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Association of regional cerebral perfusion impairment with gait and balance performance in dizzy patients using brain perfusion SPECT: Voxel-based analysis of a pilot sample

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ABSTRACT

Objective(s): The purpose of this study was to investigate regional cerebral blood flow (rCBF) reduction in patients with dizziness and perfusion-related clinical impairment using brain perfusion single photon emission tomography (SPECT).
Methods: Thirty-four patients with subjective dizziness and 13 age- and sex-matched healthy controls were studied. Dizziness-related impairments were assessed using the Dizziness Handicap Inventory (DHI) and Short Physical Performance Battery (SPPB). Brain perfusion SPECT scan was acquired from all participants. The carotid intima-media thickness (CIMT) was also measured. Brain perfusion data were qualitatively interpreted in all cases. Voxel-wise analysis was also conducted in 11 patients compared to healthy controls.
Results: Thirty-four patients (mean age=53.8±13.4 years, m/f: 19/15) and 13 age- and sex-matched controls (mean age=51.5±13.1, m/f: 7/6) were included. The dizziness severity was mild in 58.8% (n=20), moderate in 26.5% (n=9), and severe in 14.7% (n=5). Qualitative interpretation of SPECT images showed normal scans in 4 (11.2%) patients and abnormal scans in 30 (88.2%) patients. Patients with dizziness showed a significantly decreased brain perfusion in the precuneus, cuneus, occipital lobe (superior and inferior parts), frontal lobe (inferior and middle parts), temporal lobe, parietal lobe (inferior and superior parts), cerebellum, insula, and putamen nucleus. Based on both qualitative SPECT interpretation and voxel-wise analysis, perfusion defect had a significant association with the total SPPB score and the scores of two sub-domains ($p<0.05$), but not with the DHI ($p>0.05$) score .
Conclusion: The perfusion- and atherosclerosis-related impairments of gait and balance were largely independent of subjective dizziness and dizziness severity. Moreover, this study provided support for contribution of perfusion impairment to the disturbance of gait and balance in older populations along with other pathologic processes.

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Introduction

Dizziness is a common symptom in the general population with a rate of 24% in people older than 72 years old and is considered a major health issue as it increases the risk of falls and related-injuries in the elderly (1). Many factors have been suggested to be involved in development of dizziness including peripheral and central nervous system disorders and systemic comorbidities. However, the origin of

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dizziness in older people is yet to be elucidated (2).

Few studies have evaluated structural brain abnormalities in dizzy patients. One study by Ojala et al. (3) showed that 34% of the subjects with dizziness had at least one abnormality in brain computed tomography or magnetic resonance imaging (MRI), including atrophy, infarction, or demyelination. Furthermore, Ahmad et al. (4) reported similar findings; however, the frequency of detected structural abnormalities in the brain MRI is equal in people with and without dizziness.

Another study found patients with persistent postural-perceptual dizziness (PPPD) had regional hypoperfusion in insular and frontal areas and regional hyperperfusion in the bilateral cerebellar hemisphere compared with controls (5).

Furthermore, the carotid intima-media thickness (CIMT) is a widely used biomarker of atherosclerosis and is considered a strong predictor of future atherosclerotic-related consequences (i.e. myocardial infarction and stroke). Nonetheless, the relationship of CIMT and regional perfusion reduction with clinical disabilities in dizzy patients is not yet clear.

However, the literature is scarce on the role of vascular-related pathologies and perfusion impairment in the development of dizziness and its severity. We hypothesized that perfusion-related biomarkers may have a clinical impact on the patients' performance in gait, balance, and walking abilities and may be associated with dizziness severity. Thus, this study was conducted to investigate the role of brain perfusion in patients with dizziness and explore the clinical significance of perfusion impairment using brain perfusion single photon emission computed tomography (SPECT).

Methods

Patient cohort

First, dizziness was defined as a subjective feeling of fainting, light-headedness, and a sense of non-specific unsteadiness (6). Subjects who experienced intermittent or constant dizziness within the past 6 months or more were included in the study. Between January 2014 and November 2015, 34 patients with subjective dizziness and 13 age- and sex-matched healthy controls were prospectively included. Patients with true vertigo, history of chronic ear disease, use of sedative drugs, history of uncontrolled diabetes mellitus (DM) or hypertension (HTN), heart failure, hypotension, bradycardia, history of loss of consciousness, intra- and extra-cranial arterial stenosis, anemia or hematologic disorders, seizures, confirmed psychological disorders, atrial fibrillation, stroke, and autonomic dysfunction (i.e. depression and schizophrenia) were excluded. All participants provided written informed consent prior to participation. All study procedures were performed in accordance with the Declaration of Helsinki. The study was approved by Ethics Committee of Bushehr University of Medical Sciences.

Clinical and laboratory tests

All participants were visited by an experienced neurologist (>10 years of experience) on image acquisition session, during which a careful history and neurological examination were acquired. Medical history included demographic data and presence of the exclusion criteria or confounding factors such as controlled DM, controlled HTN, and hyperlipidemia. Clinical tests included the Dizziness Handicap Inventory (DHI) and Short Physical Performance Battery (SPPB) (7, 8). DHI is a widely used self-report questionnaire (25 items) that is designed to quantify the impact of dizziness on everyday life. The DHI score (range: 0 to 100) is classified into mild (0-30), moderate (31-60), and severe symptoms (≥61). The DHI is further divided into physical (DHI-p, 28 points), functional (DHI-f, 36 points), and emotional (DHI-e, 36 points) sub-domains. The DHI score is calculated by summing ordinal scale responses yes=4, sometimes=2, no=0 with a higher total score indicating more severe dizziness-related impairment. Previous studies showed good construct validity, high internal consistency, and satisfactory test-retest reliability of the DHI (9).

The SPPB includes the gait speed-4 meters (GS-4), chair stand (ChS), and balance (BL) tests. It has been demonstrated that it can independently predict mobility disability and activities of daily living disability (9). The total SPPB score ranges from 0 (worst performance) to 12 (best performance).

Laboratory tests including complete blood count, fasting blood sugar, blood urea nitrogen, creatinine, electrolytes, lipid profile, liver, and thyroid function tests were performed .

Moreover, CIMT was measured for all participants via a standard protocol using an 8-MHz transducer with a lateral and axial resolution of ≈0.500 and ≈0.385 mm, respectively (SONOLINE G20, SIEMENS) (10). Briefly, CIMT is determined as the distance between the edge of the first and second echogenic lines of the wall of the distal part of the common carotid artery on both sides. The CIMT was measured in the diastolic phase and values more than 5mm were considered abnormal.

Brain perfusion SPECT acquisition protocol

The brain perfusion SPECT was performed about 60 minutes after IV injection of 740 MBq (20 mCi) ^{99m}Tc-ECD using a dual head gamma camera (Philips (ADAC) Vertex Plus) equipped with a low-energy high-resolution collimator. The energy window was set at 140±20%. Projections were acquired with a 64×64 matrix in 64 steps (30 seconds/step). The images were reconstructed using filtered back projection and Butterworth filter (cutoff=0.5, order=5).

Image interpretation and analysis

Qualitative interpretation

Two nuclear medicine specialists that were blind to the patients' data and semi-quantitative results evaluated the images. The cortical and subcortical regions were assessed systematically. The scans were classified as normal (no decreased uptake) and abnormal (mild reduced uptake, moderate reduced uptake, severe reduced uptake). Normal brain SPECT was defined as a homogeneous regional cerebral blood flow (rCBF) with no focal hypoperfusion or observable asymmetry. Brain SPECT scans with a heterogeneous rCBF with focal hypoperfusion or observable asymmetry in at least two slice series were considered abnormal.

Voxel-wise image analysis

The protocol used for voxel-wise analysis of perfusion SPECT was described in details in our previous study (11). Briefly, SPECT images of 11 patients were preprocessed using SPM 12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) and voxel-based morphometry (VBM) (12), part of CAT12 toolbox (http: //dbm. neuro.uni-jena.de/cat/). These images were spatially normalized into a standard SPECT template (based on Montreal Neurologic Institute standard space provided by SPM12) using affine registration followed by non-linear transformation. Afterwards, the count of every voxel was standardized to the mean voxel count of the entire brain employing proportional scaling in order to account for variations in the global CBF. Then, the images were smoothed using an 8 mm full-width half-maximum isotropic Gaussian kernel in order to enhance the signal to noise ratio.

Then, an individual VBM analysis was conducted via comparing every patient with the control group to identify rCBF reduction in each patient separately. The cluster defining threshold was selected at $p<0.001$ and family-wise error (FWE) correction was applied using a minimum cluster size of 50 contagious voxels (13-15).

Statistical Analysis

SPSS for Windows version 18.0 (SPSS Inc., Chicago, Ill., USA) was used for statistical analysis. Regional impairment revealed by qualitative and voxel-wise analysis is expressed as categorial variables (normal vs. abnormal). Categorial and continuous values are expressed as absolute values and mean ±SD, respectively. Chi-square was used to evaluate significant differences in categorial variables. P-values less than 0.05 were considered significant.

Results

In total, 34 patients (mean age=53.8±13.4 years, 19 males and 15 females) with subjective dizziness and 13 age- and sex-matched healthy subjects (mean age=51.5±13.1, 7 males and 6 females) were included. Eight patients had HTN, three had DM, one had hyperlipidemia, and eight patients were smokers. There was no association between SPECT and age, sex, smoking, hyperlipidemia, HTN, and DM in patients with dizziness ($p>0.05$). A summary of the patients' characteristics is presented in Table 1.

Table1. Demographic characteristics and imaging data of participants

	Patients (n=34)	Controls (n=13)
Demographic and clinical data		
Female	15 (44.1%)*	6 (46.1%)*
Male	19 (55.9%)*	7 (53.9%)*
Age (±SD)	53 (±13.4)*	51.5 (±13.1)*
Hypertension	8 (23%)	
Diabetes mellitus	3 (8.8%)	
Hyperlipidemia	2 (5.9%)	
Smoker	8 (23.5%)	
Mild dizziness	20 (58.8%)	
Moderate dizziness	9 (26.5%)	
Severe dizziness	5 (14.7%)	
Imaging data		
CIMT (mm)	0.48 (0.3-0.8)	
QSPECT report		
Normal	4 (11.8%)	13 (100%)
Abnormal		
≤2 areas	17 (50%)	
3 areas	13 (38.3%)	

*There is no statistical significance

SD, standard deviation; CIMT, carotid intima-media thickness; QSPECT, Qualitative SPECT

Correlation of clinical tests

There was no association between the DHI score and neither the total SPPB score nor the scores of two sub-domains (ChS and BL tests) (p>0.05) (Table 2). However, there was a significant association between the dizziness severity and GS-4 score (p=0.01). Clinical scores are summarized in Table 3.

Table2. Clinical test scores of dizziness patients

SPPB score	
Total SPPB score	**Number of patients**
0	2 (5.8%)
1	1 (2.9%)
2	2 (5.8%)
3	1 (2.9%)
4	0
5	3 (8.8%)
6	3 (8.8%)
7	0
8	2 (5.8%)
9	2 (5.8%)
10	3 (8.8%)
11	5 (14.7%)
12	10 (29.4%)

SPPB: short physical performance battery

Table3. Association of different demographic and imaging variables with dizziness and clinical performance

		Clinical gait and balance scores				
		SPPB	GS-4	CHS	BL	DHI
Demographic characteristics	Sex	>0.05	>0.05	>0.05	>0.05	>0.05
	Age	**0.000**	**0.000**	**0.001**	**0.006**	>0.05
	HTN	**0.025**	**0.000**	**0.001**	**0.006**	>0.05
	DM	**0.025**	**0.000**	**0.001**	>0.05	>0.05
	HLP	**0.001**	**0.011**	**0.001**	>0.05	>0.05
	Smoker	>0.05	>0.05	>0.05	>0.05	>0.05
	CIMT	**0.000**	**0.000**	**0.000**	**0.003**	>0.05
Qualitative SPECT	Frontal	>0.05	**0.04**	>0.05	>0.05	>0.05
	Temporal	>0.05	>0.05	>0.05	>0.05	>0.05
	Parietal	**0.04**	>0.05	**0.03**	**0.03**	>0.05
	Occipital	>0.05	>0.05	>0.05	>0.05	>0.05
	Basal ganglia	>0.05	>0.05	>0.05	>0.05	>0.05

Statistically significant associations are shown in bold font

SPPB: short physical performance battery, GS-4: gait speed-4 meters, CHS: chair stand, BL: balance test, HTN: hypertension, DM: diabetes mellitus, HLP: hyperlipidemia, CIMT: carotid intima-media thickness, SPECT: single photon emission computed tomography

Furthermore, the total SPPB score were significantly associated with age, HTN, hyperlipidemia, and DM (p<0.05), but were not associated with sex and smoking (p>0.05). The BL score had a significant association with age and HTN (p<0.05), but did not an association with DM, hyperlipidemia, sex, and smoking (p>0.05). The GS-4 score had a significant association with age, HTN, hyperlipidemia and DM (p<0.05), but it had no correlation with sex (p>0.05). The ChS score showed a significant association with age, HTN, hyperlipidemia, and DM (p<0.05), but it had no association with sex and smoking (p>0.05). Moreover, there was a significant association between CIMT and the total SPPB, GS-4, BL, and ChS score (p<0.05). CIMT had no significant association with the DHI score (p>0.05).

Correlation between qualitative and voxel-wise image analysis

Qualitative assessment of perfusion SPECT scans showed four patients with normal scans and thirty patients with abnormal scans. In total, 17 patients had abnormal perfusion in less than or equal to two brain regions while 13 patients had abnormal perfusion in three brain regions. The qualitative severity of perfusion impairment was moderate in 28 patients and severe in 2 patients. Patients with dizziness showed a significantly decreased brain perfusion in the precuneus, cuneus, occipital lobe (superior and inferior parts), frontal lobe (inferior and middle parts), temporal lobe, parietal lobe (inferior and superior parts), cerebellum, insula, and putamen nucleus. In qualitative assessment of brain perfusion SPECT, no significant association was found between the extent (number of involved area) of rCBF reduction and DHI score (dizziness severity) (p>0.05). Furthermore, parietal rCBF reduction was associated with the total SPPB score as well as the scores of two sub-domains (ChS and BL tests) (p<0.05). Moreover, frontal rCBF reduction was associated with the GS-4 score (p<0.05)

Voxel-wise statistics of SPECT images in 11 patients showed rCBF reduction in all of them (Figure 1, 2). The different regions with rCBF reduction were visualized in all the included patients (Table 4). Voxel-wise analysis showed a significant hypoperfusion in the bilateral cerebellum. Moreover, no significant correlation was found between the DHI score and the extent of rCBF reduction identified by the voxel-based analysis. Voxel-wise analysis of perfusion SPECT showed no association between rCBF reduction and DHI score. Moreover, parietal rCBF reduction was associated with the total SPPB and ChS scores ($p<0.05$), while frontal rCBF reduction was correlated with the GS-4 score. Furthermore, there was no association between the extent of rCBF reduction and neither the total SPPB score nor the scores of sub-domains ($p>0.05$).

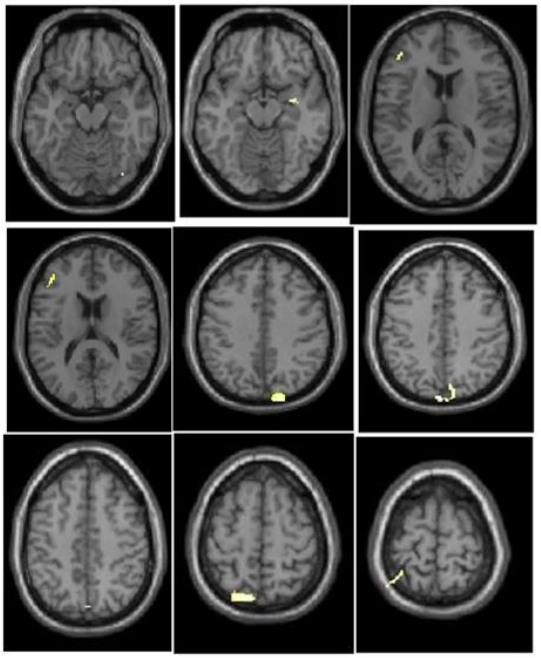

Figure 1. SPM axial slice views in nine patients with dizziness and different significant perfusion reduction regions

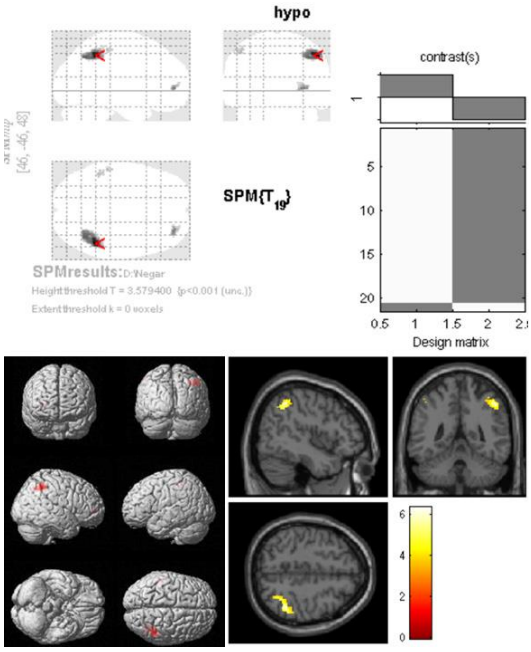

Figure 2. SPM glass and slice brain views of a patient showing regions of decreased tracer uptake in middle frontal and parietal areas

Table4. rCBF reduction in dizzy patients based on voxel-wise analysis

	Anatomic Region	Coordinate		
		x	y	z
Right	Precuneus	0	-76	52
	Cuneus	18	-92	40
	Superior occipital lobe	28	-88	48
	Inferior occipital	36	-78	-16
	Inferior frontal	42	-36	14
	Middle frontal	42	38	14
	Temporal lobe	30	-47	30
	Inferior parietal	-50	-50	44
	Cerebellum	-8	-78	-34
Left	Superior parietal lobe	-12	-72	62
	Precuneus	-22	-76	56
	Cerebellum	-8	-72	-36
	Insula	-58	12	6
	Putamen nucleus	-60	8	2

rCBF, regional cerebral blood flow

Discussion

According to the results, dizziness severity (DHI score) has no correlation with rCBF reduction in the brain perfusion SPECT. Furthermore, our study showed that frontal and parietal lobe hypoperfusion were associated with a lower physical performance. Patients with dizziness showed decreased activity in the precuneus, cuneus, occipital lobe (superior and inferior parts), frontal lobe (inferior and middle parts), temporal lobe, parietal lobe (inferior and superior parts), cerebellum, insula, and putamen nucleus in perfusion study. The CIMT found to be a clinically relevant biomarker in these patients, but it did not contribute to rCBF reduction.

Dizziness is characterized by a marked disturbance of subjective relationships and reflects a discrepancy between internal sensation and external reality (16). It suggests that dizziness is the result of a defect in the central integration of multi-sensory inputs (17). Several kinds of sensory integration errors are encountered in everyday life; nonetheless, the central nervous system usually manages to compensate them via updating the internal representation of the body in the surrounding space. Such sensory conflicts may occur between any of the vestibular, visual or somatosensory systems (16).

It seems that multiple cerebral regions contribute to the development of dizziness; however, the cause of hypoperfusion in this area has not been clarified.

Wurthmann et al. (18) studied patients with persistent postural perceptual dizziness (PPPD) and reported regional gray matter volume reduction in several areas including the temporal cortex, cingulate cortex, precentral gyrus, hippocampus, dorsolateral prefrontal cortex, caudate nucleus, and the cerebellum. Moreover, cortical atrophy was demonstrated in the visual cortex, supplementary motor area and somatosensory processing structures in patients with longer disease durations. It has been demonstrated that PPPD is a common cause of chronic (long-lasting) dizziness (18). Therefore, they provided support for the possible role of structural impairment in pathophysiology of dizziness.

Furthermore, in a case-control study using fMRI with vestibular stimulation, Indovina et al. demonstrated reduced hypoperfusion and impaired connectivity between different brain areas including the superior temporal gyrus, anterior insula/ inferior frontal gyrus, middle occipital gyrus and hippocampus in patients suffering from chronic dizziness (17).

In a case-control study, Ombergena et al found reduced functional connectivity in the right operculum (superior temporal gyrus) and augmented functional connectivity in the occipital pole were seen in patients with visually induced dizziness (VID) (19). In this study, following seed-based analysis, an increased functional connectivity was observed between the associative visual cortex and both middle frontal gyrus and precuneus in VID patients (19).

Na et al. showed that patients with PPPD had lower perfusion of insular and frontal regions and higher perfusion of both cerebellar hemispheres compared to controls (5).

Overall, some involvement regions, that indicated by these studies as well as our study, was common between dizzy patients in functional brain imaging. These areas included cerebellar hemispher, cerebral deep nuclei, temporal lobe, occipital and inferior frontal gyrus. This finding supported that occurrence of dizziness is relatively a generalized cerebral dysfunction, rather than a specific region involvement.

Our study demonstrated that rCBF reduction in parietal and frontal lobes had a significant association with clinical gait and balance measures. In a PET study, Malouin et al. (20) reported that the imagery of the standing posture was associated with the activation of the bilateral dorsal premotor areas. Ouchi et al. (21) showed that the anterior cerebellar lobe and the right visual cortex activation occurred in the standing position compared to the supine posture. In addition, Miyai et al. (22) found that patients with initial supratentorial stroke and impaired standing-balance test had significantly more lesions in the insula and sub-insular white matter compared to the healthy subjects. The results of the present study showed that parietal lobe involvement was associated with more impairment in standing and balance tests, which is in agreement with the current literature.

During the imaginary of bipedal walking, cortical activation was seen in the SMA, bilateral precentral gyrus, left dorsal premotor and in the cingulate motor area (23). Harada et al. (24) found that the prefrontal cortex, supplementary motor area and sensorimotor cortex controlled the gait speed, and the age-related decline in gait and mobility in the elderly may be affected by prefrontal cortex involvement. In another study, Willey et al. (25) found that white matter hyperintensity volume, especially in the anterior cerebral regions including frontal, parietal and anterior periventricular areas, was associated with a lower SPPB score. Wolfson et al. (26) reported that elderly patients with

mobility impairment had more white matter hyperintensity signals on MRI, especially in periventricular frontal and parieto-occipital areas, compared to subjects with normal mobility. As mentioned earlier, the anterior cerebral regions have an important role in mobility and gait speed; therefore, our results are in good agreement with this notion as we demonstrated that patients with frontal hypoperfusion had a lower gait speed.

The dizziness severity, as measured by the DHI score, did not show any association with vascular risk factors and CIMT measure. Similarly, the severity of brain perfusion using semi-quantitative analysis did not show any association with DHI. However, rCBF had an association with gait and balance performance. Therefore, it can be concluded that hypoperfusion- and atherosclerosis-related gait and balance impairments occur largely independent of dizziness and its underlying mechanisms .

This study had several limitations including a relatively small patient cohort, necessitating caution in interpreting the results. Another limitation was inability to perform voxel-based analysis in all dizzy patients because voxel count was not available for the patients whose scans were not analyzed. Another limitation was lack of structural imaging along with perfusion scan to consider possible atrophy-related regional hypoperfusion. These unmet requirements remain to be addressed in future studies.

Conclusions

The data showed that the perfusion- and atherosclerosis-related gait and balance impairments largely occurred independent of subjective dizziness and its severity. Moreover, this study provided evidence for the possible role of perfusion impairment together with other structural and connectivity changes in gait and balance performance of older populations.

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References

1. Iwasaki S, Yamasoba T. Dizziness and Imbalance in the Elderly: Age-related Decline in the Vestibular System. Aging Dis. 2015; 6(1):38-47.
2. Chau AT, Menant JC, Hubner PP, Lord SR, Migliaccio AA. Prevalence of Vestibular Disorder in Older People Who Experience Dizziness. Front Neurol. 2015; 6: 268.
3. Ojala M, Ketonen L, Palo J. The value of CT and very low field MRI in the etiological diagnosis of dizziness. Acta Neurol Scand. 1988; 78(1):26-9.
4. Ahmad N, Wilson JA, Barr-Hamilton RM, Kean DM, MacLennan WJ. The evaluation of dizziness in elderly patients. Postgrad Med J. 1992; 68(801):558-61.
5. Na S, Im JJ, Jeong H, Lee E-S, Lee T-K, Chung Y-A, et al. Cerebral perfusion abnormalities in patients with persistent postural-perceptual dizziness (PPPD): a SPECT study. Journal of Neural Transmission. 2019; 126(2):123-9.
6. Staab JP, Eckhardt-Henn A, Horii A, Jacob R, Strupp M, Brandt T, et al. Diagnostic criteria for persistent postural-perceptual dizziness (PPPD): Consensus document of the committee for the Classification of Vestibular Disorders of the Bárány Society. Journal of Vestibular Research. 2017; 27(4):191-208.
7. Jacobson GP, Newman CW. The development of the Dizziness Handicap Inventory. Arch Otolaryngol Head Neck Surg. 1990; 116(4):424-7.
8. Pavasini R, Guralnik J, Brown JC, di Bari M, Cesari M, Landi F, et al. Short Physical Performance Battery and all-cause mortality: systematic review and meta-analysis. BMC Med. 2016; 14(1):215.
9. Investigators LS, Pahor M, Blair SN, Espeland M, Fielding R, Gill TM, et al. Effects of a physical activity intervention on measures of physical performance: Results of the lifestyle interventions and independence for Elders Pilot (LIFE-P) study. J Gerontol A Biol Sci Med Sci. 2006; 61(11):1157-65.
10. Paul J, Shaw K, Dasgupta S, Ghosh MK. Measurement of intima media thickness of carotid artery by B-mode ultrasound in healthy people of India and Bangladesh, and relation of age and sex with carotid artery intima media thickness: An observational study. J Cardiovasc Dis Res. 2012; 3(2):128-31.
11. Taghizadeh Asl M, Nemati R, Chabi N, Salimipour H, Nabipour I, Assadi M. Brain perfusion imaging with voxel-based analysis in secondary progressive multiple sclerosis patients with a moderate to severe stage of disease: a boon for the workforce. BMC Neurol. 2016; 16(1):79.
12. Ashburner J, Friston KJ. Unified segmentation. Neuroimage. 2005; 26(3): 839-51.
13. Radua J, Mataix-Cols D. Voxel-wise meta-analysis of grey matter changes in

obsessive–compulsive disorder. The British Journal of Psychiatry. 2009; 195(5):393-402.
14. Pan PL, Shi HC, Zhong JG, Xiao PR, Shen Y, Wu LJ, et al. Gray matter atrophy in Parkinson's disease with dementia: evidence from meta-analysis of voxel-based morphometry studies. Neurological Sciences. 2013; 34(5):613-9.
15. Beal DS, Gracco VL, Brettschneider J, Kroll RM, Luc F. A voxel-based morphometry (VBM) analysis of regional grey and white matter volume abnormalities within the speech production network of children who stutter. Cortex. 2013; 49(8):2151-61.
16. Berthoz A, Viaud-Delmon I. Multisensory integration in spatial orientation. Curr Opin Neurobiol. 1999; 9(6):708-12.
17. Indovina I, Riccelli R, Chiarella G, Petrolo C, Augimeri A, Giofre L, et al. Role of the Insula and Vestibular System in Patients with Chronic Subjective Dizziness: An fMRI Study Using Sound-Evoked Vestibular Stimulation. Front Behav Neurosci. 2015; 9: 334.
18. Wurthmann S, Naegel S, Schulte Steinberg B, Theysohn N, Diener HC, Kleinschnitz C, et al. Cerebral gray matter changes in persistent postural perceptual dizziness. J Psychosom Res. 2017; 103: 95-101.
19. Van Ombergen A, Heine L, Jillings S, Roberts RE, Jeurissen B, Van Rompaey V, et al. Altered functional brain connectivity in patients with visually induced dizziness. Neuroimage Clin. 2017; 14: 538-45.
20. Malouin F, Richards CL, Jackson PL, Dumas F, Doyon J. Brain activations during motor imagery of locomotor-related tasks: a PET study. Hum Brain Mapp. 2003; 19(1):47-62.
21. Ouchi Y, Okada H, Yoshikawa E, Nobezawa S, Futatsubashi M. Brain activation during maintenance of standing postures in humans. Brain. 1999; 122 (Pt 2) (2):329-38.
22. Miyai I, Mauricio RLR, Reding MJ. Parietal-Insular Strokes Are Associated with Impaired Standing Balance as Assessed by Computerized Dynamic Posturography. Neurorehabilitation and Neural Repair. 1997; 11(1):35-40.
23. Wang C, Wai Y, Kuo B, Yeh YY, Wang J. Cortical control of gait in healthy humans: an fMRI study. J Neural Transm (Vienna). 2008; 115(8):1149-58.
24. Harada T, Miyai I, Suzuki M, Kubota K. Gait capacity affects cortical activation patterns related to speed control in the elderly. Exp Brain Res. 2009; 193(3):445-54.
25. Willey JZ, Moon YP, Dhamoon MS, Kulick ER, Bagci A, Alperin N, et al. Regional Subclinical Cerebrovascular Disease Is Associated with Balance in an Elderly Multi-Ethnic Population. Neuroepidemiology. 2018; 51(1-2):57-63.
26. Wolfson L, Wei X, Hall CB, Panzer V, Wakefield D, Benson RR, et al. Accrual of MRI white matter abnormalities in elderly with normal and impaired mobility. J Neurol Sci. 2005; 232(1-2):23-7.