the reproducibility of results is a challenge at high cortical parcel granularity, as anatomical definitions can vary between atlases and experts. Although our large multi-atlas set spans our investigated age range to capture the anatomical variability of adult brains, this multi-atlas set lacks modern cytoarchitectonic definitions that have relevance to brain function. Another limitation is that we did not examine the potential role of the cerebellum, the brainstem, the hypothalamus, or the thalamus in modulating the effects of age-related vestibular loss in the cortex. However, robust measures of cerebellar and brainstem structures are being developed. While we did reuse data, we did not account for dataset decay[80] because we explored a distinct research question compared to previous studies from our group that use this cohort and measurements.[40,41] This may limit the strength of our findings, and future confirmatory studies may be needed to reinforce our findings. Additionally, our findings may not generalize to the broader and younger population due to the age range used in this study and the propensity of BLSA participants to have higher levels of education and socioeconomic status than typical adults.

4.3. FUTURE WORK

While this cross-sectional study helps to clarify the relationships between vestibular function and cortical regions of interest, subsequent longitudinal studies will be needed to elucidate how vestibular function may over time impact the structure of brain regions that receive vestibular input: the limbic system, temporo-parietal junction, and frontal cortex. To gain new insights into vestibular associations with human anatomy, future work will involve utilizing peer-reviewed cytoarchitectonic atlases, such as the Julich atlas,[81] which also comprises a portion of the Eagle-449 composite atlas for vestibular research,[82] or a parcellation-based approach.[83] Future work will also incorporate sensitive measures of local structure change, like cortical thickness and shape, which complement gross volume measures, as well as measures of microstructural change gleaned from diffusion MRI. Structural equation modeling of longitudinal data can be used to investigate causal hypotheses between vestibular loss and structural changes, simultaneously accounting for possible confounding by hearing and vision loss. This framework can also help to test hypotheses that intervening brain structures such as the brainstem, the hypothalamus, the cerebellum, and thalamus modify vestibular effects on downstream structures. Additionally, changepoint analysis can identify subtle non-linearities in the trends of regional structural changes that are not captured by gross aging trends[84] and that may be associated with vestibular compensation for unilateral and bilateral vestibular end-organ function loss. The collection of changepoints for each regional structure measure can be

temporally ordered to explain the sequence of regional structural changes in relation to each other. Ultimately, these studies together can reveal the sequence and causal direction of changes in the vestibular network.

5. CONCLUSION

This study found associations between age-related vestibular end-organ functions and regional GMVs of the prefrontal and somatosensory cortices in adults. This work furthers the understanding of the role of the vestibular system in structural changes in cortical regions that receive peripheral vestibular input and are affected in clinical vestibular disorders. Moreover, these vestibular-modified structural changes may provide anatomical links between vestibular function and cognition. Future work will need to determine the temporal and spatial flow of structural alterations in the central nervous system related to peripheral vestibular function.

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CONFLICTS OF INTEREST

The authors report no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data from the BLSA are available on request from the BLSA website (blsa.nih.gov). All requests are reviewed by the BLSA Data Sharing Proposal Review Committee and are also subject to approval from the NIH institutional review board.

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SUPPLEMENTARY MATERIALS

Supplementary Materials

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