Observational Study

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# Central vestibular disorder due to ischemic injury on the parieto-insular vestibular cortex in patients with middle cerebral artery territory infarction

## Observational study

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**Abstract**

Central vestibular disorder is common after middle cerebral artery (MCA) territory infarction. The MCA supplies blood to the parieto-insular vestibular cortex (PIVC), a core region of central vestibular symptoms. We report on patients that sustained injuries of the core vestibular pathway to the PIVC with central vestibular disorder following MCA territory infarction, demonstrated on diffusion tensor imaging (DTI). Nineteen patients with MCA territory infarction and 12 control subjects were recruited. To reconstruct the core vestibular pathway to the PIVC, we defined seed region of interest (ROI) as vestibular nuclei of pons and target ROI as the PIVC. Fractional anisotropy (FA), mean diffusivity, and tract volume were measured. In the affected hemisphere, FA value of the core vestibular pathway to the PIVC revealed significant difference between all patient groups and the control group ($P < .05$). In contrast, patients with symptoms of ataxia only revealed significant decrement of tract volume compared with the control group ($P < .05$). Additionally, subgroup B revealed significant decrement of tract volume compared with that of subgroup A and the control group ($P < .05$). In the unaffected hemisphere, there was no significant difference in all DTI parameters between all patient groups and the control group ($P < .05$). Injury to the core vestibular pathway to the PIVC was demonstrated in patients that revealed typical central vestibular disorder following MCA territory infarction. Analysis of the core vestibular pathway to the PIVC using DTI would be beneficial in clinical evaluation and management of patients with MCA territory infarction.

**Abbreviations:** CST = corticospinal tract, DTI = diffusion tensor imaging, DTT = diffusion tensor tractography, FA = fractional anisotropy, FAC = functional ambulation category, MCA = middle cerebral artery, MD = mean diffusivity, MI = motricity index, PIVC = parieto-insular vestibular cortex, ROI = region of interest, TV = tract volume.

**Keywords:** ataxia, diffusion tensor imaging, middle cerebral artery, parieto-insular vestibular cortex, vestibular nucleus

## 1. Introduction

The middle cerebral artery (MCA) is one of the most complex cerebral arteries, that divides into a number of large branches. The MCA supplies blood to the portion of the frontal lobe, lateral surface of the temporal, parietal lobes, and integrative associative areas and a variety of other critical loci of cerebral function extending from the frontal to occipital lobe over lateral convexity of the brain.[1–4] The most prevalent symptom of MCA territory infarction is hemiparesis; it often results in disabilities in hand function.[5,6] Patients with MCA territory infarction may reveal deficits in posture control and balance.[7–9]

Central vestibular disorder is relatively common after MCA territory infarction.[9] The MCA supplies blood to the Sylvian triangle in the insular region, a major region of the parieto-insular vestibular cortex (PIVC).[10–12] The PIVC is a core region of vestibular input into cortex regions, in the posterior parietal operculum/retroinsular region, extending into posterior parts of the insular lobe.[13,14] Ischemic lesions caused by lacunar or territorial infarctions in the region of PIVC can cause typical vestibular symptoms, such as falling to the side.[15–17]

Recently, diffusion tensor tractography (DTT) studies, derived from diffusion tensor imaging (DTI), identify and visualize core vestibular pathways between vestibular nuclei and PVIC in the human brain.[18–20] However, much is not known about injury of the core vestibular pathway to the PIVC and central vestibular symptoms in patients with MCA territory infarction. In this study, we report patients that sustained injuries to the core vestibular pathway to the PIVC following MCA territory infarction.

## 2. Methods

### 2.1. Subjects

Nineteen patients with MCA territory infarction (12 males, 7 females; mean age, 57.6; range, 37–69) and 12 age-and

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sex-matched control subjects (7 males, 5 females; mean age, 57.4; range, 35–63) with no history of neurological or psychiatric disease were enrolled in this study. Stroke patients were consecutively enrolled from 121 patients with MCA territory infarction according to the following inclusion criteria: (1) first stroke, (2) age: 20 to 70, (3) subacute to chronic stage of infarct, (4) location of infarction confined to the PIVC, and (5) patients that did not reveal corticospinal tract (CST) injury in the affected hemisphere on diffusion tensor tractography (DTT). Patients with severe cognitive problems (Mini-Mental State Examination $<25$) and severe motor weakness (Medical Research Council grade $\leq 2$) were excluded. Data were assembled retrospectively, and the local ethics committee of a university approved the study protocol.

### 2.2. Clinical evaluation

Motor function was evaluated at time of DTI scanning. Motricity index (MI) was used for measurement of motor function of affected upper and lower extremities (maximum score: 100).[21] The Functional Ambulation Category (FAC) scale was used for determination of walking and balancing ability.[22] The FAC was designed for examination of levels of assistance required during a 15-m walk. Six categories are included in the FAC: 0 (non-ambulatory), 1 (needs continuous support from one person), 2 (needs intermittent support from one person), 3 (needs only verbal supervision), 4 (assistance is required on stairs and uneven surfaces), and 5 (can walk independently anywhere). We classified patients into two subgroups according to ability to walk independently; subgroup A: patients that could not walk independently (FAC: 3–5) due to ataxia, subgroup B: patients that could walk independently (FAC: 0–2) without ataxia.

### 2.3. Diffusion tensor imaging

Acquisition of DTI data was conducted at an average of 36 days (range: 17–53) after symptom onset using a 6-channel head coil on a 1.5 T Philips Gyro Scan Intera (Philips, Best, The Netherlands) and single-shot echo-planar imaging. For each of the 32 noncollinear diffusion sensitizing gradients, 67 contiguous slices were acquired parallel to the anterior commissure/posterior commissure line. Imaging parameters were as follow: acquisition matrix = $96 \times 96$; reconstructed matrix = $192 \times 192$; field of view = $240 \times 240\,mm^2$; TR = 10,726 ms; TE = 76 ms; parallel imaging reduction factor (SENSE factor) = 2; EPI factor = 49; $b = 1000\,s/mm^2$; NEX = 1; and slice thickness = 2.5 mm with no gap (acquired voxel size $1.3 \times 1.3 \times 2.5\,mm^3$).

### 2.4. Probabilistic fiber tracking

Diffusion-weighted imaging data were analyzed using the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL; www.fmrib.ox.ac.uk/fsl). Affine multiscale two-dimensional registration was used to correct head motion effect and image distortion due to eddy current. Fiber tracking used a probabilistic tractography method based on a multifiber model, and was applied in this study with tractography routines implemented in FMRIB Diffusion (5000 streamline samples, 0.5 mm step lengths, curvature thresholds = 0.2).

Core vestibular pathway to the PIVC was determined by selection of fibers passing through the seed region and two target regions of interest (ROIs).[20,23] To reconstruct the core vestibular pathway to the PIVC, we placed the seed ROI on the vestibular nuclei at the level of the pons corresponding to Schwalbe's nucleus and Deiters' nucleus, and the target ROI on the PIVC, based on a previous study. For analysis of the CST, the seed ROI was placed on the CST portion of the pontomedullary junction, and target ROI on the CST portion of the anterior mid-pons.[24] Core vestibular pathway to the PIVC and the CST were determined by selection of fibers passing through seed and target ROIs.

There were 5000 samples generated from the seed voxel, and the results were visualized at the threshold of 1 streamline through each voxel for analysis. Fractional anisotropy (FA), mean diffusivity (MD), and tract volume (number of voxel in the reconstructed neural fiber) of the core vestibular pathway to the PIVC were measured. The FA value was calculated from the eigenvalues λ1, λ 2, λ 3 of the diffusion tensor

$$FA = \frac{\sqrt{3}}{\sqrt{2}} \frac{\sqrt{(\lambda_1 - \lambda)^2 + (\lambda_2 - \lambda)^2 + (\lambda_3 - \lambda)^2}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}$$

The MD is an inverse measure of the membrane density and magnitude of water diffusion in tissue;

$$MD = \frac{(\lambda_1 + \lambda_2 + \lambda_3)}{3}$$

### 2.5. Statistical analysis

SPSS software (Released 2011. IBM SPSS Statistics for Windows, Version 20.0. IBM Corp., Armonk, NY) was used for data analysis. Chi-square test was used for determination of difference in incidence of central vestibular symptoms between patient subgroups. The non-parametric Kruskal–Wallis with post-hoc Mann–Whitney test was used to determine differences in values of DTI parameters between patients and normal subjects. Null hypotheses of no difference were rejected if *P*-values were less than .05.

## 3. Results

In classification according to walking ability, 11 (57.9%) of 19 patients belonged to subgroup A (FAC: 3–5) and 8 to subgroup B (FA: 0–2). All patients in both subgroups revealed intact integrity of the CST in affected and unaffected hemispheres. Subgroup A patients revealed central vestibular signs without the symptom of ataxia; vertigo (n = 1, 9.0%), dysarthria (n = 3, 27.3%), and dysphagia (n = 2, 18%). Conversely, patients in subgroup B exhibited typical ataxia with several vestibular sings; vertigo (n = 6, 75.0%), dysarthria (n = 3, 37.5%), and dysphagia (n = 4, 50.0%). Chi-square test revealed that only vertigo revealed significant difference between patient subgroups ($P < .05$).

In the affected hemisphere, FA value of the core vestibular pathway to the PIVC revealed significant difference between all patient groups and the control group ($P < .05$). However, there was no difference between subgroup A and subgroup B ($P < .05$). In addition, subgroup B revealed significant decrement of tract volume compared with that of subgroup A and the control group ($P < .05$). In contrast, MD value did not reveal significant difference between all patient groups and the control group ($P < .05$). In the unaffected hemisphere, there was no significant difference in all DTI parameters between all patient groups and the control group ($P < .05$) (Fig. 1 and Table 1).

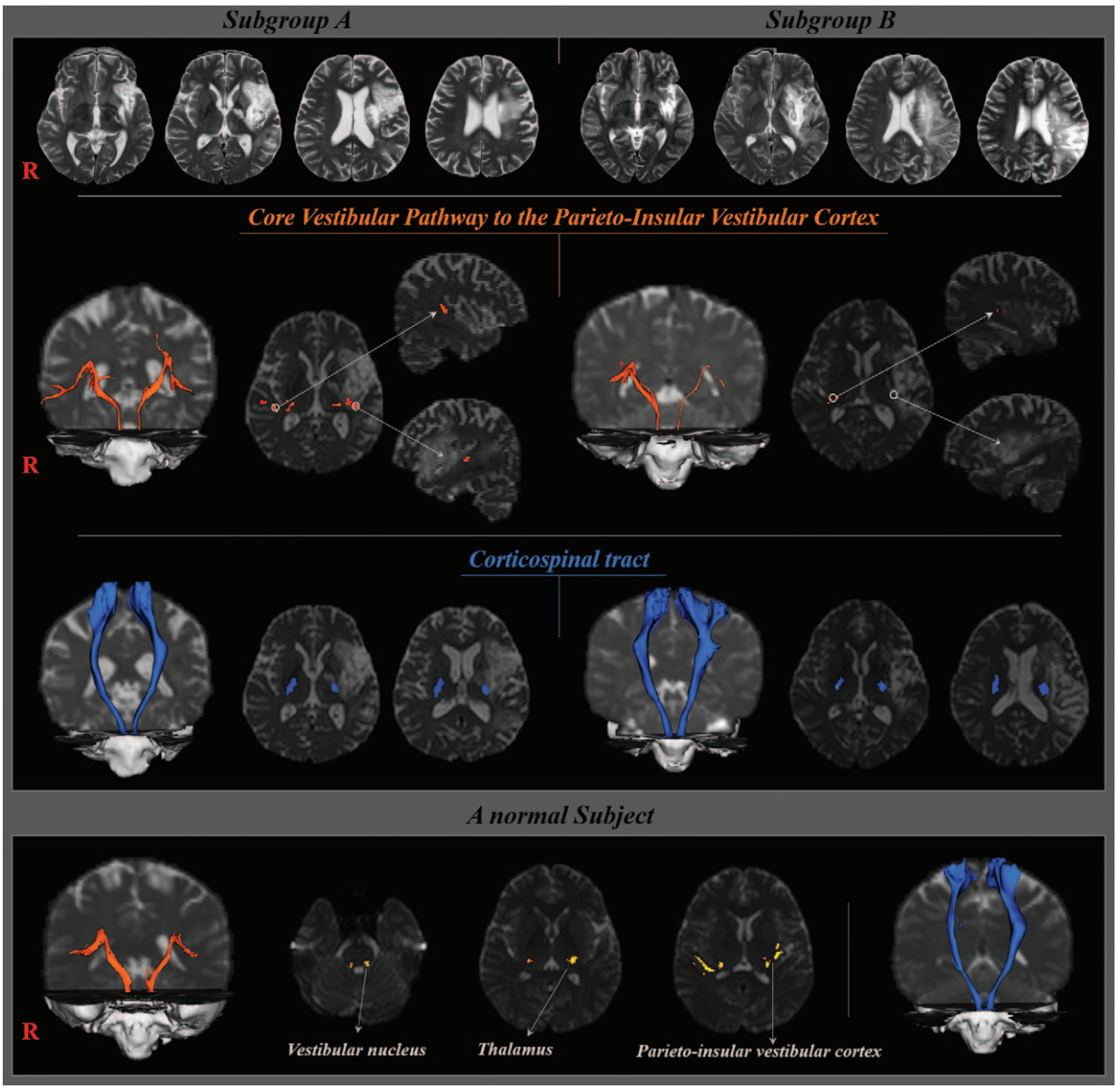


**Figure 1.** T2-weight image of a patient in subgroup A (59-year-old male) and in subgroup B (52-year-old male). Diffusion tensor tractography demonstrates the association of the core vestibular pathway to the Parieto-insular vestibular cortex and the corticospinal tract in subgroup A, subgroup B and normal subject (51-year-old male).

**Table 1**

**The Comparison of the diffusion tensor image parameter of core vestibular pathway to the Parieto-insular vestibular cortex between patients and normal control group.**

| | Affected hemisphere | | | Unaffected hemisphere | | |
|---|---|---|---|---|---|---|
| | FA | MD | TV | FA | MD | TV |
| Group A | 0.38 ± 0.03 | 0.93 ± 0.09 | 385.82 ± 263.54 | 0.44 ± 0.03 | 0.87 ± 0.07 | 552.45 ± 263.67 |
| Group B | 0.38 ± 0.09 | 0.97 ± 0.13 | 163.50 ± 133.22 | 0.46 ± 0.05 | 0.82 ± 0.03 | 397.00 ± 236.26 |
| | FA | | MD | | TV | |
| Control | 0.45 ± 0.03 | | 0.87 ± 0.09 | | 532.46 ± 150.43 | |
| | *P*-value | | | *P*-value | | |
| A vs B | .545 | .442 | .016* | .778 | .600 | .717 |
| A vs Control | .000* | .078 | .012* | .587 | .409 | .334 |
| B vs Control | .004* | .057 | .000* | .357 | 1.000 | .357 |

FA = fractional anisotropy, MD = mean diffusivity, TV = tract volume nonparametric Kruskal–Wallis test with post hoc Mann–Whitney test was used for comparison of diffusion tensor parameters between patient groups and normal control.

* $P < .05$.

## 4. Discussion

In this study, among 121 consecutive patients with MCA territory infarction, we enrolled 19 patients that revealed significant ischemic injury on the PIVC; 11 patients (subgroup) without symptom of ataxia, and 8 patients with typical ataxia. In the affected hemisphere, FA value of the core vestibular pathway to the PIVC was lower in both patient groups, compared with normal control subjects. Conversely, patients with significant central vestibular syndrome (group B) revealed significant decrement of tract volume in affected hemisphere compared with patients with less central vestibular syndrome (group A) and the normal control group. FA value indicates degree of directionality of water diffusion. It represents the white matter organization and includes degree of directionality and integrity of white matter microstructures, such as axon, myelin, and microtubule. Tract volume is determined by the number of voxels contained within a neural tract.[25] Consequently, decrement of the FA value in the affected hemisphere indicated injury of the core vestibular pathway to the PIVC following MCA territory infarction. Additionally, we consumed that degree of the decrement of the tract volume can be concerned with more severe symptoms of central vestibular syndrome.

PIVC is a core region of vestibular input into cortical regions in central vestibular system, and is involved in processing of self-motion perception, estimation of verticality, and processing of visual motion, particularly motion coherent with gravity.[23,26,27] Especially, PIVC activity is correlated with motion of the head in space (vestibular), twisting the neck (proprioceptive), and motion of a visual target.[28] Patients with central vestibular disorders commonly present neurologic symptoms including loss of consciousness, ataxia, postural instability, confusion, headache, incoordination, and visual deficits.[29–32] Additionally, pathology of PIVC among major regions of the central vestibular system influences integration and processing of sensory input from the vestibular, visual, and somatosensory systems.[33,34]

MCA territory infarction can lead to typical vestibular symptoms, such as dizziness, imbalance, and diminished functional independence, and reflect a disturbance of the central vestibular pathways in the brain.[9,35–37] In 2013, Pires et al[38] reported most acute stroke patients (92.5%) had nonrotational dizziness (52.5%), vertigo (22.5%), imbalance (12.5%), and/or vertigo and imbalance (5%). In long-term stroke, most patients (72.5%) had imbalance (65.0%) and/or nonrotational dizziness (7.5%). The authors demonstrated that dizziness and imbalance were more prevalent in long-term carotid territory stroke patients; in this regard, the patient with central vestibular pathology more often present with complaints of disequilibrium and ataxia. Recently, Dieterich and Brandt[39] reported that PIVC regions could be associated with acute transient rotational vertigo or dizziness with unsteadiness in the 10 cases of cortical vertigo due to MCA territory infarctions. Cerebral imaging revealed involvement of PIVC regions in almost all stroke patients with acute vertigo. Hence, PIVC regions are frequently affected by ischemia and insula involvement is associated with large MCA territory infarction

In terms of core vestibular pathway to the PIVC, de Waele et al[40] recorded short latency period in several cortical areas using vestibular evoked potentials, linked to the vestibular nerve in patients with unilateral vestibular impairment. Data revealed that vestibular-cortical pathways project to the PIVC regions ipsilaterally but to the contralateral hemisphere. In 2016, Kirsch et al[20] used DTT to observe a congruent functional and structural link between the vestibular nuclei and the ipsilateral and contralateral PIVC in healthy individuals. The study revealed that vestibular systems have bilateral organization based on ipsilaterally and contralaterally ascending pathways and at least 4 crossings—3 in the brainstem and 1 in the vestibular cortex. Therefore, the lesion in PIVC due to the MCA territory infarction can cause disorders of central vestibular function, such as hemispatial neglect, extremity, and facial weakness/numbness, imbalance, and gait abnormalities.

In conclusion, we investigated injury of the core vestibular pathway to the PIVC that revealed typical central vestibular disorder following MCA territory infarction. Decreased tract volume of the core vestibular pathway to PIVC is related to central vestibular disorder in patients with MCA territory infarction. Additionally, we believe analysis of the core vestibular pathway to the PIVC using DTI may be beneficial in clinical evaluation and management of patients with MCA territory infarction. In particular, early detection of injury to the core vestibular pathway to PIVC would be beneficial for prognosis and planning of intervention strategies for patients with MCA territory infarction. However, several limitations of this study should be considered. First, DTI analysis is operator dependent and, due to fiber complexity and crossing fiber effect, it may underestimate fiber tracts. Second, we could not precisely define the location of ROIs because of the small size and cramped state of vestibular nuclei. Third, we could not reconstruct the contralateral vestibular pathway. Therefore, further studies including more neural tracts related to vestibular function would be necessary.

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