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Acute vestibular disorders and vertebrobasilar stroke – Prospective evaluation of diagnostic algorithms and lesion-symptom relationship

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Ken Maximilian Möhwald

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Munich, 18 March 2025	Ken Möhwald
Place, date	Signature doctoral candidate

For my beloved family

"If you are going through hell, keep going."

- unknown, attributed to Winston Churchill

Table of content

List of abbreviations

Abbreviation	Meaning
ABCD2 score	Age, Blood pressure, Clinical features, Duration of symptoms, Diabetes mellitus score
AIS	Acute Imbalance Syndrome
AUPV	Acute Unilateral Peripheral Vestibulopathy
AVS	Acute Vestibular Syndrome
BMBF	Bundesministerium für Bildung und Forschung (Federal Ministry of Education and Research)
BPPV	Benign Peripheral Positional Vertigo
CATCH2 score	Central signs, Age, Triggers, Cover test, Head impulse test, History of vertigo or dizziness score
CN	Cranial Nerve
CT	Computed Tomography
DHI	Dizziness Handicap Inventory
DSGZ	Deutsches Schwindel- und Gleichgewichtszentrum (German Center for Vertigo and Balance Disorders)
DWI	Diffusion-Weighted Imaging
EMVERT study	EMergency VERTigo, dizziness and balance disorders study
EQ-5D-5L	EuroQol - 5 dimensions - 5 levels scale
EQ-VAS	EuroQol Visual Analogue Scale
ER	Emergency Room
FGA	Functional Gait Assessment
FLAIR	Fluid-Attenuated Inversion Recovery
HINTS	Head Impulse test, Nystagmus, Test of Skew
HIT	Head Impulse Test
INO	Internuclear Ophthalmoplegia
MNI space	Montreal Neurological Institute space
MRI	Magnetic Resonance Imaging
mRS	modified Rankin Scale
MSZ	Münchner Studienzentrum (Munich Trial Center)

NIHSS	National Institutes of Health Stroke Scale
PB	Pusher Behavior
SVV	Subjective Visual Vertical
TOF	Time Of Flight angiography
TUG	Timed Up and Go test
VAS	Visual Analogue Scale
vHIT	video Head Impulse Test
VLSM	Voxel-based Lesion-Symptom Mapping
VOG	Video-Oculography
VOR	Vestibulo-Ocular Reflex

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1 Publications

Publication I

Protocol for a prospective interventional trial to develop a diagnostic index test for stroke as a cause of vertigo, dizziness and imbalance in the emergency room (EMVERT study)

Ken Möhwald, Stanislavs Bardins, Hans-Helge Müller, Klaus Jahn, Andreas Zwergal

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Publication II

A prospective analysis of lesion-symptom relationships in

acute vestibular and ocular motor stroke

Andreas Zwergal*, **Ken Möhwald***, Elvira Salazar-López, Hristo Hadzhikolev,

Thomas Brandt, Klaus Jahn, Marianne Dieterich

*** shared first authorship**

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Publication III

Lateropulsion in right-sided stroke:

Brain anatomical correlates of severity and duration

Elvira Salazar-López, Carmen Krewer, Jeannine Bergmann,

Ken Möhwald, Friedemann Müller, Klaus Jahn

Journal of Neurologic Physical Therapy 48.1 (2024): 38-45.

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additional relevant publications

Schwindel in der Notaufnahme

Andreas Zwergal, **Ken Möhwald**, Marianne Dieterich

Der Nervenarzt 88.6 (2017): 587-596.

Modern machine-learning can support diagnostic differentiation of central and peripheral acute vestibular disorders

Seyed-Ahmad Ahmadi, Gerome Vivar, Nassir Navab, **Ken Möhwald**, Andreas Maier, Hristo Hadzhikolev, Thomas Brandt, Eva Grill, Marianne Dieterich, Klaus Jahn, Andreas Zwergal

Journal of Neurology 267 (2020): 143-152.

Health-related quality of life and functional impairment in acute vestibular disorders

Ken Möhwald, Hristo Hadzhikolev, Stanislavs Bardins, Sandra Becker-Bense, Thomas Brandt, Eva Grill, Klaus Jahn, Marianne Dieterich, Andreas Zwergal

European Journal of Neurology 27.10 (2020): 2089-2098.

Determinants of functioning and health-related quality of life after vestibular stroke

Franziska Schuhbeck, Ralf Strobl, Julian Conrad, **Ken Möhwald**, Patricia Jaufenthaler, Klaus Jahn, Marianne Dieterich, Eva Grill, Andreas Zwergal

Frontiers in Neurology 13 (2022): 957283.

2 Contribution to the publications

2.1 Contribution to paper I

Protocol for a prospective interventional trial to develop a diagnostic index test for stroke as a cause of vertigo, dizziness and imbalance in the emergency room (EMVERT study)

Ken Möhwald, Stanislavs Bardins, Hans-Helge Müller, Klaus Jahn, Andreas Zwergal

BMJ Open 7.10 (2017): e019073.

I contributed to all aspects of this paper. Prof. Dr. Andreas Zwergal and Prof. Dr. Klaus Jahn recruited me to prepare, build and conduct this study as an investigator and clinical project manager. This study was supported by the German Federal Ministry of Education and Health ("Bundesministerium für Bildung und Forschung, BMBF") within the funding of the German Center for Vertigo and Balance Disorders ("Deutsches Schwindel- und Gleichgewichtszentrum, DSGZ").

At the very beginning, I underwent a formal clinical trial investigator training at the Munich Trial Center (MSZ). Together with AZ and KJ, we discussed and finalized the inclusion and exclusion criteria as well as the study flow. In cooperation with statistician HHM, the statistical analysis was elaborated. Based on the previous experience and research conducted at the DSGZ, we then prepared the mobile diagnostic device setup including a mobile computer system, video-oculography, posturography and bucket test for the subjective visual vertical. Dr. Stanislavs Bardins had set up and adjusted the devices, which I thoroughly tested and optimized for patient measurements together with SB, AZ and KJ. I designed and composed the standardized digital and paper protocols for the informed patient consent, clinical scores and data collection.

After completion of formal requirements, AZ and I initiated the study. In the course of the study, I screened patients in the emergency room. If the inclusion and exclusion criteria were met, I reached out to the patients explaining the study and obtaining the informed patient consent. I examined patients during the acute phase of the disease with the mobile setup, which could be challenging and prolonged, when the symptoms were severe. The data collection and handling were primarily carried out by me. In the course of the study, we extended the clinical investigators regarding the recruitment of patients with me recruiting most of the patients.

I drafted the first version of the manuscript, which AZ, KJ and I carefully revised. After getting approval from all co-authors, we submitted the final manuscript for publication. AZ and I presented the research topic as well as the results of the study on national and international conferences. Throughout the years, I gave oral presentations and presented scientific posters at conferences, seminars, symposia and workshops.

Overall, I was involved in this study from start to finish with drafting, designing, initiating, conducting, analyzing and discussing the study and its findings, as it progressed.

2.2 Contribution to paper II

A prospective analysis of lesion-symptom relationships in acute vestibular and ocular motor stroke

Andreas Zwergal*, **Ken Möhwald***, Elvira Salazar-López, Hristo Hadzhikolev, Thomas Brandt, Klaus Jahn, Marianne Dieterich *** shared first authorship**

Frontiers in Neurology 11 (2020): 822.

I was engaged in every aspect of the study and paper. This study was set up within the context of paper I with the specific question to analyze lesion-symptom relationships. Together with AZ, KJ, TB and MD, we conceptualized the study and its design.

At the beginning, I was solely responsible for screening, recruiting and measuring patients, before extending the investigator team. HH and I shared most of the clinical workup from then on, while also being responsible for further data processing and management. Overall, we screened 840 patients with 351 patients being included in the study with a standardized clinical assessment and 333 receiving the follow-up measurements. This included the daily screening of patients (presentation of new patients with acute symptoms in the emergency room, inpatient ward, regular consultations with emergency physicians). When a suited patient was identified, informed patient consent was obtained and I performed a standardized detailed neuro-vestibular testing through the mobile device. As I measured patients presenting to the emergency room with acute symptoms, this could be challenging due to impaired standing/walking abilities, nausea with vomiting or premature termination of the assessment.

Overall, I recruited and measured the majority of patients in this study. HH and I obtained the MRI scans of each of the 47 patients and processed the radiological data for analysis. AZ and ESL did the initial part of the statistical analysis, then, I was involved in the analysis and interpretation of data. Regular meetings were held between the co-authors to discuss the data and prepare the manuscript. AZ drafted the first version of the manuscript. I was engaged in the further revision process, before we sent out the manuscript for further revision and finalization. All authors read and approved the final version of the manuscript.

To reflect the extensive work we had conducted, AZ and I shared first authorship for equal contribution to the study. Within this scope, I had a higher contribution to the patient recruitment and data management process, whereas AZ had contributed more to the statistical analysis and submission of the paper. AZ and I presented and discussed the study results in several national and international conferences and seminars.

In summary, here as well, my contribution to the paper included the entire study process. I conceptualized, initiated and conducted the study as outlined above, processed, analyzed and discussed the data, before drafting and revising the manuscript.

2.3 Contribution to paper III

Lateropulsion in right-sided stroke: Brain anatomical correlates of severity and duration

Elvira Salazar-López, Carmen Krewer, Jeannine Bergmann, **Ken Möhwald**, Friedemann Müller, Klaus Jahn

Journal of Neurologic Physical Therapy 48.1 (2024): 38-45.

In this study, I was involved in the analysis of lesions together with ESL. After receiving radiological data of patients (MRI or CT scans) in the subacute to chronic phase after stroke (within 1 to 25 weeks after symptom onset), the images were further processed and normalized. Utilizing MRIcron, I delineated lesions of each patient blinded for the clinical information without knowing the lesion side, size or patient's symptoms. ESL had performed the same drawing task independently of me. The aim was to test the reliability of the manual lesion detection and drawing. Thus, the hand drawn lesions between ESL and me were compared via intraclass correlation analysis with high interrater reliability.

Further analyses were conducted by the co-authors. After the initial manuscript draft, I was consulted in the analysis and interpretation of data during the manuscript revision process, before finally reading and approving the submitted publication.

3 Introductory summary

Background

Acute vertigo and dizziness are among the most frequent chief complaints in the emergency room (ER) [1-3]. After headache and motor deficits, vertigo and dizziness rank among the third most common symptoms in the ER accounting for about 12-13% of acute neurological consultations [3, 4]. Although most patients will have benign diagnoses such as benign paroxysmal positional vertigo (BPPV) or acute unilateral peripheral vestibulopathy (AUPV), some will suffer from serious diagnoses such as stroke in 4-20% of cases, which requires immediate action [1, 5].

Diagnosing stroke as a cause of vertigo, dizziness and balance disorders can be challenging. During the course of clinical assessments in a single center, up to 43% of the initial suspected diagnoses were corrected with 6% changing from benign to serious causes [5]. Around 9% of cerebrovascular diagnoses are usually being missed at initial ER presentation, especially when the symptoms are non-specific, mild or transient [6]. Many patients with vertebrobasilar stroke do not have additional focal neurological deficits, which could lead to possible misdiagnosis [6, 7].

Patients with acute vestibular syndrome (AVS) present with acute vertigo with spontaneous nystagmus, postural imbalance and nausea/vomiting [8]. The differentiation of peripheral (particularly AUPV) and central (particularly vertebrobasilar stroke) etiology has been studied thoroughly in this patient cohort [9, 10]. In a serious of studies, the HINTS criteria (Head Impulse test, Nystagmus, Test of Skew) in AVS have been established with a normal head impulse test, direction changing spontaneous nystagmus and skew deviation in the test of skew indicating a central etiology [11-13]. In the initial specific cohort, this clinical test had high sensitivity of 100% and specificity of 96% in AVS for stroke, which is even more sensitive

than early MRI for stroke detection [13]. The horizontal head impulse test (HIT) was introduced in 1988 by Halmagyi and Curthoys to identify the loss of horizontal semicircular canal function and seems to be the single best bedside test to distinguish peripheral from central etiologies (AUPV vs. pseudoneuritis, e.g., due to vertebrobasilar stroke) [13, 14]. Still, the quality of horizontal HIT performance and interpretation might vary based on clinical experience and specialization of the examining physician: Whereas the sensitivity and specificity seem to be similarly high, when performed by neurologists (sensitivity 96.7%, specificity 94.8%), the diagnostic acuity decreases drastically, when performed by a broader cohort of emergency physicians (sensitivity 83%, specificity 44%) [15]. Thus, an instrument-based video head impulse test (vHIT) via quantitative video-oculography (VOG) can further improve the clinical assessment in AVS [16-18].

However, in clinical practice, many patients will not present with AVS but with a broader range of symptoms in the absence of spontaneous nystagmus, in which the diagnostic accuracy of HINTS deteriorates [6, 17, 19]. For patients with acute onset of vertigo, dizziness and unsteadiness without spontaneous nystagmus, new terms like acute dysbalance syndrome or more commonly acute imbalance syndrome (AIS) are being coined [20-22]. Acute symptoms like vertigo, dizziness, double vision and gait imbalance can vary in intensity and duration, which complicate the diagnostic workup and lead to misdiagnoses [5, 6]. Furthermore, there seems to be a diagnostic gap within the first 48 hours after symptom onset, in which MRI examination can show falsely negative results in around 50% of the cases for small cerebral lesions below 10 mm [23-25]. After 48 hours, delayed MRI can still detect the vertebrobasilar stroke in AVS [23]. This underlines the importance of early and proper clinical assessment to detect stroke as a cause of AVS and AIS. Although established index tests and clinical scores

are currently being evaluated for AIS, a unified diagnostic approach for AVS and AIS patients is still missing [19, 21].

Therefore, we conducted several studies with the aim to answer following questions:

a) What is the optimal diagnostic algorithm to approach patients presenting with acute vertigo, dizziness, double vision and postural imbalance in the emergency room?
b) Can we develop a universal clinical index test to identify vertebrobasilar stroke for a broad range of patients presenting with acute vertigo, dizziness and imbalance including both cohorts of acute vestibular syndrome and acute imbalance syndrome?
c) What is the lesion-symptom relationship of patients presenting with acute vertigo, dizziness and double vision due to vertebrobasilar stroke or postural misalignment due to hemispheric stroke? Which lesions lead to which symptoms? How is the relationship between lesion and symptom quality, intensity and duration?

Prospective diagnostic evaluation of patients presenting with acute vertigo and dizziness

The first paper lays the groundwork for the detailed clinical and instrument-based diagnostic workup of acute vertigo and dizziness patients in the ER within the EMVERT study [20]. Patients with acute onset of vertigo, dizziness, double vision or imbalance within the last 24 hours were screened and recruited from the clinical routine workup in the ER. Patients were not included in the study, if they showed clear peripheral (e.g., BPPV in diagnostic positional maneuvers, recurrent attacks in known Menière's disease or vestibular migraine) or central signs (e.g., hemiparesis, hemihypesthesia, hemiataxia in stroke patients). Only patients with unclear etiology with symptoms lasting more than 10 minutes and the age of 18 years or older were included. This included patients with AVS as well as AIS. The study flow is depicted in Figure 1.

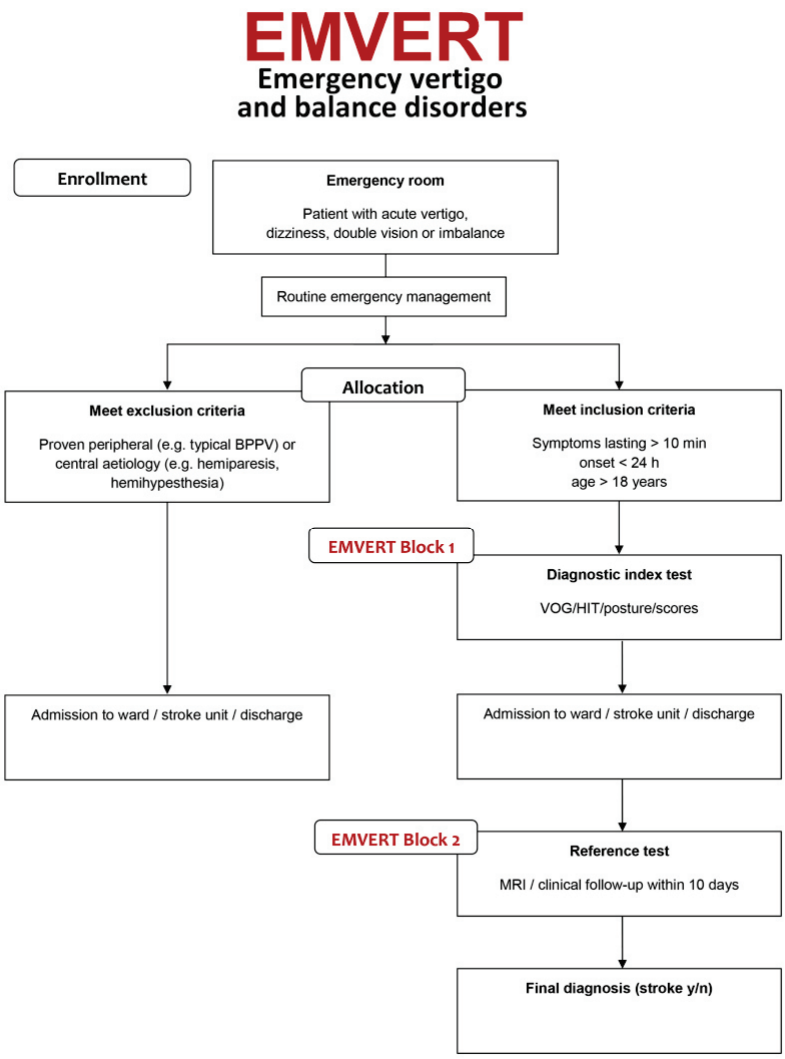

Figure 1: EMVERT study flow [20]

Abbreviations: BPPV Benign Paroxysmal Positional Vertigo, VOG Video-Oculography, HIT Head Impulse Test, MRI Magnetic Resonance Imaging.

Patients, who fulfilled the inclusion criteria, were included in the study after informed consent and underwent a standardized neuro-otology and oculomotor assessment using a mobile device setup, which was thoroughly tested and established beforehand.

The diagnostic assessment included among others:

A) Video-oculography (device: EyeSeeCam, Fürstenfeldbruck in Germany) with a protocol for evaluation of spontaneous nystagmus, gaze holding, saccades, smooth pursuit, vestibulo-ocular reflex suppression and skew deviation.

B) vHIT through VOG and inertial sensors to test the vestibulo-ocular reflex (VOR).

C) Mobile posturography (device: Wii Balance Board, company: Nintendo, Kyoto in Japan) with detection of postural sway and during sensory and motoric perturbation (stance with eyes open/closed, tandem stance with eyes open/closed).

D) Subjective visual vertical (SVV) was measured through the mobile bucket test [26].

E) A broad range of clinical scores and tests were used to address different areas of interest.

- Symptoms and risk scores: ABCD2 Score [27], modified Rankin Scale (mRS) [28, 29], National Institutes of Health Stroke Scale (NIHSS) [30, 31], Dizziness Handicap Inventory (DHI) [32], Visual Analogue Scale (VAS) for symptom intensity.
- Posture, gait and dynamic stability: Timed Up and Go test (TUG) [33], Functional Gait Assessment (FGA) [34].
- Health-related quality of life measures: EuroQol - 5 dimensions - 5 levels scale (EQ-5D-5L), EuroQol Visual Analogue Scale (EQ-VAS) [35].

The final diagnosis of stroke was determined by a second assessment within 10 days. Patients received an MRI as a reference test with predetermined sequences: T1-weighted fast spoiled gradient echo, T2-weighted imaging including brainstem fine slicing (3 mm), T2*-weighted imaging, fluid-attenuated inversion recovery (FLAIR), diffusion-weighted imaging (DWI) with brainstem fine slicing (3 mm) and time of flight angiography (TOF). Furthermore, during this observation period, patients were followed up clinically to determine, whether new symptoms emerged, that were indicative of a clear central or peripheral etiology.

Based on the collected and organized dataset of the study, further research questions were answered and studies have been published [17, 36-39]. The results of the main study with a proposed diagnostic index test called CATCH2 for AVS and AIS are currently being finalized and prepared for publication.

The lesion-symptom relationship in acute vertebrobasilar stroke

Within the context of the previous described setting, in this second study, 840 patients with acute vertigo, dizziness and double vision in the ER were screened, 351 (mean age 60.1 ± 16.7 years, 46.6% female) were included with complete initial examination with 333 receiving the follow-up assessment [36]. Here, acute stroke was detected in 49 patients by MRI with 2 patients being excluded from the analysis due to bilateral lesions (mean age of stroke patients 64.7 ± 13.0 years). Forty-seven patients (5.6% of screened patients, 13.4% of included patients, 38.3% female) received the voxel-based lesion-mapping analysis (VLSM). The flow diagram is outlined in figure 2.

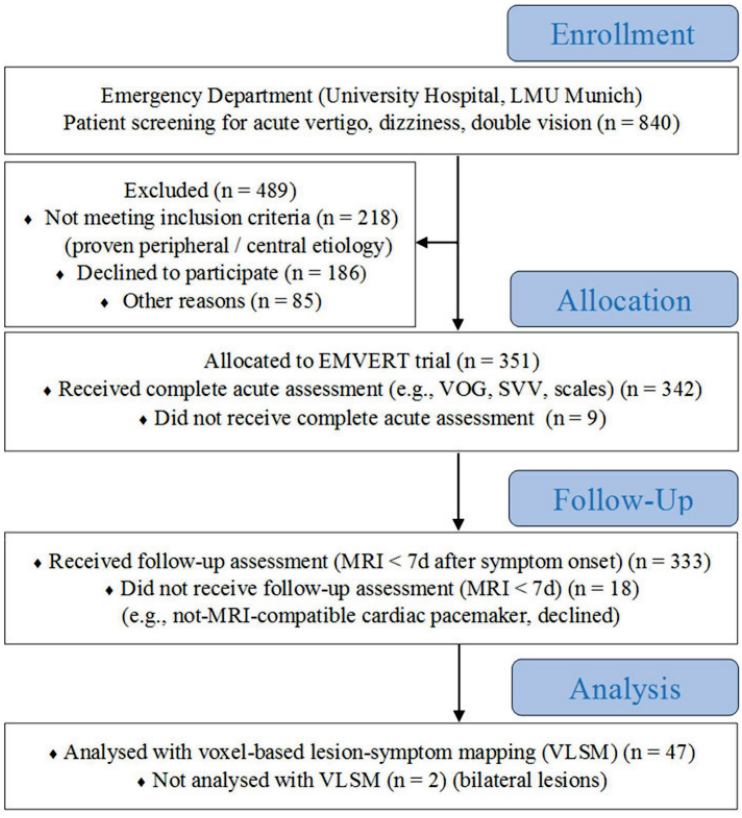

Figure 2: Study flow diagram and assessments of the EMVERT lesion mapping study [36]. Creative Commons Attribution 4.0 International (CC BY 4.0), https://creativecommons.org/licenses/by/4.0/.
Abbreviations: MRI Magnetic Resonance Imaging, SVV Subjective Visual Vertical, VLSM Voxel-Based Lesion-Symptom Mapping, VOG Video-Oculography.

Patients with acute stroke complaint of dizziness (42.6%, 66.7 ± 14.2 years), vertigo (40.4%, 63.5 ± 13.2 years) and double vision (17.0%, 61.9 ± 8.0 years) as the leading symptoms. Age did not differ significantly between the groups. Accompanying vertigo or dizziness were reported in 51% of patients with double vision as a chief complaint. AVS was present in 45% of the patient cohort and more commonly reported in patients with vertigo (74%) in contrast to patients with dizziness (30%). HINTS criteria indicated a central etiology in 93% of vertigo patients compared to 83% of patients complaining of dizziness. HIT was normal in 95% of vertigo, 85% of dizziness and 63% of double vision cases. The main causes for double vision were INO in 37% of patients, skew deviation in 25% of patients and oculomotor nerve (CN III), trochlear nerve (CN IV) and abducens nerve (CN VI) palsy (in each case 13% of patients). Vestibular as well as ocular motor characteristics are summarized in table 1.

Table 1: Vestibular as well as ocular motor characteristics of stroke patients [36].

	Vertigo (%)	Dizziness (%)		Double Vision (%)
SPN	74	30	Oculomotor palsy	13
HINTS central	68	25	Trochlear palsy	13
HIT normal	95	85	Abducens palsy	13
Skew deviation	26	20	INO	37
SVV	68	65	Skew deviation	25

Presented characteristics are shown in % of all acute patients with the respective chief complaint. AVS was more frequently observed in stroke patients with vertigo compared to patients with dizziness as a chief complaint. HINTS criteria have been applied irrespectively of AVS. Creative Commons Attribution 4.0 International (CC BY 4.0), https://creativecommons.org/licenses/by/4.0/.
Abbreviations: AVS Acute Vestibular Syndrome, HINTS Head Impulse test, Nystagmus, Test of Skew, HIT Head Impulse Test, INO Internuclear Ophthalmoplegia, SPN Spontaneous Nystagmus, SVV Subjective Visual Vertical.

Blinded for clinical information, MRI stroke lesions were drawn in manually on pre-defined sequences (DWI, T2-weighted) via MRIcron. Radiological data were processed and normalized to the Montreal Neurological Institute (MNI) space. Utilizing the non-parametric mapping statistical package, voxel-based lesion-symptom mapping (VLSM) was performed. We applied t-test for numerical variables as well as Liebermeister test for dichotomous variables with correction for multiple comparison including false discovery rate correction for the assessment of behavioral score differences between patterns of lesioned and non-lesioned voxels [40].

The analysis led to following main findings: There were large overlaps in the cerebellar hemisphere between patients with vertigo and dizziness. Patients complaining of vertigo showed stroke lesions rather in the medial cerebellar areas like nodulus, uvula, biventer lobule (layers 7b, 8, 9), whereas patients complaining of dizziness showed stroke lesions in the lateral and superior cerebellar areas (layers 8, crus 1, 2). Pontomesencephalic brainstem lesions were associated with double vision. Overlap lesion plots are shown in figure 3. Symptom intensity as well as symptom duration varied largely across lesions sites and between patients. Furthermore, medial cerebellar lesions were accompanied with higher symptom intensity and duration. Patients with vertigo as well as medial cerebellar lesions had worse health-related quality of life and functioning outcomes. Cortical or thalamus lesions were rare and showed less pronounced symptoms of shorter duration.

In conclusion, for acute vestibular and ocular motor stroke, a mere lesion-symptom topography is an insufficient clinical approach. Accounting for only symptom quality, intensity as well as duration is not enough to differentiate central from peripheral etiologies in AVS and AIS. Lesions in the cortex, thalamus and cerebellar hemispheres are associated with transient, mild

or unspecific symptoms prone to misdiagnosis. Therefore, a thorough neuro-ophthalmological and -otological clinical examination is essential in patients presenting with acute vertigo, dizziness and double vision in the absence of other central or peripheral symptoms.

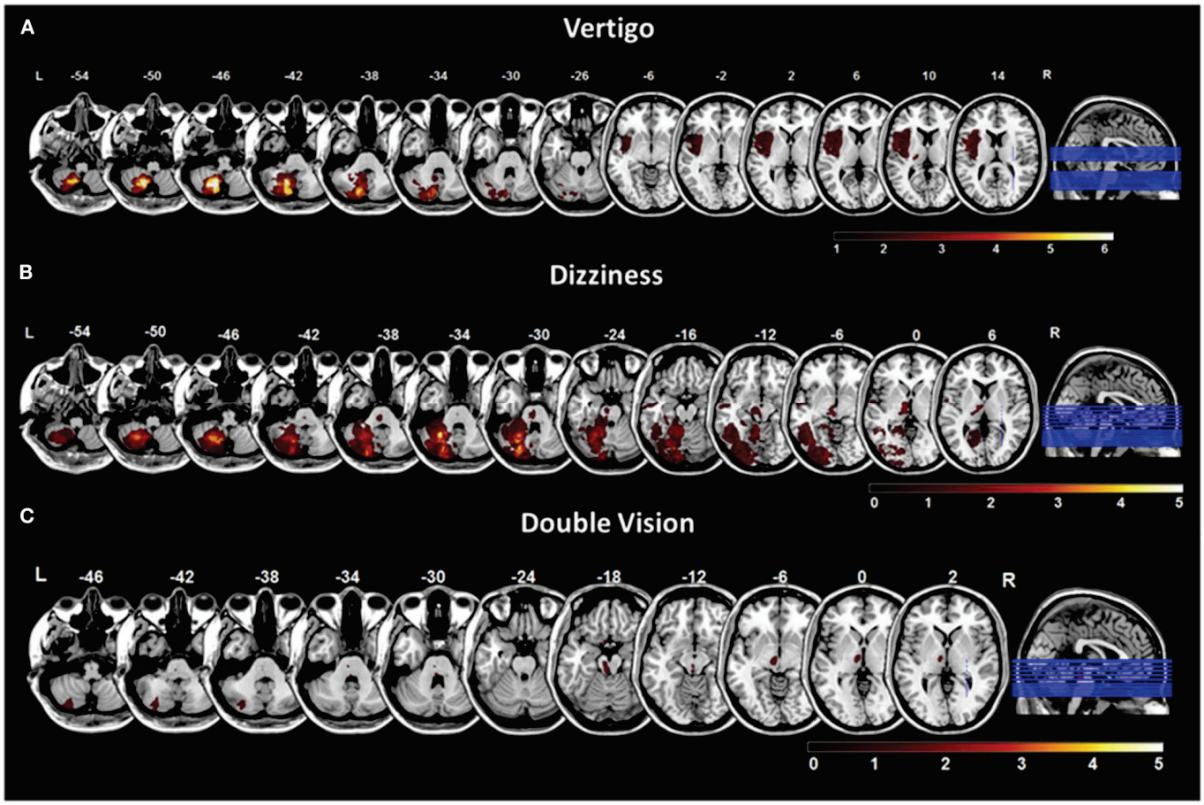

Figure 3: Lesion mapping analysis with overlap lesion plots for chief complaints [36].
Overlap lesion plots are depicted for the chief complaints of (A) vertigo, (B) dizziness and (C) double vision color coded from dark red (0) to bright yellow (5). MNI space coordinates are applied. Creative Commons Attribution 4.0 International (CC BY 4.0), https://creativecommons.org/licenses/by/4.0/.
Abbreviations: L left, MNI Montreal Neurological Institute, R right.

The lesion-symptom relationship in patients with pusher syndrome and right-sided stroke

Finally, the third publication is another lesion-mapping analysis exploring a different topic of lesion-symptom relationship in patients with lateropulsion and right-sided stroke [41]. Following unilateral left or right-sided brain damage, pusher behavior (PB) or lateropulsion is a clinical syndrome with disturbance of the body orientation and postural verticality perception. Affected patients push themselves away from the healthy unparalyzed side usually resisting any correction efforts of the tilted body posture [42]. Lateropulsion has to be considered in the

recovery after stroke and leads to prolonged neurorehabilitation and increased health care costs [43-45].

For this study, clinical and radiological data from 3 studies on the topic of pusher behavior were pooled with the aim to analyze the lesion-symptom relationship in correlation with lateropulsion severity and duration [46-48]. Altogether, 74 patients with stroke and right-sided brain lesions were included. For severity, 49 patients with PB and 25 patients without PB, for duration, 22 patients with PB were analyzed utilizing VLSM.

There are three main findings:

1) Patients with PB had higher lesion volume compared to patients without PB.

2) There were no statistically significant results in the PB severity analysis.

3) Duration analysis showed, that prolonged PB duration was associated with areas in the multisensory network: Namely, frontal (inferior frontal gyrus), temporal (hippocampus, temporal cortex), inferior parietal (inferior parietal gyrus, supramarginal gyrus, angular gyrus) and white matter as well as fiber tract areas (sagittal stratum, superior longitudinal fasciculus).

Particularly, the last finding shows that brain areas play a key role in PB duration, which are related to attention, spatial cognition and long-term memory. This might explain the better outcomes in intervention studies, which rely on implicit, non-declarative knowledge rather than explicit, conscious learning (e.g., robot-assisted gait training vs. visual cues) [47-49]. In conclusion, lateropulsion is a complex disorder affecting various areas of the multisensory network, which can prolong symptom duration and should be considered in the design of future rehabilitation programs.

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BMJ Open

Protocol for a prospective interventional trial to develop a diagnostic index test for stroke as a cause of vertigo, dizziness and imbalance in the emergency room (EMVERT study)

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ABSTRACT

Introduction Identifying stroke as a cause of acute vertigo, dizziness and imbalance in the emergency room is still a clinical challenge. Many patients are admitted to stroke units, but only a minority will have strokes. This imposes a heavy financial burden on the healthcare system. The aim of this study is to develop a diagnostic index test to identify patients with a high risk of having a stroke as the cause of acute vertigo and imbalance.

Methods and analysis Patients with acute onset of vertigo, dizziness, postural imbalance or double vision within the last 24 hours lasting for at least 10 min are eligible to be included in the study. Patients with clinically proven peripheral or central aetiology will be excluded. In the emergency room, all enrolled patients will undergo standardised neuro-ophthalmological/physiological testing (including video-oculography, mobile posturography, measurement of subjective visual vertical) (EMVERT block 1). Within 10 days, standardised MRI will be performed as a reference test to identify stroke (EMVERT block 2). Data from EMVERT block 2 will be compared with results from block 1 in order to devise a diagnostic index test with a high specificity and sensitivity to predict the risk of stroke in the emergency room.

Ethics and dissemination The study was approved by the ethics committee of the University of Munich and will be conducted according to the Guideline for Good Clinical Practice, the Federal Data Protecting Act and the Helsinki Declaration of the World Medical Association in its recent version. Study results are expected to be published in international peer-reviewed journals and will be presented at international conferences.

Trial registration number German Clinical Trial Register: DRKS00008992; Universal trial number: U1111-1172-8719); pre-results.

Strengths and limitations of this study

- The study population includes a broad range of patients presenting with acute vertigo and balance disorders instead of selecting specific subgroups, resembling the daily practice in the emergency room.
- Patients will undergo standardised video-oculography measurements during the acute phase of symptoms, as symptoms might be transient or fluctuate in acute vertigo and balance disorders.
- The assessment includes measurements of posture, since postural deficits are present in most patients with acute vertigo and balance disorders and isolated postural deficits might be present in posterior circulation strokes.
- This study is conducted in only one emergency room of a large university hospital in Germany.
- The instrument-based measurements require a mobile device, which has to be made available to the investigator.

INTRODUCTION

Acute vertigo, dizziness, balance and gait disorders are among the most frequent symptoms in the emergency department.[1 2] In the case of the typical acute vestibular syndrome (AVS), that is, acute vertigo, nausea/vomiting and gait unsteadiness in association with spontaneous nystagmus, clinical differentiation between peripheral vestibulopathy and central brainstem or cerebellar stroke is sufficiently well established.[3 4] The origin and diagnostic approaches in AVS have been well studied. Most patients with AVS have peripheral vestibular causes, 25% infratentorial strokes.[3 5] Distinguishing both can be challenging, as 50% of patients who had stroke will not have additional focal neurological deficits, and emergency imaging with CT is not sensitive enough (16%).[6] Seventeen per cent of patients with ischaemic stroke in the posterior inferior cerebellar artery present with the single symptom of vertigo and dizziness.[7] Three bedside vestibular and ocular motor findings can differentiate central from peripheral causes of AVS: the head

impulse test, nystagmus and test-of-skew (HINTS).[3 4] The horizontal head impulse test (h-HIT) is the single best predictor of stroke in AVS[8]; a bilaterally normal result in AVS increases the OR of stroke 18-fold. However, the h-HIT is technically demanding to perform and interpretation varies with expertise. Performance of the video-recorded head impulse test (vHIT) considerably helps to distinguish between peripheral and central causes of AVS.[9]

In clinical practice, most patients in the emergency room do not present with AVS but with symptoms such as isolated vertigo, dizziness and unsteadiness of stance or gait without nystagmus—in the following called acute dysbalance syndrome (ADS). In this case, the clinical diagnosis is more challenging. Differential diagnoses include peripheral vestibular disorders, stroke below the level of the vestibular nuclei, in the cerebellum (hemispheric/vermal), thalamus (thalamic astasia) or hemispheres (pushing behaviour, tilt of subjective postural vertical) as well as intoxications, acute polyneuropathy, peripheral skeletomuscular, cardiovascular (eg, exsiccosis) or psychiatric problems.[1] In ADS, HINTS signs are often absent. There have been no systematic studies, which define a common diagnostic approach in ADS.

Therefore, we aim to develop a diagnostic index test to identify stroke in patients presenting with AVS and ADS by use of prospective instrument-based vestibular, ocular motor and balance testing of consecutive patients presenting to the emergency room with acute vertigo/dizziness, double vision, gait instability or falls.

METHODS AND ANALYSIS

Trial flow

Adult patients with an acute onset of vertigo, dizziness, postural imbalance, gait instability or double vision with symptoms in the last 24 hours and a duration of at least 10 min will be screened prospectively for inclusion in this single-centre trial within business hours. The emergency room physician on duty first sees the patients and carries out routine emergency diagnostic workup and therapy as usual. Then the EMVERT physician is consulted, who performs a structured medical history and standardised clinical examination with an emphasis on ocular motor and vestibular function tests and stance and gait assessment. On the basis of the clinical workup by the EMVERT physician, patients with a clinically proven peripheral or central aetiology will be identified and excluded from the study and further treated in the routine clinical workflow (see figure 1). The following criteria are used to define a syndrome as proven peripheral or central:

Proven peripheral aetiology

- Typical signs (ie, nystagmus in the plane of the semicircular canal involved on diagnostic positioning manoeuvres) and symptoms of BPPV.

Proven central aetiology

- Clinical signs of acute hemiparesis, hemihypesthesia or hemiataxia.
- The remaining patients with unclear peripheral or central aetiology of symptoms will be defined as the subpopulation of interest for the EMVERT trial to establish the diagnostic index test (see figure 1). At the start of the trial, the EMVERT physician carries out the workup of EMVERT block 1 (see box 1), which consists of the following parts:
- Video-oculography (EyeSeeCam, Fürstenfeldbruck, Germany) recordings of skew deviation, spontaneous nystagmus, gaze holding, smooth pursuit, saccades and vestibulo-ocular reflex (VOR) suppression. Specification of quantified parameters: degree of skew deviation, nystagmus slow-phase velocity with and without fixation in five different eye positions (including straight ahead) and with provocation, smooth pursuit gain, saccade latency, peak velocity and metric, VOR gain during suppression. Testing will be done with a mobile device located in the emergency department. In order to identify pathological deviations of video-oculography parameters age-matched and gender-matched normal values will be implemented in a cohort of 80 healthy subjects.
- Video-oculography and inertial head sensors (EyeSeeCam) to document head impulses. Specification of quantified parameters: vestibulo-ocular reflex gain, compensatory and anticompensatory quick eye movement latency, peak velocity, amplitude. Testing will be done with a mobile device located in the emergency room. Normal values will be derived from testing a matched healthy control group.
- Posturography based on accelerometry of postural sway (Wii Balance Board, Nintendo, Kyoto, Japan). Specification of quantified parameters: normalised path length, root mean square and peak-to-peak values during upright bipedal standing with eyes open/closed, upright tandem standing with eyes open/closed and during postural perturbation by pull test in anterior–posterior and mediolateral direction. Testing will be done with a mobile device located in the emergency room. For comparison, healthy controls will be measured with the same setup.
- Testing of the subjective visual vertical (SVV) using the bucket test.[10] Specification of quantified parameters: mean values of 10 repetitions in a pseudorandomised order will be calculated. Pathological deviations of SVV are considered, if mean values are >2.5 or <–2.5 degrees.
- Scores: Dizziness Handicap Inventory, Functional Gait Assessment, Timed Up and Go test, frequency and severity of falls, attacks of vertigo, dizziness, imbalance, National Institutes of Health Stroke Scale, modified Ranking Scale for patients with stroke, European Quality of Life scale-five dimensions-five levels (EQ-5D-5L), visual analogue scales (VAS), EuroQol-Visual Analogue Scales (EQ-VAS) and ABCD2

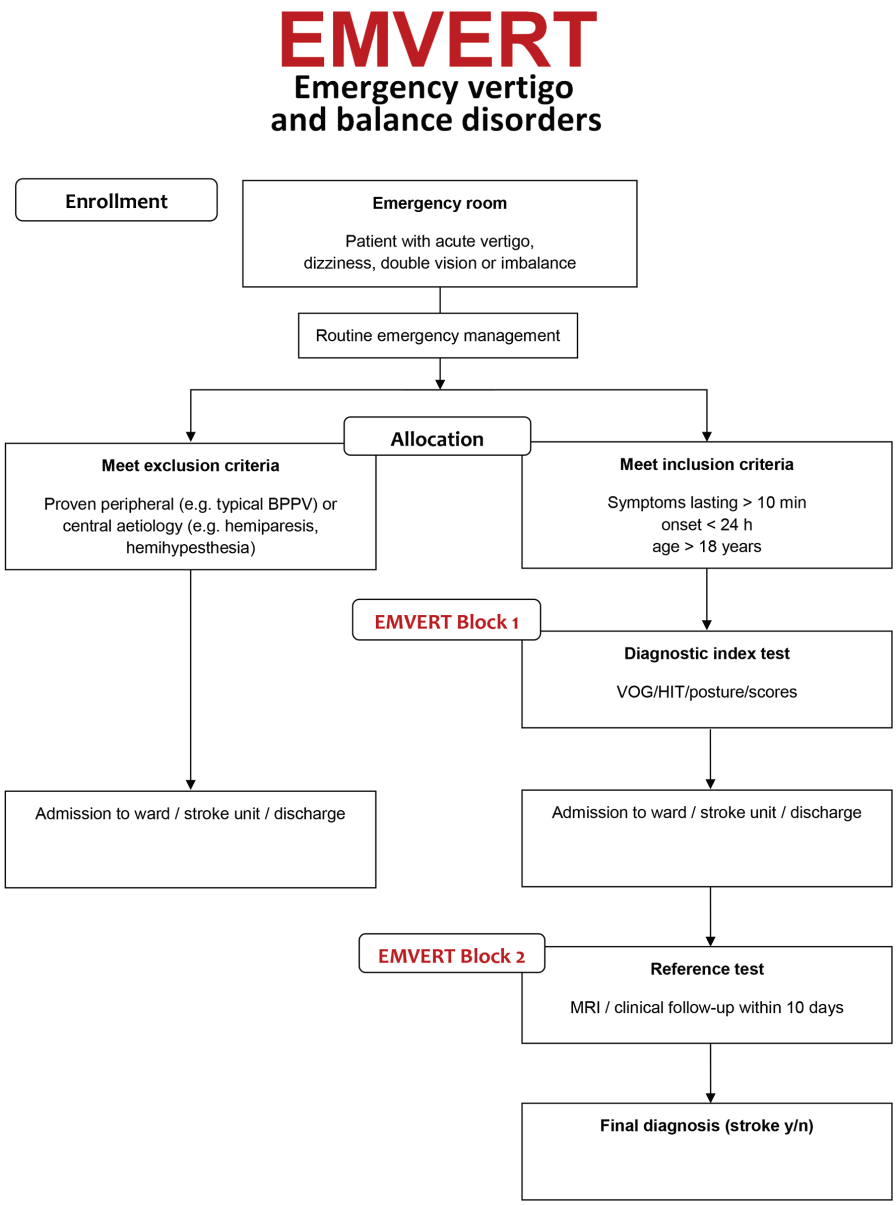

Figure 1 EMVERT trial flow. Study interventions are shown in grey. Proven peripheral or central aetiology ('no stroke') includes BPPV with typical findings on diagnostic positioning (nystagmus in the plane of the semicircular canal involved), Menière's disease with typical recurrent attacks according to Barany Society criteria and other pre-existent disorder with typical presentation in the emergency situation. BPPV, benign paroxysmal positioning vertigo; HIT, head impulse test; VOG, video-oculography.

score (Age, Blood pressure, Clinical features, Duration, Diabetes).[11]

- Afterwards, the patients in the EMVERT subpopulation will be admitted to the ward or discharged and undergo EMVERT block 2 within 10 days, which is used as the reference test.

EMVERT block 2 will include the following tests (see box 2)

- MRI 3T. Specification: the protocol includes diffusion-weighted images including brainstem fine slicing (3 mm), Fluid-attenuated inversion recovery-sequence, T2-weighted images including brainstem fine slicing (3 mm), T2*-weighted images, 3D-T1-weighted sequences (fast spoiled gradient echo 1 mm isovoxel) and time of flight angiography. All images are evaluated by two specialised neuroradiologists for the presence of ischaemic stroke or bleeding.
- Clinical observation: Specification: during the observational period of the trial, the dynamics of symptoms will be assessed. If a new symptom occurs which clarifies the aetiology as clinically proven peripheral or central (see above), this observation is included as a definite criterion for or against stroke in the reference test.

Frequency and scope of study visits

- Entry (t0; within 24 hours after emergency room consultation): confirming eligibility, obtaining

Box 1 Summary of neuro-ophthalmological and posturographic measurements as well as scaling and scoring performed at the beginning of the trial in the emergency room (EMVERT block 1). These parameters are the basis for the elaboration of a future diagnostic index test to identify risk of stroke in patients with acute vertigo and balance disorders

EMVERT block 1

Video-oculography
- Saccades
- Smooth pursuit
- Fixation nystagmus
- Spontaneous nystagmus
- Vestibulo-ocular reflex suppression
- Video head impulse test
- Head-shaking nystagmus

Cover test

Measurement of subjective visual vertical—bucket test

Mobile posturography
- Eyes open
- Eyes closed
- Tandem, eyes open
- Tandem, eyes closed

Scores and scales
- ABCD2 score
- Dizziness Handicap Inventory
- European Quality of Life scale-five dimensions-five levels, EuroQol-Visual Analogue Scale
- Functional Gait Assessment
- Modified Rankin Scale
- National Institutes of Health Stroke Scale
- Timed Up and Go Test
- Visual Analogue Scale

informed consent, structured history taking, standardised neurological workup, scores and scales, video-oculography, video head impulse test, posturography, SVV (see EMVERT block 1).

- Study MRI (t1; preferably after day 3 and within 10 days after t0) and clinical assessment of peripheral or central signs (see EMVERT block 2).

Box 2 MRI protocol and clinical assessment of peripheral or central signs to identify stroke (EMVERT block 2) within 10 days after inclusion (EMVERT block 1)

EMVERT block 2

MRI with 3T scanner
- Diffusion-weighted imaging including brainstem fine slicing (3 mm)
- Fluid-attenuated inversion recovery
- T1-weighted fast spoiled gradient echo, 1 mm isovoxel
- T2-weighted imaging including brainstem fine slicing (3 mm)
- T2*-weighted imaging
- Time of flight angiography

Clinical assessment of peripheral or central signs

Proposed sample size/power calculation

The sample size of 1000 patients to be allocated is planned on the basis of a recruitment period of 2 years. This sample size will allow robust modelling with up to four parameters in a multivariate logistic regression model assuming an a priori stroke probability of 4% in the study population (based on an analysis of patient presentations to the Munich University Hospital Emergency Room from the year 2010). All efforts will be undertaken to avoid dropouts. Of the 1000 patients to be allocated to the trial, a subpopulation of 200 patients (20%) is expected, in which the origin of symptoms can be classified as peripheral or central (stroke) to a high degree of certainty (as compared with an a priori probability of 4% of having stroke) based on the routine clinical testing. For the remaining subpopulation of 800 patients (80%), in which the a priori probability of a stroke is estimated to be 5%, the development and evaluation of a diagnostic index test for stroke is a central aim in order to guide the pragmatic decisions on further imaging and prophylactic therapy. The primary statistical two-sided test for detection of a likelihood ratio of more than 19/4=4.75 in case of a positive index test (LR+) has a power of about 80% to detect an alternative value LR+=247/37=6.6757 in a sample size of 800 patients. Given an a priori probability of pre=5%, the positive predictive value is post+=20% for LR+=4.75, post+=25% for LR+=19/3=6.333 (power 67.2%), post+=26 for LR+=247/37=6.6757 and post+=30% for LR+=57/7=8.1429 (power 98.6%). In a sample of 1072 patients (instead of 800 patients), a power of 80% would be reached for LR+=19/3=6.3333, 382 patients would be sufficient for LR+=57.7=8.1429.

Outcome measures

The primary endpoint (stroke or no stroke) will be determined on the basis of the reference test. Clinical and neurophysiological test results from EMVERT block 1 (see above) will be combined to create a diagnostic score for the risk of stroke (predictor). A first outcome measure will be the a priori probability of stroke. The second outcome measure will be sensitivity and specificity, the pair of diagnostic quality of the index test. The index test will be determined based on the receiver operating characteristic curve according to the diagnostic score with specific cut-off values for sensitivity and specificity in order to develop a stroke detection test with high sensitivity and acceptable specificity.

Methods against bias

MRI as part of the reference test will be performed after neurophysiological testing in order to ensure that the reference test is not known at the time of data acquisition for the index test. Data analysis will be done independently of data acquisition with the analyst being unaware of the reference test results. Adherence to standard procedures will be assured by training and supervision of both the emergency physicians and the EMVERT physician. Possible confounders and covariates, namely, gender, age,

previous psychotherapy, duration of symptoms and socioeconomic status will be recorded and taken into account in the analysis and in the data interpretation.

ETHICS AND DISSEMINATION

The study was approved by the ethics committee of the University of Munich on 23 February 2015 (57-15). The trial was prospectively registered in the WHO International Clinical Trial Registry Platform and the German Clinical Trial Registration on 06/08/2015 (main ID: DRKS00008992, Universal trial number U1111-1172-8719) and is currently in the pre-results stage. The diagnostic intervention has a good chance of improving the detection rate of serious causes of the acute symptoms, compared with the usual standard care. Thus, the patient will profit from the additional tests like video-oculography with quantitative head impulse testing. The inconvenience for the patient, in contrast, is minimal. No necessary intervention including medication will be delayed or withheld from patients during the entire study period. The trial will be conducted according to the Guideline for Good Clinical Practice (GCP), the Federal Data Protecting Act and the Helsinki Declaration of the World Medical Association in its recent version (revision of Fortaleza, Brazil, October 2013). The good research practices for cost-effectiveness and the measures used do not involve additional risks (routine techniques). Study results are expected to be published in international peer-reviewed journals and will be presented at international conferences.

DISCUSSION

Although AVS and ADS are very common in the emergency situation, predictive parameters to identify patients who suffer from stroke are sparse, in particular for ADS. Numerous patients are admitted to stroke units, receive extensive diagnostics and long-term treatment without evidence that they will benefit from these procedures.[12] There is a need to define objective parameters and supportive instrument-based tests that immediately help to predict whether a patient is suffering from stroke. Thus, the aim of our prospective cohort trial is to identify sets of parameters and tests that can be used in the emergency department to predict the cause and the outcome of acute symptoms. For AVS, we aim to reproduce and validate the HINTS criteria in a large prospective patient cohort and identify possible sensitive additional ocular motor signs. For ADS, a new diagnostic index test for identification of stroke should be established. The innovative aspects of the EMVERT trials are as follows. (1) To enrol a large-scale unselected population of patients with acute vertigo and balance disorders instead of selecting specific subgroups. Thereby, this study better resembles the daily practice in the emergency rooms. (2) To systematically apply video-oculography protocols in the emergency room in the acute phase of symptoms. As pathological ocular motor signs may be transient or fluctuate in acute vertigo and balance disorders early instrument-based documentation is critical to enable a definite diagnosis to be made.[13] It is well known that clinical estimation, for example, of the head impulse test may be inaccurate in certain causes, even if performed by a neuro-otological specialist.[14] Covert saccades may be overlooked.[15] As video-oculography systems become more widely available—at least in larger hospitals—translation of pin-pointed protocols into clinical practice seems possible. (3) To include objective measurements of posture. Postural deficits are present in a majority of patients with acute vertigo and balance disorders. Posterior circulation stroke can manifest with isolated postural deficits.[16]Standardised assessment of sway and falling tendency have been largely neglected in previous trials on this topic.

Definition of a standardised diagnostic index test for identification of stroke in acute vertigo and balance disorders is an important prerequisite for future multicenter validation. The long-term perspective will improve treatment of affected patients, define treatments tailored to patients' needs and develop standards of practice including aspects of cost-effectiveness.

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Contributors KM, KJ and AZ drafted the manuscript. HHM was responsible for the statistical analysis. SB established the methods used in the study. In addition, KM, SB, KJ and AZ planned, coordinated and conducted the study. KJ and AZ are the coordinating principal investigators, KM is the investigator and clinical project manager, SB is responsible for the mobile device used in the study. All authors read and approved the final manuscript.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval The study was approved by the ethics committee of the University of Munich on 23 February 2015 (ID: 57-15). For inclusion in the study, all patients need to provide written informed consent.

Provenance and peer review Not commissioned; peer reviewed for ethical and funding approval prior to submission.

Data sharing statement The EMVERT study is an ongoing prospective trial. Study data will be available through the German Center for Vertigo and Balance Disorders (DSGZ) after the end of patient recruitment.

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ORIGINAL RESEARCH
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A Prospective Analysis of Lesion-Symptom Relationships in Acute Vestibular and Ocular Motor Stroke

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Background: Diagnosing stroke as a cause of acute vertigo, dizziness, or double vision remains a challenge, because symptom characteristics can be variable. The purpose of this study was to prospectively investigate lesion-symptom relationships in patients with acute vestibular or ocular motor stroke.

Methods: Three hundred and fifty one patients with acute and isolated vestibular or ocular motor symptoms of unclear etiology were enrolled in the EMVERT lesion trial. Symptom quality was assessed by the chief complaint (vertigo, dizziness, double vision), symptom intensity by the visual analog scale, functional impairment by EQ-5D-5L, and symptom duration by daily rating. Acute vestibular and ocular motor signs were registered by videooculography. A standardized MRI (DWI-/FLAIR-/T2-/T2*-/3D-T1-weighted sequences) was recorded within 7 days of symptom onset. MRIs with DWI lesions were further processed for voxel-based lesion-symptom mapping (VLSM).

Results: In 47 patients, MRI depicted an acute unilateral stroke (13.4%). The chief complaints were dizziness (42.5%), vertigo (40.4%) and double vision (17.0%). Lesions in patients with vertigo or dizziness showed a large overlap in the cerebellar hemisphere. VLSM indicated that strokes in the medial cerebellar layers 7b, 8, 9 were associated with vertigo, strokes in the lateral cerebellar layer 8, crus 1, 2 with dizziness, and pontomesencephalic strokes with double vision. Symptom intensity and duration varied largely between patients. Higher symptom intensity and longer duration were associated with medial cerebellar lesions. Hemispheric lesions of the cortex were rare and presented with milder symptoms of shorter duration.

Conclusions: Prospective evaluation of patients with acute vestibular or ocular motor stroke revealed that symptom quality, intensity and duration were not suited to differentiating peripheral from central etiologies. Lesions in the lateral cerebellum, thalamus, or cortex presented with unspecific, mild and transient symptoms prone to being misdiagnosed.

Keywords: vertigo, dizziness, double vision, acute vestibular syndrome, stroke

INTRODUCTION

Vertigo, dizziness or double vision may be symptoms of an acute cerebral ischemia or hemorrhage (1). Overall, 4–10% of patients in the emergency department (ED) presenting with vertigo and balance disorders suffer from stroke (2). Sixteen percentage of diplopia-related ED visits result from stroke or TIA (3). Patients with vestibular or ocular motor stroke often have no additional focal neurological deficits and therefore are at greater risk of being misdiagnosed (4, 5).

Cerebral lesions presenting with vertigo, dizziness, or double vision mostly involve vestibular and ocular motor circuits in the brainstem and cerebellum, whereas thalamo-cortical networks are affected only occasionally (6, 7). The reason for this lesion distribution can be found in the functional anatomy of the bilaterally organized central vestibular system, which converts direction-specific signals of each labyrinth into more global position-in-space signals along the ascending vestibular projections (8). Consequently, the vestibular syndromes of the lower brainstem present with severe vertigo and ipsilesional falling tendency, while lesions of the parieto-insular vestibular cortex may cause "higher vestibular symptoms" such as altered spatial perception or neglect (9). However, previous knowledge about the topography and symptoms of pure vestibular or ocular motor strokes is mostly based on retrospective analyses, which lack detail in the description of the quality, intensity, and time course of clinical symptoms.

Therefore, in the prospective EMVERT (EMergency VERTigo) lesion trial, symptoms and lesion topography were characterized in consecutive patients, who presented to the ED of a tertiary referral center with acute vertigo, dizziness or double vision due to stroke (10). This approach focuses on the clinical triage practice in the ED, which initially is based on the description of symptoms by the patient rather than on vestibular and ocular motor signs. The major question was whether symptom characteristics could be sufficient to differentiate peripheral from central disorders. A further aim was the evaluation of the distribution of lesion sites in pure vestibular and ocular motor stroke in relation to the quality, intensity, and time course of the accompanying chief complaint.

METHODS

Patient Characteristics

Eight hundred and forty consecutive patients with an acute presentation of vertigo, dizziness or double vision were prospectively screened for inclusion in the EMVERT lesion trial at the ED of the University Hospital, Ludwig-Maximilians-University, Munich. Four hundred and eighty-nine patients were excluded, because of the following reasons: definite peripheral vestibular or ocular motor disorders (like nystagmus typical for BPPV during repositioning maneuvers, recurrent attacks of definite Menière's disease, definite peripheral N III, N IV, N VI palsy without central ocular motor signs, vertigo/dizziness, or SVV deviation on the non-paretic eye) ($n = 203$); strokes with accompanying non-vestibular symptoms (like hemiparesis, hemihypesthesia, hemiataxia) ($n = 15$); decline to participate ($n = 186$); incapability to be included for other reasons (e.g., communications problem, psychiatric co-morbidity, cognitive deficits, critical illness, symptoms <10 min) ($n = 85$). Three hundred and fifty-one patients (60.1 ± 16.7 years, 46.6% female) with isolated vertigo, dizziness or double vision of unclear etiology were included (**Figure 1**). Two hundred and sixty patients had persistent symptoms at the time of inclusion. Fifty eight percentage of symptomatic patients had spontaneous nystagmus (SPN) at acute examination.

Protocol Approval and Patient Consent

The study was approved by the Ethics Committee of the University of Munich on 02/23/2015 (57-15). The study was conducted according to the Guideline for Good Clinical Practice, the Federal Data Protecting Act and the Helsinki Declaration of the World Medical Association (revision of Fortaleza, Brazil, October 2013). All subjects gave their informed, written consent to participate in the study.

Trial Flow

Adult patients with an acute onset of vertigo, dizziness, or double vision within the last 24 h and a duration of at least 10 min were screened prospectively for inclusion in this single center trial (10). A structured medical history and standardized clinical examination with an emphasis on vestibular and ocular motor function tests was performed in the ED. Patients with a clinically proven peripheral etiology (e.g., typical signs of BPPV, recurrent attacks of definite Menière's disease, peripheral N III, N IV, N VI palsy), and central etiology (e.g., signs of acute hemiparesis, hemihypesthesia, hemiataxia) were excluded. The remaining patients with unclear etiology of isolated vertigo, dizziness or double vision were defined as the subpopulation of interest for the EMVERT trial. Patients, who consented to participate, were included and received a comprehensive assessment of vestibular, ocular motor and postural signs by videooculography (VOG, EyeSeeCam®), mobile posturography, measurement of SVV, as well as scores and scales in the ED. A standardized magnetic resonance imaging (MRI) protocol was applied within 7 days after symptom onset to identify acute stroke (time to MRI: 2 ± 2.8 days, 93% of cases > 1 day) (**Figure 1**).

Scoring and Scaling of Chief Complaint, Symptom Duration, and Functional Impairment

At admission, the patients were asked to categorize their chief complaint as either vertigo (sensation of apparent self-motion), dizziness (unspecific sensation without self-motion), or double

Abbreviations: AICA, Anterior Inferior Cerebellar Artery; BPPV, Benign Peripheral Positional Vertigo; CT, Computed Tomography; DHI, Dizziness Handicap Inventory; DWI, Diffusion-Weighted Image; EMVERT, EMergency VERTigo and balance disorders; EQ-5D-5L, European Quality of life scale–5 Dimensions–5 Levels; EQ-VAS, European Quality of life scale—Visual Analog Scale; FLAIR, Fluid Attenuated Inversion Recovery; FSPGR, Fast Spoiled Gradient Echo; INO, internuclear ophthalmoplegia; MNI, Montreal Neurological Institute; MRI, Magnetic Resonance Imaging; mRS, modified Rankin Scale; PICA, posterior inferior cerebellar artery; SCA, superior cerebellar artery; T, Tesla; VAS, Visual Analog Scale; VLSM, Voxel-based Lesion-Symptom Mapping; VOR, Vestibulo-Ocular Reflex.

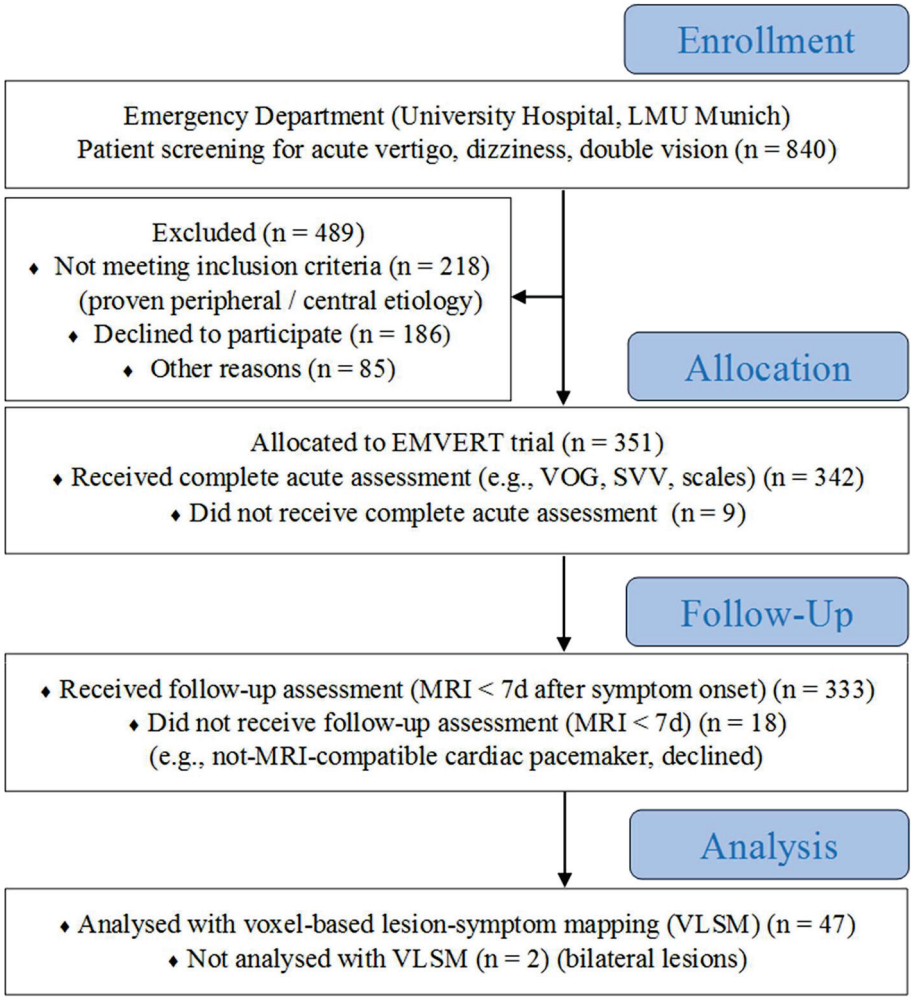

FIGURE 1 | Flow diagram of the EMVERT lesion trial. Eight hundred and forty consecutive patients with an acute presentation of vertigo, dizziness, or double vision were prospectively screened for inclusion in the EMVERT lesion trial at the Emergency Department (ED) of the University Hospital, Ludwig-Maximilians-University, Munich. Four hundred and eighty nine patients were excluded, because of the following reasons: definite peripheral vestibular or ocular motor disorder (like definite BPPV, recurrent attacks of definite Menière's disease, definite peripheral N III, N IV, N VI palsy) ($n = 203$); stroke with accompanying non-vestibular symptoms (like hemiparesis, hemihypesthesia, hemiataxia) ($n = 15$); decline to participate ($n = 186$); incapability to be included for other reasons (e.g., communications problem, psychiatric co-morbidity, cognitive deficits, critical illness, symptoms < 10 min) ($n = 85$). Three hundred and fifty one patients (60.1 ± 16.7 years, 46.6% female) with isolated vertigo, dizziness or double vision of unclear etiology were included. Three hundred and forty two patients received complete acute assessment in the ED, 333 patients a follow-up MRI within 7 days after symptom onset. Forty-seven of 49 patients with a stroke on MRI were included in the voxel-based lesion-symptom mapping analysis (2 excluded because of bilateral lesions). MRI, magnetic resonance imaging; SVV, subjective visual vertical; VLSM, voxel-based lesion-symptom mapping; VOG, videooculography.

vision. If mixed phenotypes (e.g., vertigo/double vision) were reported, the patient had to choose the predominant one. Accompanying vegetative symptoms like nausea or vomiting were documented. The maximum intensity of the chief complaint was measured using a visual analog scale (VAS, range 0–10). Decline of symptoms intensity was estimated by repeated testing of VAS for the chief complaint. Duration of vestibular or ocular motor symptoms was categorized in <1 days, 1–4 days, and >4 days based on daily reports of the patients. The Dizziness Handicap Inventory (DHI) and European Quality of Life scale-5 dimensions-5 levels (EQ-5D-5L) were performed as additional scores for graduation of symptom severity, quality of life (QoL) and functioning at admission (11). The Modified Ranking Scale (mRS) was documented at the time of discharge from the hospital.

Assessment of Vestibular and Ocular Motor Signs

The following vestibular and ocular motor signs were documented by VOG in the ED: nystagmus in straight ahead position (slow-phase velocity with/without fixation), gaze holding (lateral/vertical gaze positions), smooth pursuit (horizontal/vertical direction), saccades (horizontal/vertical direction), horizontal vestibulo-ocular reflex (VOR) (gain

threshold: 0.7, presence of compensatory saccades), horizontal VOR-suppression, skew deviation and ocular motility deficits (cover test in lateral, vertical and straight ahead gaze position). The main criterion of skew deviation (in contrast to vertical misalignment due to N III or N IV palsy) was that the amount of vertical deviation from both eyes was the same in different eye positions on alternating cover test. VOG recording was done at the non-paretic eye, if monocular motility was restricted. Binocular subjective visual vertical (SVV) was measured in general, using the bucket test. SVV was determined via the non-affected eye in case of monocular paretic eye movements. Ten repetitions were performed (5 clockwise, 5 counterclockwise) and the mean SVV deviation was calculated (normal range: 0 ± 2.5°) (12).

MRI Protocol

The standardized protocol included whole brain and brainstem fine slice (3 mm) DWI, FLAIR-, T2-, T2*-weighted images, 3D-T1-weighted sequences (FSPGR 1 mm) and time-of-flight angiography. All images were evaluated for the presence of ischemic stroke or bleeding by two specialized neuro-radiologists.

Voxel-Based Lesion-Symptom Mapping

Lesions were directly manually delineated on DWI sequences (MRI < 3 days post stroke) or T2-weighted sequences (MRI > 3 days post stroke) by an experienced imaging scientist, blinded for the clinical information, on a slice-by-slice basis using MRIcron (13). DWI or T2-images were co-registered with 3D-T1 images to enrich the normalization process. Normalization quality of lesion maps was visually checked by a second operator. Right-sided lesions were flipped to the left for the purpose of analysis. Patients presenting with bilateral lesions ($n = 2$) were discarded for analysis. Patients with simultaneous lesions in the medial and lateral cerebellum, in the medulla and cerebellum and in multiple unilateral locations were included in the analysis. None of the patient had critical ischemic edema. Images were normalized to Montreal Neurological Institute space (MNI) by Statistical Parametric Mapping Software (SPM 8) employing an established template. For descriptive analysis, the lesion site was assigned to the respective vascular territory/territories [posterior inferior cerebellar artery (PICA), anterior inferior cerebellar artery (AICA), superior cerebellar artery (SCA), brainstem perforators, middle cerebral artery (MCA), posterior cerebral artery (PCA)] and the affected anatomical structure(s) (cerebellar midline: nodulus, uvula, pyramis, tonsil, lingula, central lobule; cerebellar hemispheres: flocculus, biventer, inferior/superior semilunar, posterior/anterior quadrangulate lobule; brainstem: medulla, pons, midbrain; thalamus: dorsolateral, anteromedial; cortex: parieto-insular cortex, occipital cortex).

Voxel-based lesion-symptom mapping (VLSM) was performed using the statistical package Non-Parametric Mapping (NPM) implemented in MRIcron. For lesion analysis a custom-made mask was applied (**Supplement 1**), which included all relevant hubs of the cerebral vestibular network (e.g., brainstem, cerebellum, thalamus and insula). *T*-test (numerical variables) or *Liebermeister*-test (dichotomous variables) corrected for multiple comparison with false discovery rate (FDR) were calculated to assess whether behavioral scores differed significantly between the patients' pattern for lesioned and non-lesioned voxels (14). Since NPM toolbox interprets that a lower value in the behavioral scoring refers to a poorer performance, the different behavioral scores were computed reversed when necessary for statistical purposes. Only voxels affected in 15% of the sample were computed in each analysis to avoid inflated *z*-scores. Areas with significant differences in VLSM were labeled using the Automated Anatomical Labeling template (AAL-Atlas) (15).

Statistics

ANOVA with *post-hoc* testing was used to compare the scoring and scaling data (e.g., lesion volume, VAS) between subgroups (e.g., stroke/non-stroke, left-/right-sided lesions, vertigo/dizziness) using SPSS®24 (IBM). Pearson's correction coefficient was calculated for the correlation of lesion volume and VAS in the total group and subgroups (vertigo, dizziness, double vision).

Data Availability

Data reported in this article will be shared with any appropriately qualified investigator on request after pseudonymization.

RESULTS

Patient Characteristics

MRI indicated acute unilateral stroke in 47 patients (13.4% of enrolled patients, 5.6% of screened patients, 29 men). The mean age of stroke patients was 64.7 ± 13.0 years. The most frequent chief complaint in stroke patients was dizziness (42.5%), followed by vertigo (40.4%) and double vision (17.0%). Fifty percentage of patients with the chief complaint double vision reported accompanying vertigo or dizziness. 40.4% of stroke patients had nausea or vomiting, none had hiccups. Age did not differ significantly between the subgroups dizziness (66.7 ± 14.2 years), vertigo (63.5 ± 13.2 years), and double vision (61.9 ± 8.0 years). Forty four patients with vestibular or ocular motor stroke were symptomatic at the time of acute VOG assessment. In these patients spontaneous nystagmus (SPN) was detected in 45%. In total 74% of patients with vertigo and 30% of patients with dizziness had SPN (**Table 1**). In these cases, HINTS had a central pattern in 93% vs. 83% of patients (vertigo vs. dizziness). The head impulse test (HIT) was normal in 95, 85, and 63% of cases (vertigo, dizziness and double vision). Skew deviation appeared in 26% of patients with vertigo, 20% of patients with dizziness and 25% of patients with double vision. SVV was pathological in 68, 65, and 88% of patients with vertigo, dizziness, and double vision. The etiologies of double vision were internuclear ophthalmoplegia (37%), skew deviation (25%) and N III, N IV, N VI nuclear/fascicular palsy (13%, each) (**Table 1**).

Lesion Topography and Chief Complaint

In the total group, the most common lesion sites were in the cerebellum (PICA > SCA territory), followed by the brainstem (pontomedullary > mesencephalic tegmentum), thalamus and

TABLE 1 | Vestibular and ocular motor signs in patients with stroke.

	Vertigo (%)	Dizziness (%)		Double Vision (%)
SPN	74	30	Oculomotor palsy	13
HINTS central*	68	25	Trochlear palsy	13
HIT normal	95	85	Abducens palsy	13
Skew deviation	26	20	INO	37
SVV	68	65	Skew deviation	25

*An acute vestibular syndrome with SPN was more frequent in patients with vertigo compared to dizziness. HINTS had a high diagnostic sensitivity, if SPN was present, irrespective of the chief complaint. Data are shown as % of all patients with the respective chief complaint. HINTS, head impulse, nystagmus, test of skew; HIT, head impulse test; INO, internuclear ophthalmoplegia; SPN, spontaneous nystagmus; SVV, subjective visual vertical. *HINTS is supposed to be applied only in patients with SPN. The reported HINTS sensitivity in the table is irrespective of the presence of SPN.*

cortex. Lesion volume did not differ in patients with right-sided (mean: 8.0 cc, range 0.01–33.6 cc) and left-sided lesions (mean: 8.6 cc, range 0.01–102.2 cc) ($p = 0.89$). Patients with vertigo most frequently had lesions in the medial PICA territory (biventer lobule 58%, inferior semilunar lobule 37%, nodulus 37%, uvula 32%, tonsil 32%) and the pontomedullary brainstem (medulla 16%, pons 21%) (**Figure 2A**, **Supplement 2**). In patients with dizziness the lesions were found mostly in the lateral PICA territory (biventer lobule 25%, superior semilunar lobule 25%), SCA territory (posterior/anterior quadrangulate lobule 15%, each), the pontomesencephalic brainstem tegmentum (midbrain 25%, pons 20%) and the thalamus (dorsolateral/anteromedial 5%, each) (**Figure 2B**, **Supplement 2**). Lesions of patients with vertigo and dizziness showed a considerable overlap in the PICA territory (biventer, inferior semilunar lobule). Patients with double vision had pontomesencephalic and mesodiencephalic lesions (**Figure 2C**). Lesion volume was different in patients with vertigo (13.2 ± 24.3 cc), dizziness (7.4 ± 7.7 cc) and double vision (0.5 ± 0.6 cc) ($p = 0.04$). Patients with strokes in the medial cerebellum (PICA territory) had nausea or vomiting in 91%, in the lateral cerebellum, pontomesencephalic brainstem and thalamus in only 17%, respectively. Symptomatic stroke patients without SPN ($n = 24$) had lesions in the lateral PICA territory (30%), medial PICA territory (8%), SCA territory (8%), pontomesencephalic brainstem (38%), thalamus (8%), and insular cortex (8%).

VLSM in vestibular networks revealed that lesions in the medial cerebellar layers 7b, 8, 9 were significantly associated with the vertigo [*Liebermeister*-test, $p = 0.05$ (FDR-corrected), $Z = 1.66$] (**Figure 3A**). For the chief complaint dizziness, a lesion core area was found in the lateral cerebellar layer 8 and Crus 1, 2 using VLSM [*Liebermeister*-test, $p < 0.05$ (uncorrected), $Z = 0.65$] (**Figure 3B**). VLSM analysis conducted in patients with double vision did not reveal a significant association to a certain brain area (data not shown).

Lesion Topography and Symptom Intensity

The maximum symptom intensity (measured by VAS) was higher in the dizziness group (8.4 ± 1.8) and vertigo group (8.3 ± 2.3) and lower in the double vision group (6.2 ± 1.6) ($p = 0.015$ compared to the dizziness group and $p = 0.04$ compared to the vertigo group). Patients with nausea or vomiting had a higher VAS during the attack (9.5 ± 1.2), compared to patients without (7.0 ± 2.1) ($p < 0.0001$). VAS at symptom onset did not differ between patients with right-sided (7.7 ± 2.8) and left-sided lesions (8.2 ± 2.0) ($p = 0.99$). The mean decline of VAS per day was not significantly different between groups (dizziness group, 3.0 ± 1.7; vertigo group, 3.7 ± 1.7; double vision group, 1.9 ± 2.2). Lesions in patients with a high symptom intensity (VAS > 8) were larger and located in the cerebellar hemispheres (PICA > SCA territory) and pontomedullary brainstem (**Figure 4A**), while patients with a lower symptom intensity (VAS < 8) had smaller lesions in the cerebellar cortex (PICA/SCA territory), pontomesencephalic brainstem, thalamus and parieto-insular cortex (**Figure 4B**).

VLSM conducted with VAS at symptom onset showed significant voxels in the cerebellar layers 7b, 8, 9 in all patients with higher symptom intensity (*t*-test, $p = 0.05$ (FDR-corrected), $Z = 1.75$) (**Figure 4C**). In patients with cerebellar stroke, lesion volume was higher if symptoms were more severe ($r = -0.42$, $p = 0.03$), while in patients with cortical and thalamic lesions no correlation was found ($r = -0.15$, $p = 0.85$). Analysis of lesion volume and VAS at symptom onset by subgroups indicated no correlation for patients with vertigo ($r = -0.1$, $p = 0.97$), dizziness ($r = -0.14$, $p = 0.63$), or double vision ($r = -0.14$, $p = 0.91$).

Lesion Topography and Symptom Duration

In 6 patients symptom duration was <1 day, in 12 patients 1–4 days and in 29 patients >4 days. Duration of symptoms was not significantly different between the subgroups with vertigo, dizziness or double vision. In the total group, patients with a shorter symptom duration (<4 days) had lesions mostly in the lateral and distal cerebellar hemisphere (PICA territory), pontomesencephalic brainstem and parieto-insular cortex (**Figures 5A,B**), while patients with symptoms lasting >4 days had larger lesions involving the medial and lateral cerebellar hemispheres (PICA > SCA territory), the mesencephalon and thalamus (**Figure 5C**). Comparison of patients with a symptom duration of less and more than 4 days using VLSM showed that areas in the cerebellar layer 7b, 8, 9, and Crus 1, 2 were associated with longer symptom duration [*Liebermeister*-test, $p = 0.05$ (FDR-corrected), $Z = 1.72$] (**Figure 5D**).

Lesion Distribution, QoL, and Functioning Parameters

The health-related QoL measured by the EQ-5D-5L questionnaire was worse in the vertigo (12.2 ± 4.0) compared to the dizziness group (9.4 ± 3.6; $p = 0.02$). In the vertigo group higher scores were found in the EQ-5D-5L subtests for mobility ($p = 0.047$), overall activity ($p = 0.042$), and anxiety ($p = 0.024$). Similarly, DHI was higher in the vertigo (52.0 ± 22.1) compared to the dizziness group (34.4 ± 20.2, $p = 0.01$) and lowest in patients with double vision (42.3 ± 27.9).

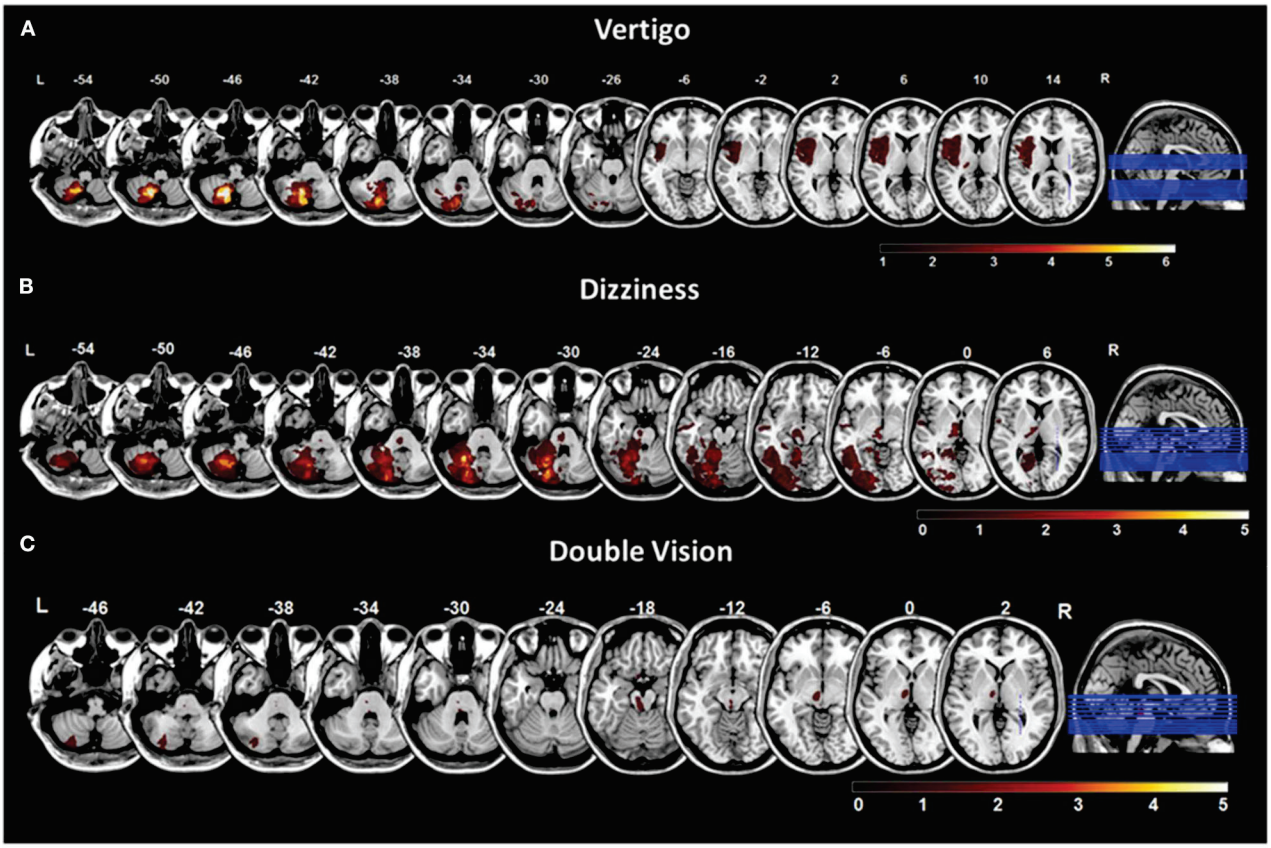

FIGURE 2 | Overlap lesion plots for chief complaints. Overlap lesion plots for the chief complaints vertigo **(A)**, dizziness **(B)**, and double vision **(C)**. The number of overlapping lesions is illustrated by the color bar from dark red ($n = 0$) to bright yellow (maximum number). Coordinates are given in MNI space. MNI, Montreal Neurological Institute; L, left; R, right.

VLSM in vestibular networks indicated that areas in cerebellar layers 8, 9, and Crus 2 were associated with higher EQ-5D-5L scores in the total group (t-test, $p = 0.05$ (FDR-corrected), $Z = 1.69$). VLSM for the subtest anxiety/depression showed a significant specific engagement of cerebellar layer 8 [t-test, $p = 0.05$ (FDR-corrected), $Z = 1.79$]. The analysis within patient subgroups revealed that the cerebellar layer 6 and Crus 1 correlated with worse QoL in patients with vertigo (**Figure 6A**), while the cerebellar layer 8 was related to higher EQ-5D-5L scores in patients reporting dizziness (**Figure 6B**). When VLSM was performed for DHI, areas in cerebellar layer 8 were significantly associated with higher DHI scores.

DISCUSSION

In the prospective EMVERT lesion trial, symptoms of patients with acute vestibular or ocular motor stroke were systematically documented and correlated to lesion topography. The major findings were the following: (1) Vertigo and dizziness were equally frequent in vestibular stroke and underlying lesions showed a large overlap in the cerebellar hemisphere. Vertigo was more likely associated with medial cerebellar lesions (biventer lobule, nodulus, uvula), while dizziness appeared more frequently in lateral and superior cerebellar lesions. (2) Symptom intensity and duration varied largely in vestibular and ocular motor stroke patients. Higher symptom intensity and longer symptom duration were associated with medial cerebellar lesions. Cortical lesions presented with milder symptoms of shorter duration. (3) QoL and functioning was worst in patients with vertigo and lesions in the medial cerebellar structures.

Symptom Characteristics and Diagnostic Classification of Vestibular Stroke

The diffuse lesion-symptom topography in vestibular and ocular motor stroke has direct practical implications for the processing of patients. The symptom quality does not allow differentiation of peripheral and central etiologies of vestibular syndromes. Therefore, the traditional approach of assessment by the symptoms vertigo, dizziness, postural instability or disequilibrium has major limitations in acute vestibular disorders (16, 17). Similar conclusions have been drawn in previous studies, where symptom quality was imprecise even in peripheral vestibular disorders (18).

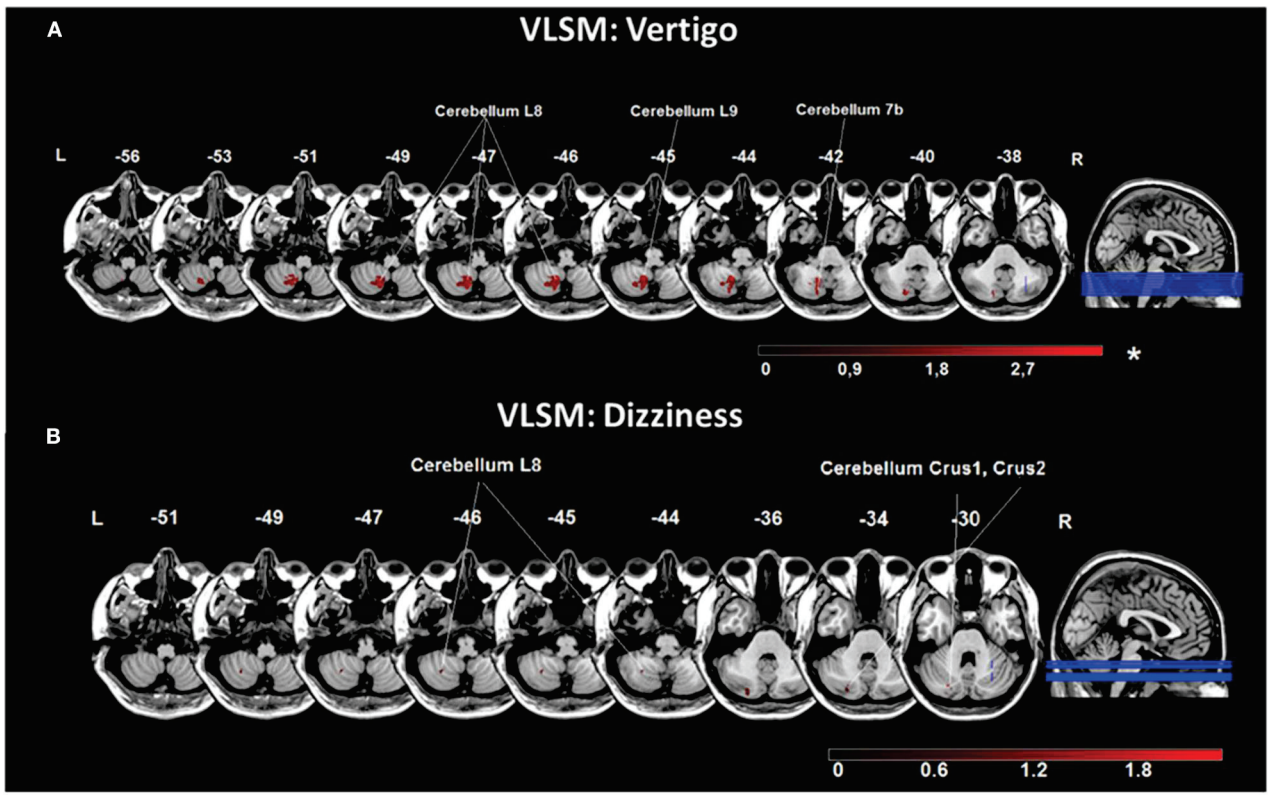

FIGURE 3 | Voxel-based lesion-symptom mapping (VLSM) analysis for the chief complaints vertigo and dizziness. **(A)** VLSM for the presence of the chief complaint vertigo showed an association with areas in the medial cerebellar hemisphere (cerebellar layers 7b, 8, 9). **(B)** VLSM analysis for the chief complaint dizziness indicated related voxels more laterally in the cerebellar hemisphere (cerebellar layer 8, Crus 1, 2). Presented are voxels that exceed a $p < 0.05$ (*FDR-corrected for vertigo; uncorrected for dizziness). The color bar from dark to light red indicates the z-scores. Coordinates are given in MNI space. MNI, Montreal Neurological Institute; L, left; R, right.

In the current study, symptom duration and intensity varied largely and consequently could not be taken as an indicator or criterion for exclusion of stroke. A recent study showed that functional impairment in acute central vestibulopathies is lower than in acute unilateral peripheral vestibulopathies, which may increase the risk of a false-benign diagnosis in vestibular stroke (19). Furthermore, previous studies described that suspected ischemic attacks with vestibular symptoms may present with short-lasting and transient symptoms (50% lasting <1 h) (20–22). Consequently, modern concepts of symptom-based differentiation of vestibular disorders rely more on the presence of triggers preceding vestibular symptoms and the time course of symptom onset and evolution (e.g., TiTrATE algorithm, including timing, trigger, and targeted examination) (23, 24).

Symptom Characteristics and the Risk of Misdiagnosis of Vestibular Stroke

Based on a recent meta-analysis, unspecific presentations of dizziness, short duration, and subtle intensity of symptoms may increase the risk for a misdiagnosis in patients with acute vestibular stroke (5). In these scenarios, the probability for missing stroke was about 10-fold compared to other focal neurological presentations. In total about 10% of strokes were missed at first contact in the ED (25). This problem is also reflected in a 50-fold increased risk of being readmitted to a hospital with a secondary stroke diagnosis in the first week, and a 9.3-times higher stroke risk after 30 days in patients discharged from the ED with a suspected benign diagnosis of acute vertigo or dizziness compared to matched controls (26). Lesion-symptom relationships from the current EMVERT lesion trial point out that especially patients with lesions in the lateral cerebellar hemispheres, mesencephalon and parieto-insular cortex may be at risk of being falsely processed. In these localizations patients do complain about more unspecific symptoms (such as dizziness, unsteadiness), transient symptoms (<1 day), lower symptom intensity (VAS < 8), and less vegetative symptoms (like nausea or vomiting) (**Figures 2**, **3**, **5**). Furthermore, patients with lesions in the lateral cerebellum, upper midbrain and cortex do not show clinical signs of an acute vestibular syndrome (e.g., SPN), which further complicates the diagnosis. HINTS is not applicable in the majority of these cases. In contrast, lesions in the pontomedullary tegmentum and medial cerebellar

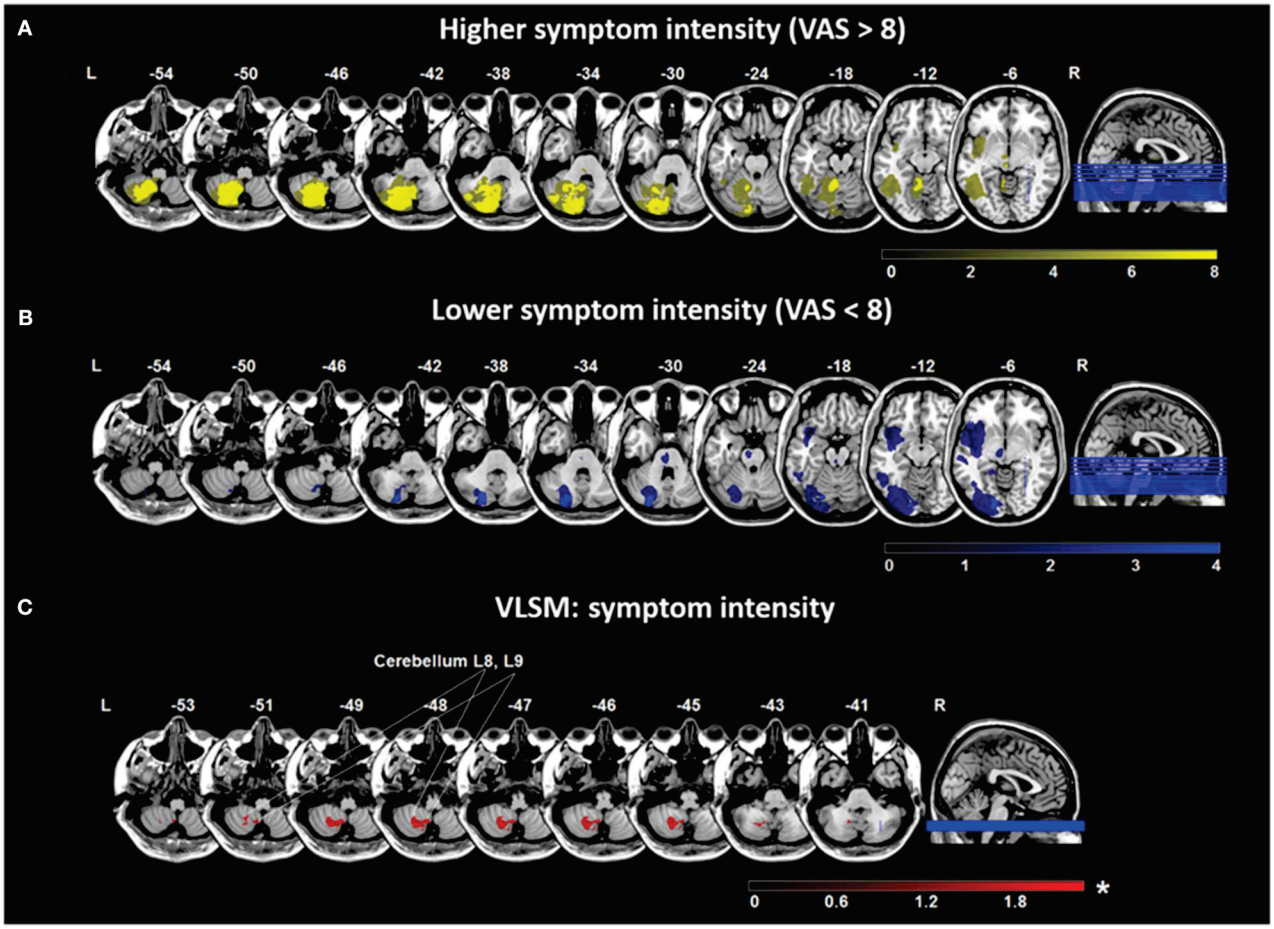

FIGURE 4 | Overlap lesion plots and voxel-based lesion-symptom mapping (VLSM) for symptom intensity. Maximum intensity of the chief complaint was measured by the visual analog scale (VAS) (range 0–10). Overlap lesion plots for patients with higher symptom intensity (VAS > 8) ($n = 34$) **(A)** and lower symptom intensity (VAS < 8) ($n = 13$) **(B)**. The degree of lesion overlap is illustrated by color bars from dark to bright yellow or blue. **(C)** VLSM analysis in 47 patients based on VAS indicated an area in the medial cerebellar hemisphere (cerebellar layer 8, 9) related to more severe symptoms. Presented are voxels that exceed a $p < 0.05$ (*FDR-corrected). The color bar from dark to light red indicates the z-scores. Coordinates are given in MNI space. MNI, Montreal Neurological Institute; L, left; R, right.

hemispheres may be more apparent, because patients report more intense and longer-lasting symptoms and show more prominent clinical signs (such as SPN, ocular tilt reaction, and HINTS central pattern) (27–29). Lesion size may be another relevant factor, because patients with smaller lesions had less intense vertigo. For lesions <10 mm, MRI has a high false-positive rate (about 50%) in the first 1–2 days after symptom onset, which questions the rationale of a purely imaging-based diagnosis of acute vestibular or ocular motor stroke (30). Patients in our study received MRI in 93% of cases later than 1 day post symptom onset to increase the sensitivity to capture small DWI lesions.

Pathophysiological Principles Behind Lesion-Symptom Relationships in Vestibular Stroke

Despite the variety of symptomatic presentations across lesion sites, some general principles seem to exist: (1) Lesions in the nodulus, uvula, and medial cerebellar hemisphere are associated with vertigo symptoms of the highest intensity and a high rate of nausea or vomiting. The most likely explanation is that these regions are directly involved in processing of vestibular and ocular motor signals. The nodulus has been implicated in integration of otolith and semicircular canals signals, tilt suppression of post-rotatory vertigo and the judgement of verticality perception (7, 31–33). Nodular lesions often present with SPN and ocular tilt reaction (34). Anatomically, the nodulus has inhibitory ipsilateral projections to the vestibular nucleus (31). Functionally, medial cerebellar lesions cause an excitation of the ipsilesional vestibular nucleus (via disinhibition) and resemble the clinical picture of a vestibular nucleus lesion on the other side. The lateral and superior cerebellar hemispheres are not specifically dedicated to vestibular processing but rather to sensorimotor and posture control. Therefore, lesions may cause less specific dizziness, as a sign of disturbed multisensory integration or balance control, and only rarely

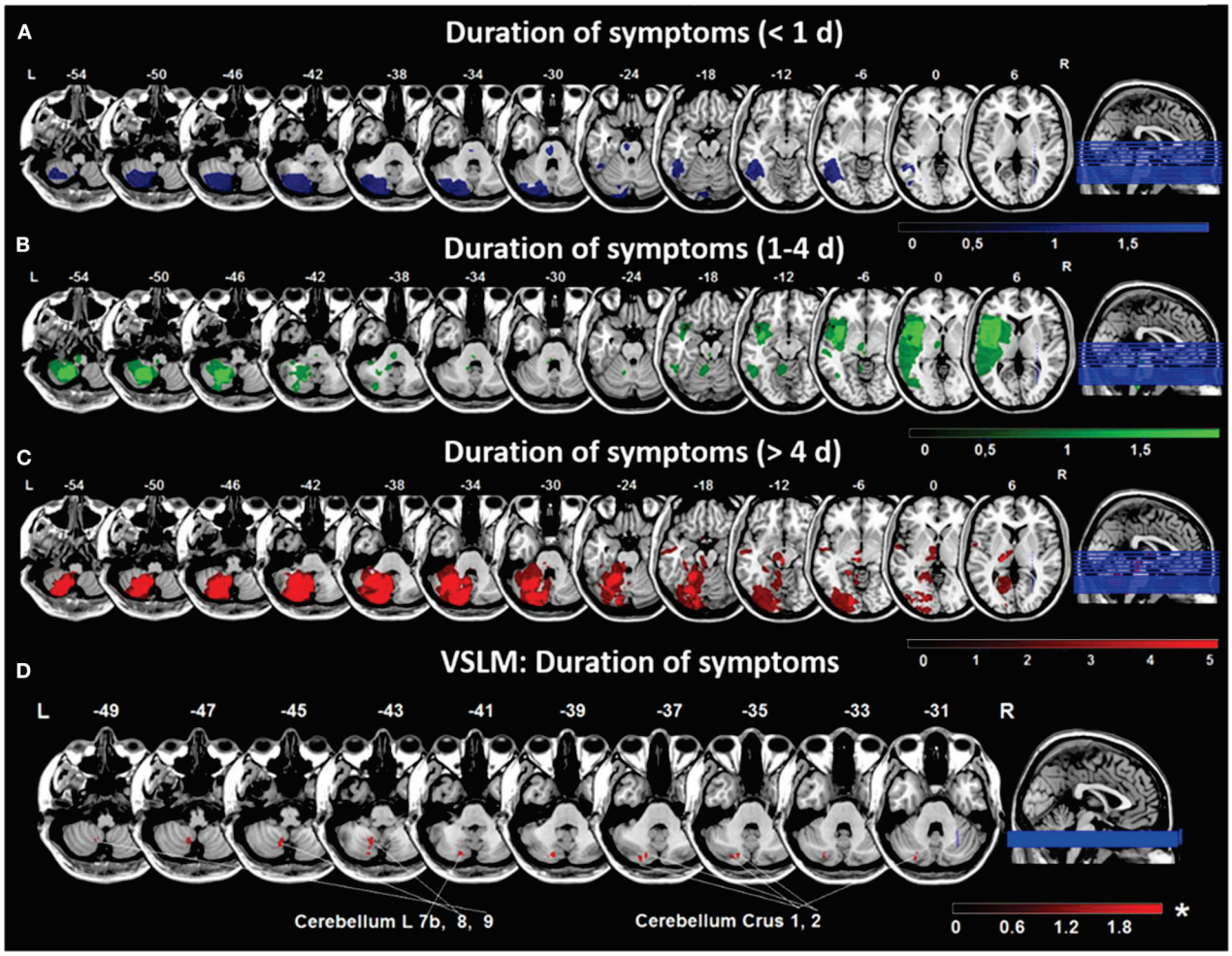

FIGURE 5 | Overlap lesion plots and voxel-based lesion-symptom mapping (VLSM) for duration of symptoms. Overlap lesion plots are shown for patients with a duration of symptoms <1 day ($n = 6$) **(A)**, 1–4 days ($n = 12$) **(B)** and > 4 days ($n = 29$) **(C)**. The degree of lesion overlap is illustrated by color bars from dark to bright blue, green or red. **(D)** VLSM analysis in 47 patients based on symptom duration in days showed an area in the medial cerebellar hemisphere (cerebellar layer 7b, 8, 9, and Crus 1, 2) associated with longer duration of symptoms. Presented are voxels that exceed a $p < 0.05$ (*FDR-corrected). The color bar from dark to light red indicates the z-scores. Coordinates are given in MNI space. D, day; MNI, Montreal Neurological Institute; L. left; R, right.

nausea or vomiting. (2) Perceived impairment of QoL and functioning follows the degree of vestibular asymmetry. Patients with vertigo had a higher EQ-5D-5L anxiety score than dizzy patients. VLSM found an association of higher EQ-5D-5L scores in the medial cerebellar hemisphere. In accordance, a recent study found that the degree of horizontal SPN is the most important factor for worse health-related quality of life in acute vestibulopathies (19). In another previous study, patients with unilateral vestibular disorders had more anxiety than patients with bilateral vestibulopathy (35). (3) Symptom duration was higher in medial compared to lateral cerebellar and thalamo-cortical lesions. This finding could be explained either by the different peak levels of initial symptoms in these subgroups or by a less effective central compensation of strategic lesions in vestibular cerebellar networks. The latter hypothesis may be substantiated by the finding that patients with medial cerebellar lesions had a prolonged course of compensation (36). Furthermore, symptoms from unilateral parieto-insular cortex lesions may be compensated by the intact cerebral hemisphere (6). (4) Symptom quality changed along the brainstem-thalamic axis from more direction-specific symptoms (i.e., vertigo) in the lower brainstem to more position-specific symptoms (i.e., dizziness) in the midbrain and thalamus. The reason for this topography may be the specific computation of vestibular signs at different brain levels. Vestibular signs at the lower brainstem level drive direction-specific ocular motor and postural responses. Along the ascending vestibular projections head direction signals from both sides are integrated to head position in space signals (37, 38). In the thalamo-cortical networks, a global percept of the environment is built by integration of multisensory information. In consequence, lesions at the midbrain level and above will rather give dizziness as a

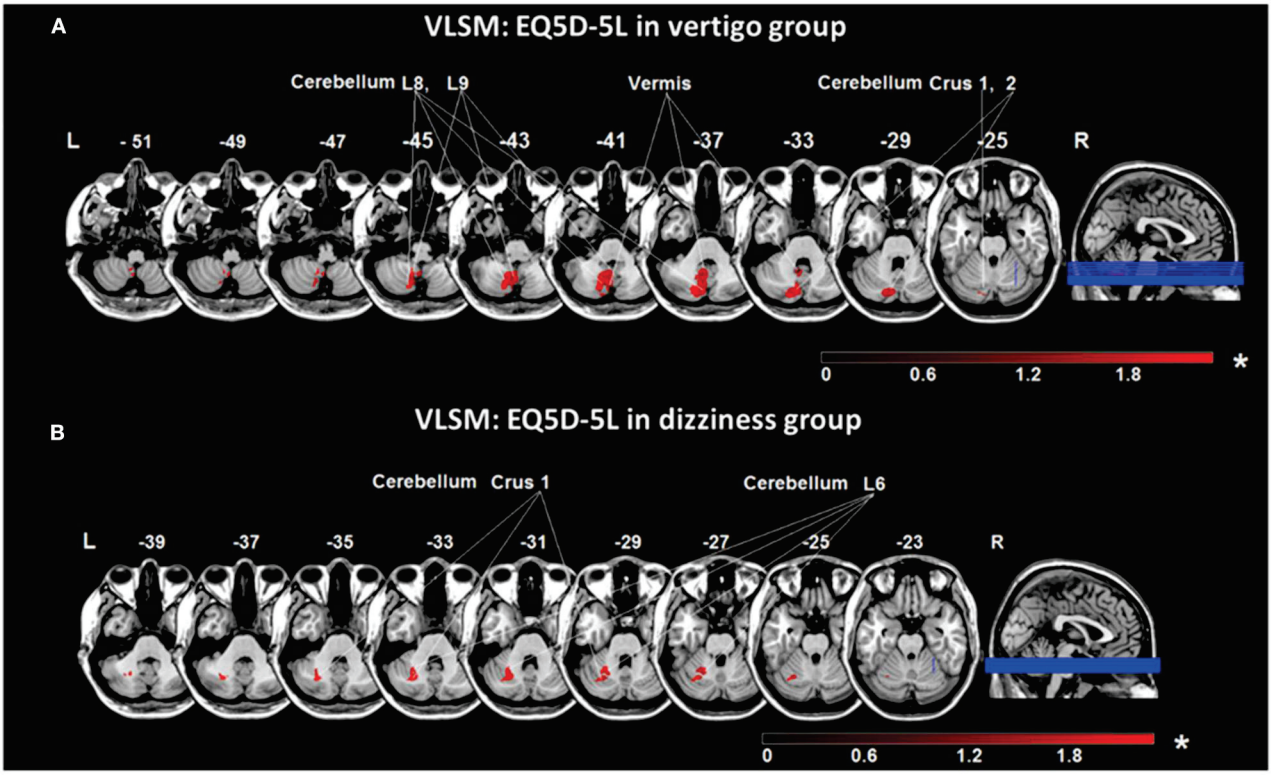

FIGURE 6 | Voxel-based lesion-symptom mapping (VLSM) analyses based on the QoL scale EQ5D-5L. **(A)** VLSM based on EQ5D-5L in the vertigo subgroup showed an association of voxels in the medial cerebellar hemisphere (cerebellar layers 8, 9, vermis, and crus 1, 2) with worse QoL scores. **(B)** VLSM analysis using EQ5D-5L in the dizziness subgroup indicated a more lateral area (cerebellar layer 6, and Crus 1) engaged in higher EQ5D-5L scores. Presented are voxels that exceed a $p < 0.05$ (*FDR-corrected). The color bar from dark to light red indicates the z-scores. Coordinates are given in MNI space. EQ5D-5L: European Quality of Life scale −5 dimensions −5 levels, MNI, Montreal Neurological Institute; L, left; R, right.

disturbed perception of the environment without the feeling of self-motion (6).

CONCLUSIONS

A simple symptom-lesion topography in acute vestibular and ocular motor stroke is an inappropriate clinical approach. Symptom quality, intensity, and duration are not suited to differentiate peripheral from central etiologies of vestibular presentations. Clinicians should be aware that rare lesion sites in the lateral cerebellum, thalamus, or cortex may present with rather unspecific, mild, and transient symptoms and therefore are at risk of being categorized as false-benign. Symptom intensity and perceived impairment are highest in lesions, which directly affect pontomedullary and medial cerebellar vestibular hubs. Lesions in ascending vestibular projections above the VOR brainstem circuit, rarely present with direction-specific vestibular symptoms (namely vertigo). Detailed neuro-ophthalmological and -ototological examinations are required in all patients with monosymptomatic vertigo, dizziness, or double vision.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the University of Munich on 02/23/2015 (57-15). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AZ: drafting/revising the manuscript, study concept and design, acquisition of data, analysis and interpretation of data, and statistical analysis. KM: drafting/revising the manuscript, study concept and design, acquisition of data, and analysis and interpretation of data. ES: drafting/revising the manuscript, analysis and interpretation of data, and statistical analysis. HH: drafting/revising the manuscript and

acquisition of data. TB and MD: revising the manuscript, study concept and design, and analysis and interpretation of data. KJ: drafting/revising the manuscript, study concept and design, and analysis and interpretation of data. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.00822/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Lateropulsion in Right-Sided Stroke: Brain Anatomical Correlates of Severity and Duration

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Background and Purpose: Lateropulsion (LP) is a profound disorder of postural control that has a significant impact on neurorehabilitation. Knowledge of relevant brain areas could guide decisions on appropriate intervention methods. Although LP severity and duration are highly variable in individuals with LP, imaging studies on LP have not sufficiently considered these aspects. The aim of this study was to investigate the lesion location in individuals after stroke and the correlation with LP duration and severity.

Methods: A retrospective case-control study using voxel lesion symptom mapping (VLSM) in 74 individuals with right-sided brain lesion (49 *with* and 25 *without* LP) was performed to analyze the correlation between lesion location and LP severity. Duration was investigated in a subsample of 22 individuals with LP. LP was diagnosed by means of the Scale for Contraversive Pushing.

Results: Individuals with LP showed significantly larger lesion sizes compared with the individuals with no LP. VLSM analysis of LP severity did not reveal statistically significant results. VLSM analysis showed a statistically significant association with longer LP duration for the inferior frontal gyrus, the hippocampus, the inferior parietal gyrus, the supramarginal gyrus, the angular gyrus, the temporal cortex, the sagittal stratum, and the superior longitudinal fasciculus.

Discussion and Conclusion: LP-relevant areas are located in the multisensory network. Areas of the frontoparietal network, which are related to spatial cognition, memory, and attention, were found to be relevant for duration and severity. The findings, especially those regarding duration involving the middle temporal cortex, could explain the better intervention outcomes for methods based more on implicit than on explicit knowledge of verticality.

Video Abstract available for more insights from the authors (see the Video, Supplemental Digital Content 1 available at: http://links.lww.com/JNPT/A433).

Key words: *lesion mapping, postural vertical, spatial orientation, verticality perception*

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INTRODUCTION

Lateropulsion (LP) is a disorder of postural control that has a significant impact on motor recovery after brain lesions.[1,2] Its most frequent etiology is stroke.[3] Individuals with LP push themselves away from their nonparetic body side and/or resist any attempt to transfer weight over to the nonparetic side.[4-6] Depending on its severity, LP can be present not only during standing but also during sitting, during postural transitions, or even while lying down. It is assumed that an underlying mechanism of LP is a disturbed internal reference frame for the representation of postural verticality.[6,7] Individuals with LP were found to perceive their body as oriented upright when it was actually tilted to the ipsilesional side,[6,8] and conversely, also when tilted to the contralesional side.[7,9,10]

LP hampers and prolongs the rehabilitation process and thus increases health care costs.[11] As a recently published review on LP and rehabilitation outcome concluded, people with LP after stroke can achieve similar levels of function and have a similar likelihood of returning home as their counterparts with no LP but require a longer period of rehabilitation to achieve these outcomes.[2] The duration of LP, however, varies widely among individuals. Some show LP only for a few weeks, while others exhibit it for several months or even years.[3,12] The longer the behavior persists, the worse the rehabilitation outcome.[3] The identification of factors associated

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One of the 3 studies for which imaging data were analyzed was registered before participant recruitment: German Clinical Trials Register (registration number: DRKS00003444).

The authors declare no conflict of interest.

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with persisting LP is important for the selection of appropriate interventions and discharge planning.

The brain areas engaged in the manifestation and evolution of LP have not been completely clarified, specifically with regard to duration and severity. A recent review, which included 7 studies,[13] found that the brain areas associated with LP in voxel-based lesion behavior mapping analyses (VLBM) were the thalamus (ventral posterior and lateral posterior nuclei of the posterolateral thalamus), the internal capsule, and the caudate nucleus in both hemispheres.[14,15] After a stroke without thalamic involvement, the left posterior insula and superior temporal gyrus, the left inferior parietal lobule, and the right postcentral gyrus were relevant regions for LP.[16] Other areas with a tendency to be involved in LP are the posterior insular cortex, the superior temporal gyrus, and the operculum.[17] For individuals with left-sided brain damage, the anterior insular cortex, the operculum, the internal capsule, and the lateral thalamus were associated with LP.[17] Frontal white matter lesions involving the corticospinal tract and superior longitudinal fasciculus were found to be relevant for individuals who maintained LP for at least 24 days after stroke onset.[18] In a cohort with extrathalamic lesions, the thalamus was neither structurally damaged nor malperfused.[19]

So far, LP and related lesion sites have mainly been investigated in individuals in an acute stage after their stroke[14-17,20] or in a very early subacute phase in which LP was diagnosed at day 24 or earlier.[18,19] However, it is important to study LP also in individuals in a later subacute or chronic stage, as persistent LP considerably worsens the rehabilitation process.[1,3] Thus, there is still a lack of knowledge about the neural substrates that lead to long-term persistent LP. In addition, more severe impairment is associated with a delayed recovery.[21] The aim of this study was to examine the association between lesion location and duration and severity of LP. We hypothesized that duration and severity might be dependent on the involvement of areas attributed to sensory processing and/or cognitive function. Knowledge about the brain areas associated with severe and long-term LP might help us better understand the effects of the different therapeutic intervention approaches and might allow customized interventions based on the individual's lesion sites.

METHODS

Data from 3 studies on the same population were used for a retrospective secondary analysis.[3,22,23] These 3 studies were initially performed to investigate LP and its influence on rehabilitation outcome,[3] or the effectiveness of therapeutic interventions.[22,23] One study was registered before participant recruitment (DRKS00003444).[23] In 2 studies, all participants or their legal representatives provided written informed consent.[22,23] The data analysis performed in the third study was done on clinical routine data, for which consent was given with admission to the hospital.[3] The studies were performed December 2006 to December 2007,[3] January 2010 to May 2011,[22] and December 2011 to July 2016.[23]

Participants

Clinical data and brain images (computed tomography [CT] and magnetic resonance imaging [MRI]) of participants in one of the aforementioned studies were analyzed and met the following criteria: (1) ischemic or hemorrhagic stroke in the right hemisphere according to the definitions of the World Health Organization[24]; (2) hemiparesis based on the neurologic examination; and (3) no previous infarcts, bilateral lesions, or other substantial brain structural changes. Individuals with right-hemispheric lesions were selected as the right hemisphere is the most frequently affected hemisphere in imaging and prevalence studies reporting a prevalence of LP during the acute phase and over time.[25]

Outcome Parameters

LP was assessed by means of the Scale for Contraversive Pushing (SCP), which consists of 3 components: (1) the symmetry of spontaneous body posture, (2) the use of the nonparetic arm or leg to increase pushing force, and (3) the resistance to passive correction of posture.[6] Each component is tested in sitting and standing, yielding a score between 0 and 2, that is, a total score between 0 and 6. We used the cutoff score of greater than zero per component to diagnose LP, that is, a total score in each subscore, sitting plus standing, greater than zero.[26]

This categorization (LP/non-LP) was used to compare individuals with and with no LP.

The classification of LP severity was calculated from the specific SCP score documentation. An individual was diagnosed as having LP based on the scoring mentioned previously. In addition, if LP could be detected only by means of the subscore "sitting" (>0 per component in sitting), the individual was categorized as having severe LP. This information (LP/severe LP) was used to analyze the severity of LP.

In a subsample ($n = 22$), LP was assessed weekly until LP resolved or the individual was discharged.[3] This data set derived from 1 study was used to analyze the duration of the behavior. By using the SCP as the assessment tool for LP, the analyzed individuals could also be labeled as having pusher behavior, a term used related to this scale.

Lesion Location

Participants had either T2-weighted axial fluid-attenuated inversion recovery sequences (Flair, slice thickness 5 mm/interslice gap 5.5 mm) or CTs (axial section thickness between 2.4 mm and 9 mm) conducted in the subacute or chronic stage within 1 and 25 weeks after stroke onset (mean = 6, SD = 24). Differences in lesion size between the group of participants showing and those not showing LP were analyzed by means of a *t* test.

Lesions were manually delineated by 1 author (E.S.L.), who was blinded for participants' clinical information and performance on the SCP on a slice-by-slice basis using MRIcron.[27,28] The volumes of interest were normalized to adapt to the Montreal Neurological Institute space (http://mcgill.ca/neuro/) using the Statistical Parametric Mapping Software (SPM 8, the Welcome Department of Imagining Neuroscience, London, England, http://www.fil.ion.ucl.ac.uk) employing a template created from older adults that matched standard stereotaxic space in order to make lesions suitable for statistical analysis.[29] The normalization quality of lesion maps was visually checked afterward.

Table. Patients' Characteristics for the Different Analyses[a]

		Patients With LP			
			Severity		
	Patients With No LP n = 25	Overall n = 49	LP, n = 25	Severe LP, n = 24	Duration n = 22
Age at stroke, y	62.8 (15.1), 27.5-84.3	70.8 (10.5), 38.7-87.5	71.8 (9.1), 54.1-86.7	70.3 (11.7), 38.7-87.5	69.0 (12.0), 38.7-87.5
Sex (women/men)	8/17	18/31	11/14	8/16	5/17
Etiology of stroke (ischemic/hemorrhagic)	12/13	30/19	16/9	14/10	18/4
Time from stroke to first SCP, wk	5.9 (6.2), 1-25.3	8.1 (13.7), 0.3-98.6	6.7 (3.7), 0.3-14.7	9.3 (19.0), 0.6-98.6	8.0 (20.5), 0.3-98.6
SCP score[b]	1, 0-1	3, 3-5	3.5, 3-3.75	4.875, 3-5.8125	3, 3-3.375

Abbreviations: LP, lateropulsion; SCP, Scale for Contraversive Pushing.
[a]Values are mean (SD), minimum-maximum. SCP values are median, quartile 1–quartile 3.
[b]In severely affected patients, testing SCP in standing is not always possible.

To test the reliability of the method of manual lesion drawing, an intraclass correlation analysis was conducted for the lesion volume in 20% of the sample delineated by 2 authors (E.S.L, K.M.), showing high interrater reliability (intraclass correlation = 0.99).

Lesion and Statistical Analysis

Voxel lesion symptom mapping (VLSM) was performed using the statistical package Non-Parametric Mapping (version 02/05/2016) implemented in MRIcron, using *t* test for multiple comparison with false discovery rate correction to assess whether behavioral scores differed significantly between participants' pattern for lesioned or nonlesioned voxels, respectively.[30] Only voxels affected in 15% of the sample were computed in each analysis to avoid inflated *z* scores. The statistical threshold selected to plot significant results was 0.05. Since the Non-Parametric Mapping toolbox interprets that a lower value in a certain behavioral scoring refers to a poorer performance, the SCP was computed inversely for statistical purposes (ie, 0, higher degree of LP; 6, no LP). The identification of the areas was depicted using the Automated Anatomical Labelling template (AAL-Atlas)[31] and the MRI Atlas of Human White Matter (JHU-White Matter).[32]

Results

A total of 74 individuals were analyzed, 49 with and 25 with no LP. Out of 79 participants with LP and a right-sided stroke who participated in 1 of the 3 aforementioned studies (45 participants from the study by Krewer et al[3]; 11 participants from the study by Krewer et al[22]; and 23 participants from the study by Bergmann et al[23]), a CT scan or an MR image was available for analysis in 49 individuals. Out of 75 participants with a right-sided stroke but with no LP (66 participants without the ability to stand upright from the study by Krewer et al[3]; and 9 participants from the study by Krewer et al[22]), a CT scan or an MR image was available for analysis in 25 individuals. A CT scan or an MR image was collected only when already available but was not specifically scheduled for study purposes.

The 74 individuals were aged 68.3 ± 12.7 years at the time of the stroke and included 26 female participants. Stroke etiology was ischemic in 42 participants and hemorrhagic in 32 participants. The time from stroke to the first LP testing was 43 ± 33 days. A more detailed description of patients' characteristics is provided in the Table.

Lesion Analysis: LP Versus Non-LP

Figure 1 illustrates the lesion overlay plots of individuals presenting and not presenting LP. The maximum overlap of lesions in both groups is located in the center of the perisylvian region.

The group of individuals presenting LP showed significantly larger lesions compared with the group of individuals not presenting LP (LP: n = 49, $M = 156.7$ cc, range: 4-514.2 cc; non-LP: n = 25, $M = 108.1$ cc, range: 11.9-333.5 cc; $t_{72} = 1.98$, $P_{(1\text{-tailed})} = 0.026$; see Figure 1).

VLSM, in general, relates the score in a certain behavioral parameter to the presence or absence of a damaged voxel in the brain. Figure 2 shows the results of the VLSM analysis employing the (inverse) SCP scoring, revealing no statistically significant areas. Areas showing the highest *z* values, however, were the superior occipital gyrus (3.98), precuneus (3.66), angular gyrus (3.63), parietal superior and inferior lobe (3.65, 3.58), middle frontal gyrus (3.63), cuneus (3.57), postcentral gyrus (3.52), superior frontal gyrus (3.50), posterior corona radiation (3.42), and posterior thalamic radiation (3.42).

Lesion Analysis for Severity of LP

For LP severity analysis, a subgroup of individuals showing LP mainly in a standing position (n = 25) was compared with a subgroup of individuals showing LP in both sitting and standing positions (severe LP, n = 24).

VLSM analysis of LP severity did not show any statistically significant areas. The highest *z* values, however, were found for the middle temporal gyrus (*z* value of 4.22), postcentral (4.18) and precentral (3.96) gyrus, middle frontal gyrus (3.87), superior longitudinal fasciculus (3.7), superior temporal gyrus (3.68), and Rolandic operculum (3.64).

Lesion Analysis for Duration of LP

Duration of LP was evaluated in a subgroup of 22 individuals. The number of weeks those individuals showed LP was used to conduct lesion analysis. Inverse coding of the number of weeks (1 week [worst value] to 20 weeks [best

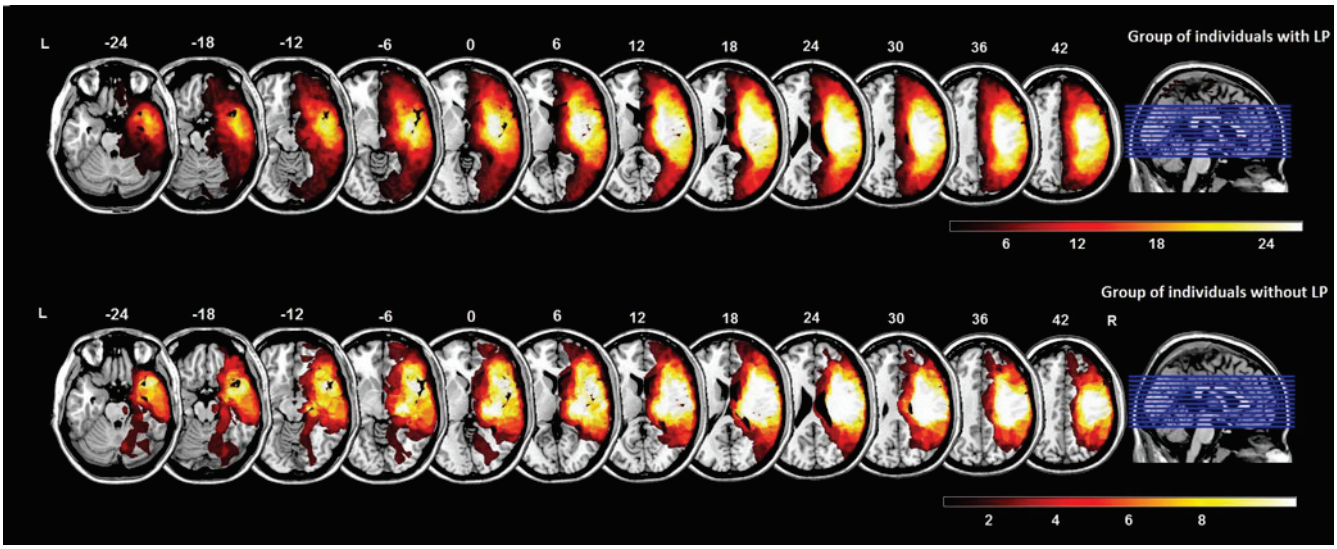

Figure 1. Overlap of the binarized lesions of individuals presenting lateropulsion (LP, n = 49) and not presenting lateropulsion (n = 25). The color bars indicate the degree of overlap of lesions. LP, lateropulsion. This figure is available in color online (www.jnpt.org).

value]) was used for the analysis. The results show a statistically significant engagement (*t* test, $P < 0.05$, false discovery rate corrected, $Z = 3.46$; see Figure 3) of the following areas: orbital part of the inferior frontal gyrus (4.41), angular gyrus (4.08), superior temporal gyrus (4.08), middle temporal gyrus (3.88), inferior temporal gyrus (3.88), temporal pole (3.84), sagittal stratum (3.84), hippocampus (3.84), superior longitudinal fasciculus (3.5), inferior parietal lobe (3.48), and supramarginal gyrus (3.5).

DISCUSSION

This study is the first addressing LP with VLSM to investigate a large cohort of subacute and chronic individuals after a right-hemispheric stroke (n = 74), focusing on the duration and the severity of LP. Individuals with LP showed significantly larger lesion sizes compared with the individuals with no LP. VLSM analysis on LP severity did not reveal statistically significant results. VLSM analysis showed statistically significant results for an association of a longer LP duration with the inferior frontal gyrus, the hippocampus, the inferior parietal gyrus, the supramarginal gyrus, the angular gyrus, the temporal cortex, the sagittal stratum, and the superior longitudinal fasciculus.

Santos-Pontelli et al[12] investigated brain images in individuals showing LP by means of the SCP (cutoff ≥ 1 in each subscale) with a duration of LP ranging from 8 up to 789 days after the brain damage, focusing on the severity and duration of LP.[9] Santos-Pontelli et al, however, performed a frequency analysis that was limited to only a small number of regions of interest, that is, the thalamus, insula, postcentral gyrus, and posterior parietal region. They state that these brain structures have been identified in previous studies as being responsible for the occurrence of LP. Focusing on only these 4 brain areas, however, means that other structures with a potential relevance for severity and duration are neglected. As the results of the study presented here show, the relevance of brain

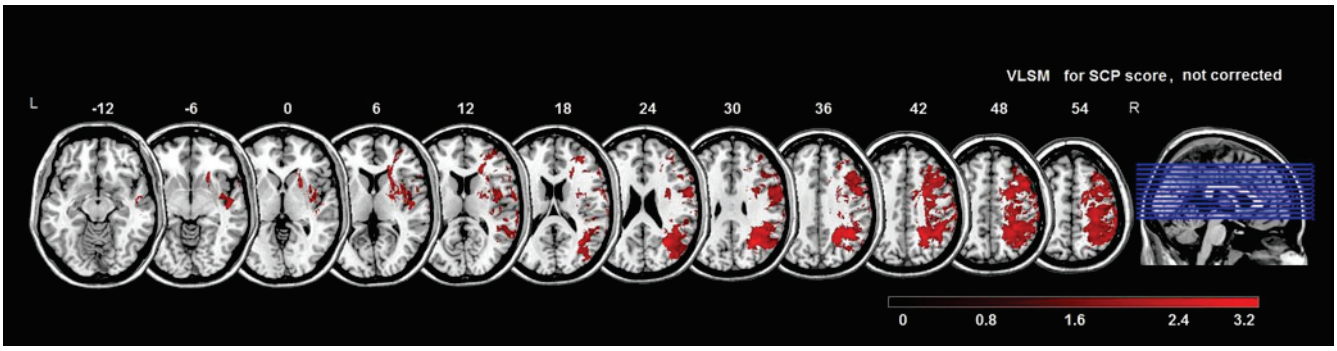

Figure 2. VLSM showing a trend for the SCP scoring. Color bars indicate *Z* score; results from *t* test $Z = 1.64$, $P < 0.05$; not corrected (dark to light red). SCP, Scale for Contraversive Pushing; VLSM, voxel lesion symptom mapping. This figure is available in color online (www.jnpt.org).

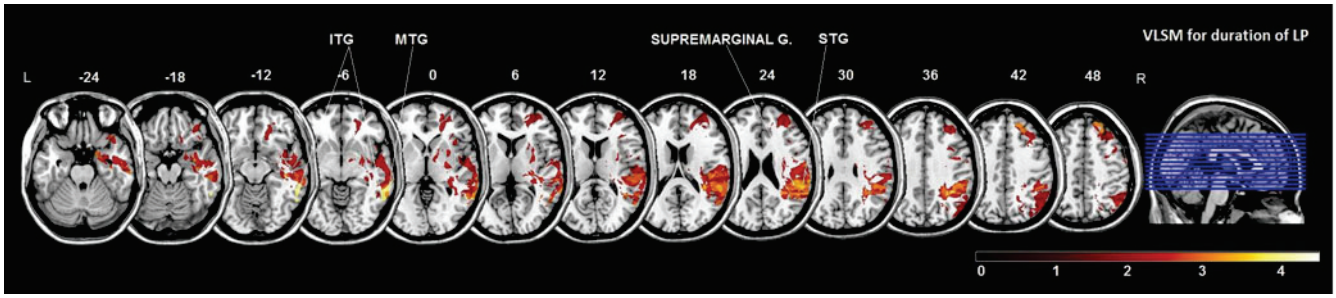

Figure 3. VLSM for the duration of LP (inverse coding of time; maximum 20 weeks). Color bars indicate *z* score; *t* test thresholded at $P < 0.05$, false discovery rate corrected; only those areas corresponding to voxels surviving the threshold are labeled (light yellow). ITG, inferior temporal gyrus; LP, lateropulsion; MTG, middle temporal gyrus; STG, superior temporal gyrus; VLSM, voxel lesion symptom mapping. This figure is available in color online (www.jnpt.org).

areas certainly differs with respect to the particular aspect of LP, whether it is the general occurrence of LP, the severity, or the duration.

Findings on the general occurrence of LP, when LP is contrasted to non-LP, that is, using a dichotomous classification of the LP diagnostic scale, are biased as they were not controlled for LP severity (eg, using the sum score of the LP diagnostic scale) or for LP duration. This is true for the results of the present study as well as the findings from all previous studies investigating imaging in LP. To focus on the brain structures contrasting LP versus non-LP, we will not discuss those brain structures that were found to be relevant for LP severity or for LP duration in our study but only the remaining structures. Consequently, in comparing the brain lesions of individuals with and with no LP, the superior occipital gyrus, the precuneus, the superior parietal lobe, the cuneus, the superior frontal gyrus, the posterior corona radiation, and posterior thalamic radiation were found to be relevant areas for LP. These brain areas mainly belong to the multisensory network with a predominance of structures relevant for visual processing,[33] or are involved in self-awareness in coordination with the action of the sensory system, like the superior frontal gyrus.[34] The corona radiata has been identified as part of the white matter tracks engaged in verticality perception.[7,35,36] Previous studies investigating brain images in individuals with LP after a lesion in the right hemisphere also found relevant structures that belong to the multisensory network. The posterior thalamus was described by Karnath et al[14,15] as a structure fundamentally involved in the control of upright body posture (SCP cutoff ≥ 1 in each subscale). The postcentral gyrus representing the primary sensory cortex was found to be the only relevant brain area by Johannsen et al[16] (SCP cutoff ≥ 1 in each subscale) and Babyar et al[37] (Burke Lateropulsion Scale), and the inferior parietal lobe as an area involved in visuovestibular processing was detected by Ticini et al[19] (SCP cutoff ≥ 1 in each subscale). The brain structures found to be relevant in the present study in individuals in a rehabilitation setting, however, have not been reported before for an acute or early subacute phase, whereas the finding of larger lesions in individuals with LP compared with individuals with no LP was also identified by Karnath et al[15] and Babyar et al.[37]

The thalamus, specifically the posterior thalamus, was reported to be a relevant brain structure for LP in 3 studies.[14,15,19] None of our analyses revealed the thalamus as relevant, as in studies by Baier et al[17] (SCP cutoff ≥ 1 in each subscale), Abe et al[18] (SCP cut off >0 in each subscale), Babyar et al,[37] and Lee et al[38] (cutoff >0 in each subscale). The posterior thalamic radiation, however, originating in the posterior thalamus, was found to be a relevant structure (among the 10 structures with the highest *z* values), projecting to the primary visual area and sensory associated areas of the parietal, occipital, and temporal lobes.[39] As a critical note, in our study—as may be the case in other studies as well in which the thalamus was not detected—the thalamus was analyzed as 1 single area and not split into different parts. This was done despite the findings by Karnath et al,[15] who found a clear separation, showing that lesions of individuals with LP were centered in the posterior thalamus, whereas the anterior part of the thalamus was more frequently affected in individuals with no LP. If the participants in the current study had a similar lesion pattern and the same amount of voxels were affected—albeit in different parts of the thalamus—the VLBM would not show a difference between these groups in this brain region. One should keep in mind that although the thalamus was not detected as a relevant brain area, the thalamic network might be involved because of the findings involving the posterior thalamic radiation, potentially leading to similar deficits.

Severity of LP

Analysis of LP severity revealed the middle temporal gyrus, the postcentral and precentral gyrus, the middle frontal gyrus, the superior longitudinal fasciculus, the superior temporal gyrus, and Rolandic operculum as relevant structures. Of those, the middle frontal gyrus, the postcentral and precentral gyrus, and the Rolandic operculum were specifically relevant areas for LP severity but not for LP duration. The more profound the LP was, the stronger the association with the postcentral gyrus, which has also been reported by Johannsen et al[16] and Babyar et al.[37] Along with the primary sensory cortex, the secondary sensory cortex in the operculum also plays a role in LP severity. A lesion in the middle frontal and the precentral gyri also led to a more severe LP. The frontal eye field (Brodman area 8) is located at the intersection of these 2 gyri. It has an important role in the control of visual attention and eye movements. The middle frontal gyrus also supports executive functions and plays a role in sensory selection and modulation. Similar to the method used to analyze LP severity in the current study, Baier et al[17] and Babyar

et al[37] used sum scores for their analyses and not a binary group selection (ie, LP vs non-LP) with mean SCP values of 73.8% (SD: 20.5%) to 75.5% (SD: 18.8%) of the total SCP score, or mean Burke Lateropulsion Scale values of 4.5 (SD: 2.9) points, respectively. However, although these 2 studies include a severity grading, the results might be biased because individuals with no LP are included in the analysis. When investigating LP severity, the analyzed sample should include only those individuals with different levels of LP but no individuals with no LP.

Duration of LP

In analyzing LP duration, a statistically significant association was found for the orbital part of the inferior frontal gyrus, the angular gyrus, the temporal gyrus (superior, middle, and inferior parts, and the temporal pole), the sagittal stratum, the hippocampus, the superior longitudinal fasciculus, the inferior parietal lobe, and the supramarginal gyrus. Four of these structures were also detected by Ticini et al,[19] who investigated 8 study participants with extrathalamic brain lesions with and with no LP. Using perfusion-weighted imaging, subtraction images revealed perfusion deficits in the structurally intact inferior frontal gyrus, the middle temporal gyrus, and the inferior parietal lobule, and small parts of the superior longitudinal fasciculus were affected. The authors discussed the relevance of these brain areas with regard to the general occurrence of LP. Duration of LP was not assessed in this study. The participants investigated, therefore, could have been coincidentally suffering from persistent LP. Again, as stated previously, without knowledge of the duration of the behavior, the findings on LP occurrence are potentially superimposed by brain areas relevant for duration.

Implication for Interventions

Most of the areas found to be relevant for LP duration in the present study belong to the frontoparietal network, which is known to be a network for cognitive control,[40] specifically in executive control, that is, the ability to deliberately guide action based on goals.[41] In addition, the temporal cortex, particularly the middle temporal cortex, receives highly processed sensory information from all sensory regions and is generally accepted to play an important role in memory-related networks and in long-term memory. These areas involved in working memory and attention are more active during explicit learning. A lesion in these areas could cause a reduction in effectiveness of therapeutic interventions relying on explicit knowledge and instead increase the potential of interventions in which important information is given to build up implicit, nondeclarative knowledge. This hypothetical construct could be used to explain the findings of some therapeutic intervention studies in which a driven gait orthosis was found to be more effective than physiotherapy focused on visual cues.[22,23,42] While walking by means of a driven gait orthosis, the exercising individual can be kept in an upright body posture for an extended period of time while the information on verticality is presented in an implicit, unconscious manner. In contrast, feedback or information based on external visual stimuli requires a patient's ability to translate the received information into a specific motor behavior. This process relies more on declarative knowledge. Future research should be performed to verify this hypothesis, also considering several measures of verticality, specifically the visual vertical when applying visual cues.

Limitations

Despite the huge advantages of employing images of individuals to disentangle brain function, the technique of lesion mapping still suffers from weaknesses that have not been clearly addressed.[43] Lesion distribution is usually restricted to the brain territory irrigated by the blood vessel engaged in the cerebrovascular accident, although in many cases continuous voxels are affected, increasing and confounding the area of impact of the lesion in the studied neuropsychological impairment. These voxels might or might not have a direct influence on the behavior. Although they are equally included in the statistical analysis, the independence of voxels supposed in the statistical analysis might not be true. In addition, part of this tissue can be white matter tracts belonging to a specific network that could see their function partially interrupted not directly because of the lesion. The evolution of this damage with time could be responsible for the differences observed in our group of individuals who suffered from LP during the weeks immediately after the stroke but not after a few weeks, that is, different functional disruption not directly connected with the damaged vessel could be responsible for LP at the beginning that is properly recovered with time, while fundamental areas engaged in the vestibular system are responsible for LP in the long term. For this study, we analyzed only those individuals with right-sided lesions. Brain correlates for individuals with left-sided lesions might lead to different findings.

CONCLUSIONS

This is the first study linking brain areas to the findings of therapeutic intervention studies. Previous findings that individuals with LP have larger lesion sizes compared with individuals with no LP can be confirmed by the study presented here. In comparing the brain lesions of individuals with and with no LP, the superior occipital gyrus, the precuneus, the superior parietal lobe, the cuneus, the superior frontal gyrus, the posterior corona radiation, and posterior thalamic radiation were found to be relevant areas for LP. These brain areas mainly belong to the multisensory network with a predominance of structures relevant for visual processing, or are involved in self-awareness in coordination with the action of the sensory system, like the superior frontal gyrus. The corona radiata has been identified as part of the white matter tracks engaged in verticality perception.

In analyzing LP severity and duration, areas, such as the inferior frontal gyrus, the hippocampus, the inferior parietal gyrus, the supramarginal gyrus, the angular gyrus, the temporal cortex, the sagittal stratum, and the superior longitudinal fasciculus, which are known to be involved in spatial cognition and in memory and attentional processes, were found to be relevant. These areas involved in working memory and attention are more active during explicit learning. A lesion in these areas could cause a reduction in the effectiveness of therapeutic interventions relying on explicit knowledge and

instead increase the potential of interventions in which important information is given to build up implicit, nondeclarative knowledge. This hypothetical construct could be used to explain the findings of some therapeutic intervention studies in which a driven gait orthosis was found to be more effective than physiotherapy focused on visual cues.

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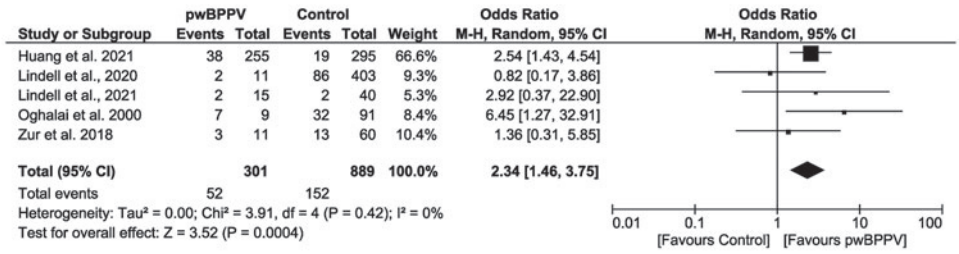
CORRIGENDUM

Gait and Falls in Benign Paroxysmal Positional Vertigo: A Systematic Review and Meta-analysis: Corrigendum

In Figure 10, about the odds ratio of falls in people with BPPV, the labeling of the axes was switched. The [favours pwBPPV] should be on the right side, [favours control] on the left. The data and results in the figure are still correct. The corrected figure is reprinted below.



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