BMC Neurology

RESEARCH

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A comparative study of vestibular projection connectivity and balance in healthy young adults and elderly subjects

Sang Seok Yeo[1], Seunghue Oh[2] and In Hee Cho[3*]

Abstract

Objective Vestibular function is controlled by interactions between various neuropathways that have different effects on balance and are connected to various brain areas. However, few studies have investigated the relation between changes in VN connectivity and aging using neuroimaging. We investigated neural connectivities in the vestibular nucleus (VN) and ventralis intermedius (VIM) nucleus of the thalamus in young and old healthy adults by diffusion tensor imaging.

Methods This study recruited twenty-three normal healthy adults with no history of a neurological or musculoskeletal disease, that is, eleven old healthy adults (6 males, 5 females; mean age 63.36 ± 4.25 years) and 12 young healthy adults (7 males, 5 females; mean age 28.42 ± 4.40 years). Connectivity was defined as the incidence of connection between the VN, VIM, and target brain regions. Incidence of connection was counted from VN and VIM to each brain region. The subjective visual vertical (SVV) and the Berg balance scale (BBS) were used to assess vestibular function and balance.

Results The VN showed high connectivity with brainstem (dentate nucleus, medial longitudinal fasciculus, and VIM), but relatively low connectivity with cerebral cortex (parieto-insular vestibular cortex (PIVC) and primary somatosensory cortex) at a threshold of 30 streamlines. In particular, VN connectivity with PIVC was significantly lower in elderly adults (> 60 years old) than in young adults (20–40 years old) ($p < 0.05$). VIM showed high to mid connectivity with brainstems and cerebral cortexes at a threshold of 30, but no significant difference was observed between young and old adults ($p > 0.05$). SVV and BBS showed no significant differences between young and old adults ($p > 0.05$).

Conclusion We investigated incidences of neural connectivities of VN and VIM in young and old healthy adults. Our results provide basic data that might be clinically useful following injury of vestibular-related areas.

Keywords Vestibular nucleus, Ventralis intermedius, Connectivity, Diffusion tensor imaging, Aging

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Introduction

Balance control is required to maintain the center of mass within the support base and is an important consideration for ambulation and reducing fall risk [1, 2]. Balance ability requires the complex integration of visual, vestibular, and somatosensory systems [1, 3], but age-related degenerative changes in the neuromuscular system adversely affect balance ability, and thus, fall risk [1, 2, 4]. Previous studies have suggested age-related reductions in balance ability are caused by diminished abilities of the musculoskeletal, visual, somatosensory, and vestibular systems [1, 2]. In particular, some studies have investigated the effect of age on the relation between the vestibular system and balance ability [5, 6]. The vestibular system plays an important role in controlling head, body, and eye movements [7, 8]. However, unlike other sensory systems, previous studies have suggested that it has limitations to easily measure changes in vestibular functions because the assessment techniques are not various and not easily applicable [3, 6, 7, 9]. Furthermore, the need for sensitive measurement techniques that are capable of allowing evaluation of central and peripheral vestibular functions has increased in parallel with societal aging [10, 11]. Recent studies have demonstrated relations between vestibular functions and aging using the subjective visual vertical (SVV), which is a sensitive, simple neurophysiological technique, and have reported vestibular function diminishes with age [12–14].

Especially, vestibular function is mainly controlled by central neural system that interactes between various brain areas and neuropathways [15, 16], the latter of which may have different effects on balance depending on the brain areas and volume they project [15–17]. Many authors have suggested that vestibular projection pathways mainly connect with the parieto-insular vestibular cortex (PIVC), ventralis intermedius (VIM) nucleus of the thalamus, medial longitudinal fasciculus (MLF), vestibular nucleus (VN), and dentate nucleus (DN) of cerebellum [13, 18–21]. Previous studies have reported that the PIVC in the posterior parietal operculum/retroinsular region is a core region of vestibular input [22–24]. The PIVC contributes to the processing of bodily self-consciousness, estimation of verticality, and to the integration of visual motion [23, 25]. The VIM nucleus is located laterally to the thalamus between the ventral posteromedial nucleus and ventral lateral nucleus, whereas the MLF is situated in the medial part of the ipsilateral midbrain [17, 26], and the VIM and MLF play important roles in the sensing of body rotation and head tilt [17, 26]. Several authors have suggested correlations exist between the VIM and MLF and vestibular function based on visual vertical data, and have reported VIM and MLF receive vestibular signals related to visual vertical from the VN [9, 17, 27]. The DN of cerebellum is a main contributor to vestibular function because it receives vestibular input through projection pathways. In particular, the DN receives vestibular information from the VN and outputs information processed in the DN of cerebellum [28, 29]. Some researchers have emphasized a relation between the VN in brainstem and vestibular function because most vestibular inputs related to the PIVC, VIM, MLF, and cerebellum pass through the VN [9, 23, 27, 30]. In 2014, Conrad et al. reviewed the role and function of vestibular structures in the central vestibular system, and reported vestibular projection pathways ascended through the superior VN and that vestibular input was transmitted from the VN to other vestibular structures(9).

Diffusion tensor imaging (DTI) enables functional connectivity and anatomical structures to be visualized and reconstructed by imaging water diffusion patterns [31–33]. DTI provides images of the diffusion properties of white matter by quantifying diffusion in multiple directions [31–33]. Previous studies have reconstructed human neural connectivity in the VN and in other brain areas in three dimensions [23, 24, 28], and other studies have reported age-related changes in DTI parameters [34–36]. However, few studies have investigated the relation between changes in VN connectivity and aging.

In the present study, we reconstructed neural connectivity in the vestibular and ventralis intermedius nuclei of thalamus by DTI and investigated the association between neural connectivity and balance ability related to visual vertical in young and old healthy adults.

Materials and methods

Subjects

Twenty-three normal healthy adults with no history of a neurological or musculoskeletal disease were recruited for this study, that is, eleven old healthy adults (6 males, 5 females; mean age 63.36±4.25 years) and 12 young healthy adults (7 males, 5 females; mean age 28.42±4.40 years). Inclusion criteria for this study were as follows: (1) participants who had previously not been diagnosed with the musculoskeletal, neurologic and cognitive problems; (2) participants who were not diagnosed with problems related to brain injury by doctors. All participants provided informed consent prior for DTI and balance ability assessments. The study protocol was approved by the institutional review board of Yeungnam University Hospital (YUMC 2019-04-050-001).

Diffusion tensor image and probabilistic fiber tracking

The DTI data were acquired using a sensitivity-encoding head coil on a 1.5 T Philips Gyro scan Intera (Philips, Best, The Netherlands) with single-shot echo-planar imaging. For each of the 32 non-collinear diffusion sensitizing gradients, 67 contiguous slices (acquisition

matrix=96×96; reconstructed matrix=192×192; field of view=240×240 mm^2; TR=10,726 ms; TE=76 ms; b=1000 s/mm^2; NEX=1; and a slice thickness of 2.5 mm) were collected parallel to the anterior commissure-posterior commissure line [22].DTI data was analyzed using the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL; www.fmrib.ox.ac.uk/fsl). Head motion effect and image distortion due to eddy currents were corrected for using affine multi-scale two-dimensional registration. Fiber tracking was performed using a probabilistic routines based on a multifiber model in FMRIB Diffusion (5000 streamline samples, 0.5 mm step length, curvature threshold=0.2) [37]. To reconstruct VN connectivity, a seed ROI was placed on the VN at the level of the pons equivalent to Deiters' nucleus and Schwalbe's nucleus (Fig. 1) [38]. VIM connectivity was reconstructed by placing a seed ROI between the ventral caudalis and the ventral oralis (anterior and posterior) nucleus at the level of the ventral thalamus (Fig. 2) [39]. 5000 samples were generated from the seed voxel, and results were visualized at a threshold of 1, 10 and 30 streamlines through each voxel for analysis.

Determination of connections between the VN, VIM nucleus of the thalamus and target brain regions

Connectivity was respectively defined as the incidence of connection between the VN, VIM and the following target brain regions and calculated by whether the results passed through each target brain regions: (1) primary somatosensory cortex (S1), PIVC, VIM nucleus of the thalamus, MLF and DN of cerebellum, and (2) S1, PIVC, MLF, VN, and DN of cerebellum. Incidence of connection was counted from the VN and VIM nucleus to each brain region.

Functional evaluation

Subjective visual vertical (SVV)

Subjective visual vertical (SVV) was assessed using an opaque plastic bucket. A vertical straight line was placed on the interior bottom of the cylindrical bucket using color tape [40]. A protractor was then attached on the exterior bottom of the bucket so that the interior vertical straight line and protractor's zero line were aligned [40]. A pendulum was positioned on the exterior bottom so as to match the zero line of the protractor [40]. The participants received the bucket after random rotation and were instructed to look at the line inside the bucket and to turn the buck so that the line was disposed vertically in a sitting position [40]. We measured angular deviations from true vertical regardless of whether they were clockwise or counter clockwise. SVV testing was performed in a subdued light to avoid a reflection from the protractor. The SVV test was performed three times and results were averaged.

Berg balance scale (BBS)

The Berg balance scale (BBS) was developed to evaluate balance in old adults [41]. The scale is composed of 14 items that address activities of daily living such as standing, moving, and turning. Items were each scored from 0 to 4, and thus, possible total scores varied from 0 to 56, where higher scores represented better balance. The BBS was conducted three times and results were averaged.

Statistical analysis

SPSS ver. 20.0 (SPSS, Inc., Chicago, Illinois) was used to analyze results. The chi-square test was used to determine the significances of differences in the incidences of connectivity in the VN and VIM nucleus of the thalamus in young and old adults. Differences of SVV and BBS between young and old adults were analyzed using Mann-Whitney U-test. Statistical significance was accepted for p values <0.05.

Results

Structural connectivities of the VN and VIM

Connectivity of the VN

Reconstruction of VN connectivity is shown in Table 1; Fig. 1. VN showed 100% connectivity with the DN in the young and old groups regardless of the streamline threshold used. At thresholds of 1, 10, or 30, connectivity with the PIVC steadily decreased in young (100%, 95.83% and 79.17%, respectively) and old adults (100%, 86.36% and 50%, respectively). Notably, at a threshold of 30, connectivity with the PIVC was significantly lower in old (50%) than in young adults (79.17%) ($p<0.05$). Connectivities with S1, VIM nucleus, and MLF, but not connectivities with the PIVC also showed decrements with increasing threshold in young and old adults, but connectivities at each threshold were not significantly different in the two groups ($p>0.05$) (Table 1).

Connectivity of the VIM nucleus of the thalamus

VIM connectivities are summarized in Table 2; Fig. 2. VIM showed 100% connectivity with target brain regions (S1, MLF and VN) in old adults regardless of threshold. In contrast, young adults showed lower connectivities with S1 (95.83%), MLF (95.83%) and VN (95.83%) at a threshold of 30. However, no significant difference was observed between the VIM connectivities of young and old adults ($p>0.05$). At thresholds of 1, 10, and 30 streamlines, VIM connectivities with PIVC and DN of cerebellum steadily reduced in young and old adults, but no significant difference was observed between young and old adults ($p>0.05$) (Table 2).

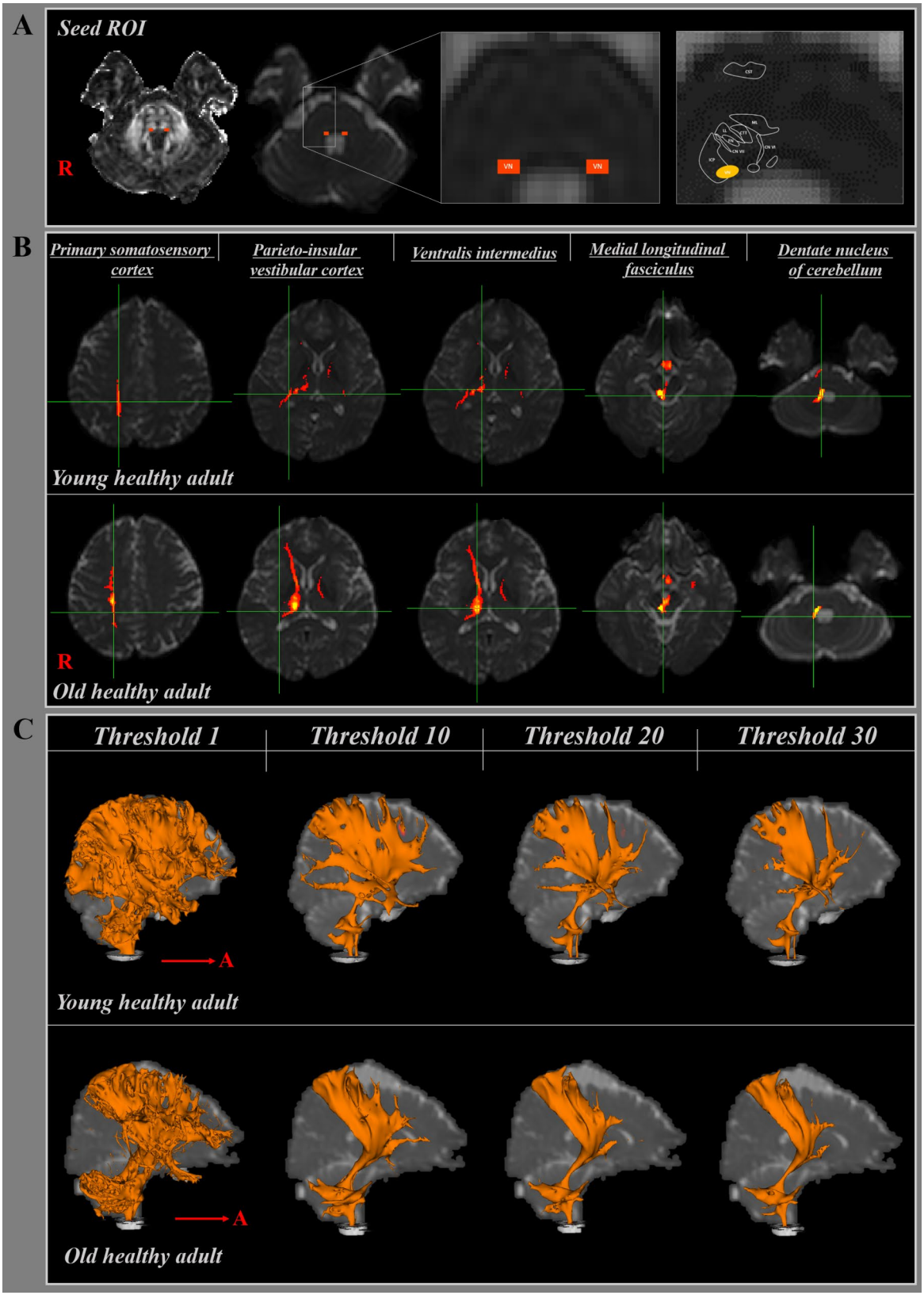

Fig. 1 (**A**) Seed ROI used to determine connectivity of the VN (Deiters' nucleus and Schwalbe's nucleus) at the pons level. (**B**) Results of neural connectivity between the VN and vestibular-related areas (S1, PIVC, VIM nucleus of the thalamus, MLF, and DN of the cerebellum) in young and old healthy adults. (**C**) The structural connectivity of the VN at 1, 10, 20 and 30 streamlines as determined by DTI

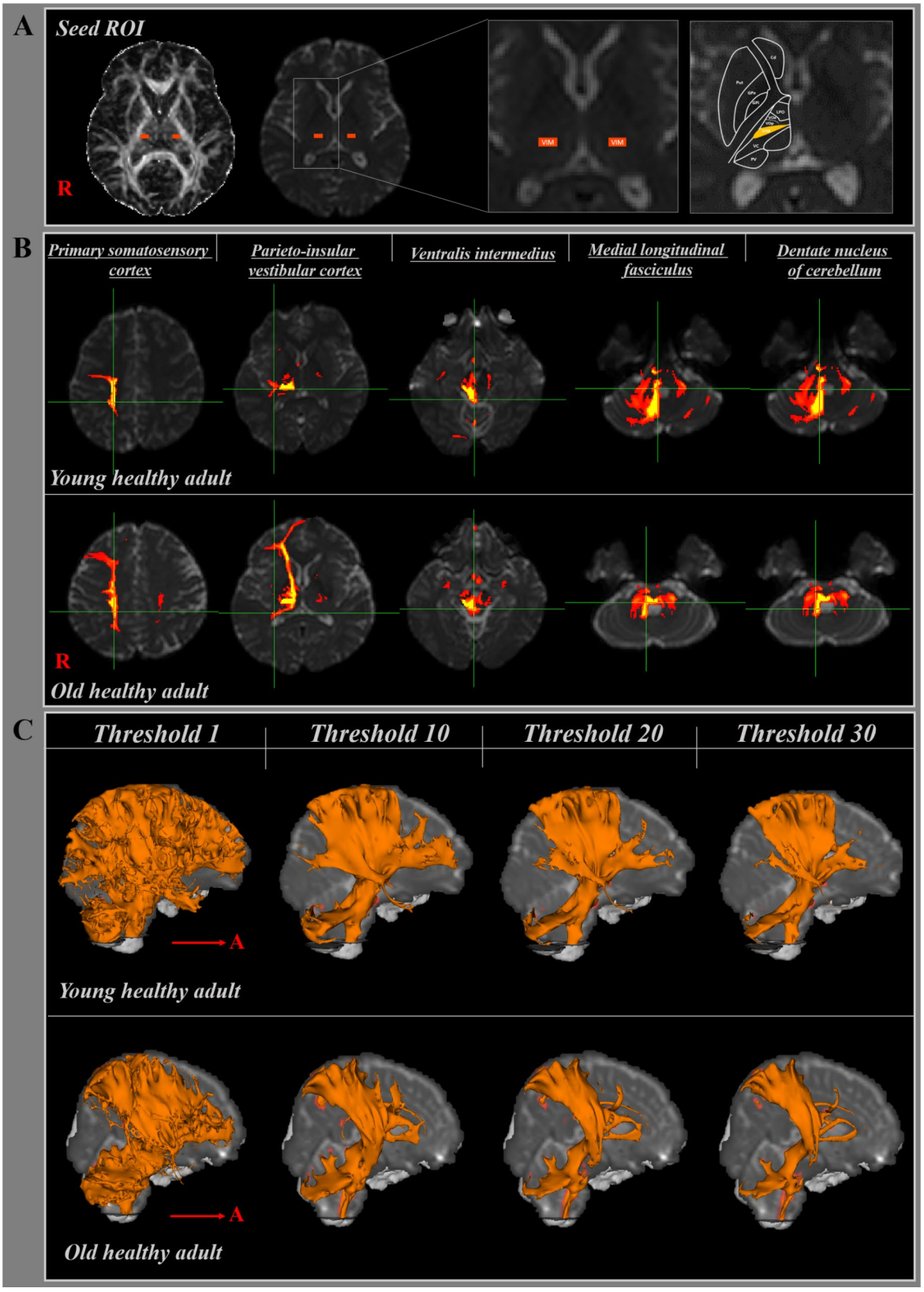

Fig. 2 (**A**) Seed ROI for connectivity of the VIM nucleus of the thalamus was placed between the ventral anterior and posterior nucleus at the ventral thalamus level. (**B**) Results of neural connectivity between the VIM nucleus of the thalamus and vestibular-related areas (S1, PIVC, MLF, VN and DN of cerebellum) in young and old healthy adults. (**C**) The structural connectivity of the VIM thalamus at thresholds of 1, 10, 20 and 30 streamlines as determined by DTI

Table 1 Comparison of incidence of connectivity (%) from VN to target brain regions between young and old healthy adults

	Threshold (streamline)								
	1			10			30		
Target brain region	Young	Old	p	Young	Old	p	Young	Old	p
S1	95.83	100.00	0.333	79.17	90.91	0.268	62.50	63.64	0.936
PIVC	100.00	100.00	1.000	95.83	86.36	0.255	79.17	50.00	0.038*
VIM	100.00	100.00	1.000	100.00	95.45	0.291	91.67	90.91	0.927
MLF	100.00	100.00	1.000	100.00	100.00	1.000	95.83	100.00	0.333
DN	100.00	100.00	1.000	100.00	100.00	1.000	100.00	100.00	1.000

VN: vestibular nucleus; S1: primary somatosensory cortex; PIVC: parieto-insular vestibular cortex; VIM: ventralis intermedius; MLF: medial longitudinal fasciculus; DN: dentate nucleus

* $p<0.05$

Table 2 Comparison of incidence of connectivity (%) from VIM nucleus on thalamus to target brain regions between young and old healthy adults

	Threshold (streamline)								
	1			10			30		
Target brain region	Young	Old	p	Young	Old	p	Young	Old	p
S1	100.00	100.00	1.000	100.00	100.00	1.000	95.83	100.00	0.333
PIVC	100.00	100.00	1.000	100.00	95.45	0.291	87.50	72.73	0.207
MLF	100.00	100.00	1.000	100.00	100.00	1.000	95.83	100.00	0.333
VN	100.00	100.00	1.000	95.83	100.00	0.333	95.83	100.00	0.333
DN	100.00	95.45	0.291	95.83	95.45	0.950	91.67	86.36	0.564

VIM: ventralis intermedius; S1: primary somatosensory cortex; PIVC: parieto-insular vestibular cortex; MLF: medial longitudinal fasciculus; VN: vestibular nucleus; DN: dentate nucleus

* $p<0.05$

Table 3 Comparison of the results of SVV and BBS between young and old healthy adults

	SVV (deg)	BBS (score)
Young	1.75 (1.08)	56.00 (0.00)
Old	2.68 (1.65)	55.91 (0.30)
p	0.152	0.296

Values represent mean (±standard deviation)

SVV: subjective visual vertical; BBS: Berg balance scale

* $p<0.05$

Functional evaluation

SVV scores of the two groups were not significantly different, though the SVV scores of young adults tended to be lower ($p>0.05$) (Table 3). Furthermore, although mean BBS scores also tended to be lower for old adults, there was no significant difference between young and old adults ($p>0.05$) (Table 3).

Discussion

We investigated differences between the vestibular connectivities of the VN and VIM in young and old adults using probabilistic DTI tractography. We found high connectivity between the VN and vestibular-related areas in the diencephalon and which were commonly affected by brain stem lesion (DN:100%, MLF: 97.8%, VIM: 91.3% at a threshold of 30 streamlines), but a relatively low level of connectivity with cerebral cortex (PIVC: 65.2% S1: 63.0% at 30 streamlines). Notably, VN connectivity with the PIVC was significantly lower in old adults. The VIM vestibular connectivity showed high to mid connectivity with the brain stem (VN: 97.8%, MLF: 97.8%, DN: 89.1% at a threshold 30) and cerebral cortex (S1: 97.8%, PIVC: 80.4% at a threshold 30). However, VIM connectivities to vestibular-related areas were non-significantly different in young and old adults. Summarizing, no significant age-related relations between VN and VIM connectivities to vestibular related areas was observed, with the exception of the PIVC. These results suggest no significant differences in balance or visual vertical functions between young and old adults. On the other hand, diminished VN connectivity to the PIVC observed in old adults might be associated with aging with the vestibular system.

The PIVC processes and integrates vestibular information and makes allowances for gravity when body and head positions change, and is known to receive vestibular information from the vestibular nucleus through the VIM of the ventrolateral thalamus [42, 43]. Postural vertical and visual vertical adjustment based on gravitational information are the most important roles of the PIVC and thalamic nucleus associated with vestibular function [9, 24, 44, 45]. In terms of visual vertical testing, SVV tilt is commonly caused by bilateral vestibular dysfunction or a unilateral lesion of the labyrinth, vertical semicircular canal, or vestibular related nucleus [27, 42, 46]. According to previous study, SVV deviation caused

by a peripheral lesion increased under condition where the visual background was rotated unlike in static visual background condition [42]. It was suggested that visual vertical was not controlled solely by vestibular system but by interplay between the vestibular and somatosensory systems [42]. Likewise, previous studies regarding SVV tilt caused by a central lesion reported on pathologic SVV tilt in patients with brain injury such as posterolateral, paramedian infarction and medial temporal gyrus hemorrhage [47, 48]. These results suggested vestibular function may be connected to various cortical areas around the core vestibular cortex as the PIVC [47, 48]. In other words, maintaining visual vertical to gravity or postural change is probably controlled by complex interactions between various brain regions and systems such as the vestibular, visual, and somatosensory systems, rather than a single nervous system or brain region.

In terms of vestibular projection pathways, several studies have recently used neuroimaging techniques to investigate the functional and structural connectivities of vestibular related areas [24, 49, 50]. According to the previous studies, the VIM and the ventralis oralis posterior (VOP) of the thalamic nucleus have different connectivities with brain regions with regard to motor thalamus. Especially, VIM showed greater connectivity to the ipsilateral M1 and the contralateral cerebellum than the VOP [49]. As regards the VN, it has been reported functional and structural connectivities with vestibular-related regions, that is, with the thalamic nucleus, PIVC, and VN [24]. In details, the left VN was functionally connected with the contralateral VN, both piriform cortexes, both insular cortexes, and the contralateral perirhinal cortex [24], and the right VN showed functional connectivities with the contralateral VN, both insular cortexes, and the ipsilateral posterior entorhinal cortex [24]. In addition, a recent study showed that VN to the vestibular related region was 100% connected with cerebellum, thalamus, oculomotor nucleus, trochlear nucleus, abducens nucleus, and reticular formation [50]. In contrast, VN connectivity to the premotor cortex, posterior parietal cortex, and prefrontal cortex showed relatively low connectivity (< 50% at a threshold of 15) [50]. These results of previous studies are consistent with high connectivities of VN and VIM to brainstem and the cerebral region and relatively low connectivities to the cerebral cortex.

Although no significant age-related association was found between neural connectivity and balance ability, our results indicate an age-related association between connectivities of the VN and VIM and the PIVC related to vestibular according to aging and provide basic data that might be clinically useful in cases involving injury to vestibular-related areas. According to previous study, the vestibular neural pathway projecting from vestibular nucleus to PIVC was decreased as age was increased [51] It is consistent with the results of this study, which showed that the connectivity between the VN and PIVC was significantly decreased with age. Another study reported that the vestibular nucleus was connected to various brain areas such as cerebellum, thalamus and posterior insular cortex and the changes of these vestibular projections were affected by age [52]. In other words. these suggested that vestibular function may be decreased because connectivity between vestibular-related areas is decreased according to aging. However, some of the results of this study are inconsistent with the results of previous studies, and the reasons for this are as follows: First, generalizations of our findings are difficult because of the small numbers of subjects recruited and we suggest that future study need to recruit the participants as conducting G*Power sample size calculations. Second, we only evaluated the balance ability using BBS and vestibular function using SVV. It is necessary to evaluate the balance ability using various assessment techniques such as mini-balance evaluation systems test and the vestibular function is needed to assess using VEMP and VOR. Third, we could not sufficiently rule out the effects of changes in visual function and somatosensory system on balance and visual vertical function due to aging. Finally, it was difficulty to locate ROIs accurately because of the diminutive size of the VIM nucleus and we only considered connectivity of the ipsilateral projection. Therefore, we suggest future research be conducted to investigate the association between neural connectivity and vestibular-related areas in contralateral projection.

Abbreviations

SVV	Subjective visual vertical
PIVC	Parieto-insular vestibular cortex
VIM	Ventralis intermedius
MLF	Medial longitudinal fasciculus
VN	Vestibular nucleus
DN	Dentate nucleus
DTI	Diffusion tensor imaging
S1	Primary somatosensory cortex
VOP	Ventralis oralis posterior

Author contributions

All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Conceptualization: S.S.Y. Methodology: S.S.Y. and I.H.C. Investigation: .S.H.O. and I.H.C. Formal Analysis: I.H.C. Writing - Original Draft: S.S.Y. and I.H.C. Writing - Review & Editing: S.S.Y. Visualization: S.H.O. and I.H.C.

Funding

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (No. RS-2022-00165732).

Data availability

The raw data supporting the conclusions of this manuscript will be made available on request to the corresponding author.

Declarations

Ethics approval and consent to participate
All procedures performed in studies involving human participants were in accordance with the Medical Ethics Committee of Yeungnam University Hospital and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All participants provided informed consent prior for DTI and balance ability assessments. The study protocol was approved by the institutional review board of Yeungnam University Hospital (YUMC 2019-04-050-001).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 2 April 2024 / Accepted: 22 August 2024
Published online: 06 September 2024

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