

Impairments in path integration, rotational memory and balancing in patients with temporal lobe epilepsy

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ABSTRACT

Objectives The vestibulo-medial temporal lobe (MTL) axis model proposes that the vestibular system and the MTL are tightly linked both structurally and functionally so that alterations of one structure should entail disturbances in the other. Accordingly, patients with temporal lobe epilepsy (TLE) with their functional and possible structural temporal lobe pathology should show deficits in vestibular-related behaviour. This study aimed at assessing behavioural deficits related to a suspected disturbance of the vestibulo-MTL axis in patients with TLE.

Methods Twenty patients with TLE (46.7±15.1 years, seven females) and their age-matched and gender-matched controls (46.7±15.1, seven females) underwent three test batteries that challenged vestibular and MTL functions: balancing, path integration (triangle completion test) and rotational memory. In addition, participants underwent a structural MRI for grey matter analysis using voxel-based morphometry.

Results Compared with controls, patients with TLE showed significantly inferior performance in all three behavioural tests, with large effect sizes. There were no significant grey matter differences between the two groups.

Conclusion These results indicate a potential disturbance in the vestibulo-MTL axis in TLE; these are to be verified by future large-scale studies. In the current study, these behavioural deficits emerged without evidence of any brain volume differences between the patients and their controls as depicted by high-resolution MRI. This speaks for a dissociation between functional and structural alterations in TLE.

INTRODUCTION

Studies on animals and humans^{1–6} suggest a strong anatomical and functional interdependency between the vestibular system and the medial temporal lobe (MTL) regions. Accordingly, here we propose and test a novel concept termed ‘vestibulo-MTL axis’ using temporal lobe epilepsy (TLE) as a model of impaired MTL function and of resulting vestibular deficits.

Several studies reported diverse volumetric grey matter differences in temporal regions—including the hippocampus—of patients with TLE when compared with

healthy controls.^{7,8} In line with these anatomical changes, MTL-dependent memory dysfunctions in patients with TLE have been reported.^{9,10} Other cognitive functions found to be impaired in TLE refer to spatial orientation,^{10–12} because successful orienting in space—including path integration—requires the integrity of place and grid cells in the hippocampus and the entorhinal cortex. For this purpose, MTL regions receive inputs from the vestibular system.^{14–6,13} Accordingly, patients who had undergone a temporal lobectomy because of drug-resistant TLE showed deficits in path integration as determined by the triangle completion test (TCT).^{14,15}

Another cognitive function that relies on vestibular input to the MTL’s memory system is rotational memory (RM), which pertains to one’s ability to memorise the amplitudes and directions of passive rotations while the eyes remain closed. Whether RM is altered in TLE, has—to the best of our knowledge—never been assessed before.

For both path integration and RM, an interaction between the vestibular and the MTL memory system is mandatory. The presumed vestibulo-MTL axis model, however, also predicts that alterations within the MTL should entail deficits in ‘vestibular only’ functions such as the successful maintenance of balance,^{16–18} which can be tested, for example, with the clinical balance test (CBT).^{4,6,19,20}

Indeed, patients with TLE often show clinical vestibular manifestations, such as dizziness and sense of imbalance.²¹ To the best of our knowledge, the vestibular-dependent balancing abilities of patients with TLE have not been investigated up to now.

Therefore, here we asked whether three sets of behavioural functions, which should rely on the proposed vestibulo-MTL axis, namely (1) path integration, (2) RM and (3) balancing, are altered in patients with TLE. We also asked whether these behavioural changes are related to differences in grey

matter volumes between patients and healthy persons. To that end, high-resolution 3D MRI images were analysed using voxel-based morphometry (VBM).

METHODS

Subjects

Twenty patients with TLE (46.7±15.1 years, seven females) were recruited for this study (table 1) and were age-matched and gender-matched by the control participants (46.7±15.1, seven females) in a pairwise manner and received the same amount of money. The sample size was based on our previous studies.^{22,23} Eligible patients for this study were all those with a TLE diagnosis aged from 18 to 70 years. All TLE patients were recruited through referral from the Epilepsy Department of the Otto-von-Guericke-University Clinic in Magdeburg. The epileptogenic zone²⁴ was determined by video electroencephalography (EEG) monitoring (ie, seizure semiology and ictal EEG) and neuroimaging evaluation (MRI and (positron emission tomography)), which included the detection of epileptogenic lesions such as hippocampal sclerosis. No patient had clinical signs of a cerebellar syndrome, typically seen in patients with drug-induced vestibular dysfunction. Patients suffered either from short-term (several minutes) focal aware or non-aware seizures. Nine of the

20 patients had undergone a temporal lobe resection (table 1). Seventeen of 20 patients were employed at the moment of testing, 2 were retired and 1 was performing home-related duties.

Experimental design

This study was cross-sectional with one factor: group (control, epilepsy). All the measurements took place in the German Center for Neurodegenerative Diseases from January to December 2018.

Behavioural tests of vestibular function

Triangle completion test

For assessment of non-visual spatial orientation, the triangle completion test (TCT) from our previous studies was used.⁴⁻⁶ In brief, six triangular paths were marked on the floor of a room, three in the left and three in the right direction, giving thus three pairs of triangular paths, with turning angles of 60°, 90° and 120°. Each participant was walked (active) and pushed (passive) once along each of the paths, giving thus 12 trials per participant in total (3 to the left and 3 to the right, times 2 conditions). Participants' task was to walk back to the starting point, using the shortest possible way back. The main outcome variables were the distance and the angular error.

Table 1 Clinical characteristics of patients with TLE

Patient (P)	Time since last seizure	Disease duration (in years)	Lateral	No of AEDs at time of the study	Surgery (TLR)	MTL sclerosis
P1	1 week	11	Left	3	No	Yes
P2	3 years	33	Left	3	No	No
P3	2 years	8	Left	3	No	No
P4	24 years	22	Left	5	TLR	TLR
P5	4 years	20	Right	2	TLR	TLR
P6	4 years	9	Left	2	TLR	TLR
P7	2 years	5	Bilateral	2	No	No
P8	1 year	24	Bilateral	1	No	No
P9	1 month	11	Left	2	No	No
P10	5 years	34	Left	3	TLR	TLR
P11	1 month	24	Left	3	TLR	TLR
P12	2 weeks	27	Left	2	No	Yes
P13	2 years	5	Left	3	No	No
P14	5 years	7	Left	1	TLR	TLR
P15	1 year	17	Left	4	No	Yes
P16	1 year	50	Left	1	TLR	TLR
P17	1 year	25	Right	1	No	No
P18	5 years	11	Left	2	TLR	TLR
P19	5 years	51	Right	4	TLR	TLR
P20	1 year	6	Right	2	No	Yes

AEDs, anti-epileptic drugs; MTL, medial temporal lobe; TLR, temporal lobe resection.

Rotational memory

A subject was seated in a chair that rotates (Interacoustics, Denmark) about an earth horizontal axis (left and right rotations). Eyes were blindfolded and ears closed. After one or more rotations in one or both directions had been executed by the software, the subject was asked to return to the initial position, by instructing the examiner on how much to rotate the chair manually until the initial position has been reached.

The following rotations were executed twice each by the software: one, two, four and eight rotations. After each trial, the chair was automatically rotated back to the initial position.

Clinical balance test

The CBT has been described in detail in our previously published work.⁴⁻⁶ In brief, it consists of standing on stable and unstable surfaces and walking conditions, all of which further contain subconditions with open and closed eyes. In total, there are 30 assessment items and the maximum amount of points that could be collected was 90, with each condition carrying the minimum of 0 and the maximum of 3 points.

MRI

MR images were acquired on a 3 Tesla Siemens MAGNETOM Verio scanner (Syngo MR B17) using a 32-channel head coil. High-resolution T1-weighted MPRAGE sequences were acquired using a 3D magnetisation-prepared rapid gradient echo imaging protocol (224 sagittal slices, voxel size: 1 mm×1 mm×1 mm, repetition time: 2500 ms, echo time: 3.47 ms, inversion time: 1100 ms and flip angle: 7°).

VBM is a whole-brain unbiased technique for analysis of regional gray matter volume and tissue changes (Ashburner and Friston, 2000). Preprocessing involved grey matter segmentation, template creation via DARTEL, spatial normalisation to standardised Montreal Neurological Institute (MNI) space and smoothing with a Gaussian kernel of 8 mm full width at half maximum. Whole brain analysis was performed first and was followed by region of interest (ROI) analysis of MTL regions, including the hippocampus and the parahippocampus on both sides. Patients who underwent a surgical removal of temporal lobe areas (n=9) were not included in this analysis.

Assessment of general cognitive function

For determining the patients' general cognitive status, they underwent the standardised neuropsychological test battery Consortium to Establish a Registry for Alzheimer's Disease (CERAD).²⁵ The CERAD test battery includes assessments of language, visuoconstructive abilities, processing speed, executive functions, verbal and nonverbal short-term and long-term memory.

Statistical analysis

The outcome variable for the neuroanatomical analysis was the structural difference in brain neuroanatomy as observed by VBM. In order to analyse the difference in GM volume changes between groups, an independent t-test with the factor group (epilepsy, control) was applied. For both the whole-brain and ROI between-group comparisons, multiple comparison correction was performed in the form of family-wise error correction, where the results were considered significant at $p < 0.05$.

Table 2 Results of all tests and conditions

Test	Condition(s)	Mean±SD Controls	Mean±SD Patients	P value	Effect size (d)
Triangle completion test	Angle				
	All conditions	36.5±30.9	69.2±23.1	***0.001	1.20
	Walk	32.5±33.1	75.2±34.4	***0.001	1.27
	Wheelchair	40.4±30.4	63.1±23.2	*0.013	0.84
	Distance				
	All conditions	164.9±78.0	263.1±63.5	***0.001	1.40
Rotational memory	All conditions	22.2±10.5	45.8±16.1	***0.001	1.73
	One rotation	14.6±8.1	37.7±23.3	***0.001	1.32
	Two rotations	22.0±14.4	55.0±39.0	**0.002	1.12
	Four rotations	32.2±21.3	46.3±24.6	0.072	0.61
	Eight rotations	20.1±16.0	44.1±33.6	**0.009	0.91
Clinical balance test	All conditions	66.0±8.1	57.0±8.7	**0.002	1.07
	Open eyes	53.0±7.4	46.7±7.6	*0.014	0.84
	Closed eyes	13.0±1.7	10.3±2.1	***0.001	1.44

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

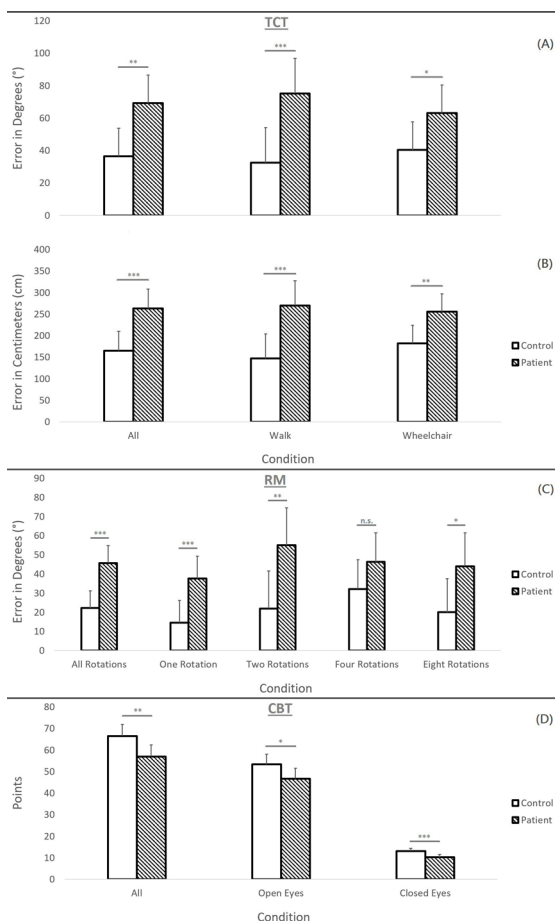


Figure 1 Errors on TCT (A and B), RM (C) and score on CBT (D) on all conditions for both patients and controls; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. CBT, clinical balance test; RM, rotational memory test; TCT, triangle completion test.

Data were analysed with MatLab (MathWorks, USA) and VBM8-Toolbox within SPM12 (UCL, Great Britain).

Analysis of the behavioural data was performed with SPSS V.21 (IBM, USA). First, a repeated-measures analysis of variance with the between-group factor group was applied to inspect main and interaction effects. This was followed then by an independent t-test. The data were checked for assumptions of normality and homogeneity of variance.

In tables and figures, the respective means with 95% CIs of the difference are presented. In addition, the effect sizes (Cohen's d) are listed.

The collected data were analysed by MD who was blinded to the data collection.

RESULTS

Behavioural tests of vestibular function

As summarised in [table 2](#), patients with epilepsy performed significantly worse on all tests related to the vestibular system compared with control subjects.

In the TCT, the patients performed worse in all subconditions and on both outcome variables (angle and distance, see [figure 1A,B](#)). Thus, they demonstrated

decreased ability to return to the starting point, represented by a higher angular deviation from the correct path towards the original starting point as well as by a larger distance from the point where they ended up to the original starting point. The effect sizes were again large to very large for all comparisons ([table 2](#)).

Likewise, as presented in [figure 1C](#), patients' performance on the rotational chair were significantly worse than in controls. Their ability to detect rotational movements based on inputs from the vestibular system, and to recall this movement immediately thereafter, was decreased on all conditions—both those with only one rotation and those with multiple rotations, involving therefore memory of previous rotations. Effect sizes on the rotational memory test were large to very large ([table 2](#)).

[Figure 1D](#) shows the difference between two groups on the CBT, for overall scores as well as for conditions with open and closed eyes separately. Patients with epilepsy achieved significantly lower scores overall and on each of the conditions compared with the controls, with large to very large effect sizes for each of the comparisons ([table 2](#)).

Subgroup analyses

Surgery versus no surgery

Patients were divided into two subgroups: those who had undergone a temporal lobe resection and those who had not. Results of this comparison are listed in [table 3](#). As shown, there were no significant differences on any of the behavioural tests.

Cognitive (CERAD) deficit versus no deficit

Cognitive impairments are well known for patients with epilepsy.²⁶ To test whether the observed differences between the two groups (patients vs controls) were related specifically to vestibulo-MTL functions or resulted from general cognitive impairments instead, we used the CERAD score to divide the patients into two subgroups: (1) cognitively deficient and (2) cognitively normal (within normal range on all tests). Consequently, we compared performance of these two subgroups on all behavioural tests (TCT, RM and CBT). Patients without cognitive deficiency ($n=7$, 39.4 ± 16.6 years) were younger than the deficient ones ($n=10$, 50.2 ± 11.7 years). As depicted in [figure 2](#), there were no significant differences on TCT and RM between cognitively deficient and non-deficient patients. On CBT, however, significant differences ([figure 3](#)) between the subgroups were seen.

Age has been shown to have a strong effect on balancing capabilities.²⁷ Hence, it might have been the case that the differences between the two cognitive subgroups in CBT performance were driven by their age rather than by their cognitive abilities. Therefore, we assessed whether age affected performance in the CBT in the control group, too. We performed a median split to divide our control group into two subgroups: (1) younger (34.6 ± 7.7 years) and (2) older (60.4 ± 7.8

Table 3 Results of all tests and conditions for the two subgroups (OP vs no-OP)

Test	Condition(s)	Mean±SD Surgery	Mean±SD No surgery	P value	Effect size (d)
Triangle completion test	Angle				
	All conditions	69.5±22.9	68.9±24.7	0.952	0.04
	Walk	77.1±35.6	73.0±34.9	0.800	0.16
	Wheelchair	61.9±21.4	64.5±26.5	0.811	0.15
	Distance				
	All conditions	261.8±64.2	264.6±66.5	0.923	0.06
	Walk	272.3±94.0	268.0±96.7	0.922	0.06
	Wheelchair	251.2±50.3	261.2±58.9	0.687	0.26
Rotational memory	All conditions	45.8±15.2	53.8±29.6	0.442	0.48
	One rotation	34.5±22.9	57.5±51.4	0.200	0.82
	Two rotations	61.8±42.5	49.2±33.5	0.477	0.47
	Four rotations	44.5±21.4	45.6±29.5	0.930	0.06
	Eight rotations	42.3±38.8	63.1±55.6	0.338	0.61
Clinical balance test	All conditions	53.8±14.6	56.7±8.3	0.610	0.34
	Open eyes	44.2±11.6	46.6±7.8	0.608	0.34
	Closed eyes	9.6±3.4	10.1±1.9	0.713	0.24

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.
OP, operation.

years). As shown in Figure 5B, there was a significant difference between the two subgroups, with the results resembling those of the two patients subgroups. Furthermore, we observed significant correlations of age with the CBT score of controls ($r = -0.782$, $p < 0.05$) and that of patients without cognitive deficits ($r = -0.776$, $p < 0.05$), but not with CBT score of patients with cognitive deficits ($r = -0.009$, $p = 0.98$). These data signify a strong association of age with CBT score, with higher age leading to lower scores.

Other subgroup analyses

Analyses related to sidedness (right vs left) and to the presence of hippocampal sclerosis (sclerosis vs no-sclerosis) failed to reach significance; this is very likely due to the low number of patients in the compared groups (<5).

To exclude the possibility of a drug-induced vestibulo-cerebellar dysfunction, we excluded the three patients who were taking sodium channel blockers and repeated all analyses. With these three patients excluded, the same significant differences between the patients and healthy participants on all three behavioural tests (RM, CBT and TCT) were observed (online supplemental table 1).

MRI

Using whole brain VBM analysis, we could not find any significant differences in grey matter volumes between patients with TLE and controls. Likewise, the ROI analysis of hippocampal and parahippocampal areas revealed no significant differences between the two groups.

DISCUSSION

This study investigated the abilities of patients with TLE for path integration, RM and balancing. With their suspected compromised vestibulo-MTL axis, we expected all three abilities to be impaired in TLE. Indeed, the patients in comparison with healthy controls performed worse in all three corresponding tests: (1) TCT, (2) RM test and (3) CBT. No group differences in volumes of relevant brain regions (as seen by VBM) were found.

Deficits in TCT and RM could arise exclusively from an MTL dysfunction,²⁶ that is, these deficits do not necessarily imply a disruption of the assumed vestibulo-MTL axis. Indeed, many prior patient studies reported difficulties in traditional tasks of hippocampal function such as spatial and associative memory in patients with TLE.^{10 12} However, our data provide a sound level of evidence that patients' deficits went beyond a mere MTL dysfunction and involved the vestibulo-MTL system. First, the patients with TLE performed worse in the CBT, a specific test of balancing abilities that does not involve any hippocampus-related function. Second, they performed significantly worse in all memory tests that eliminated visual control and, thus, enforced the use of vestibular input. Third, in all of our patients with TLR we found the same functional deficit as in the non-operated patients. Fourth, patients with a general cognitive deficit performed as good as patients without deficit on TCT and RM. Finally, our earlier study indicated that training of the vestibular system leads to improvements in path integration, suggesting a link between the two systems.⁶ In summary,

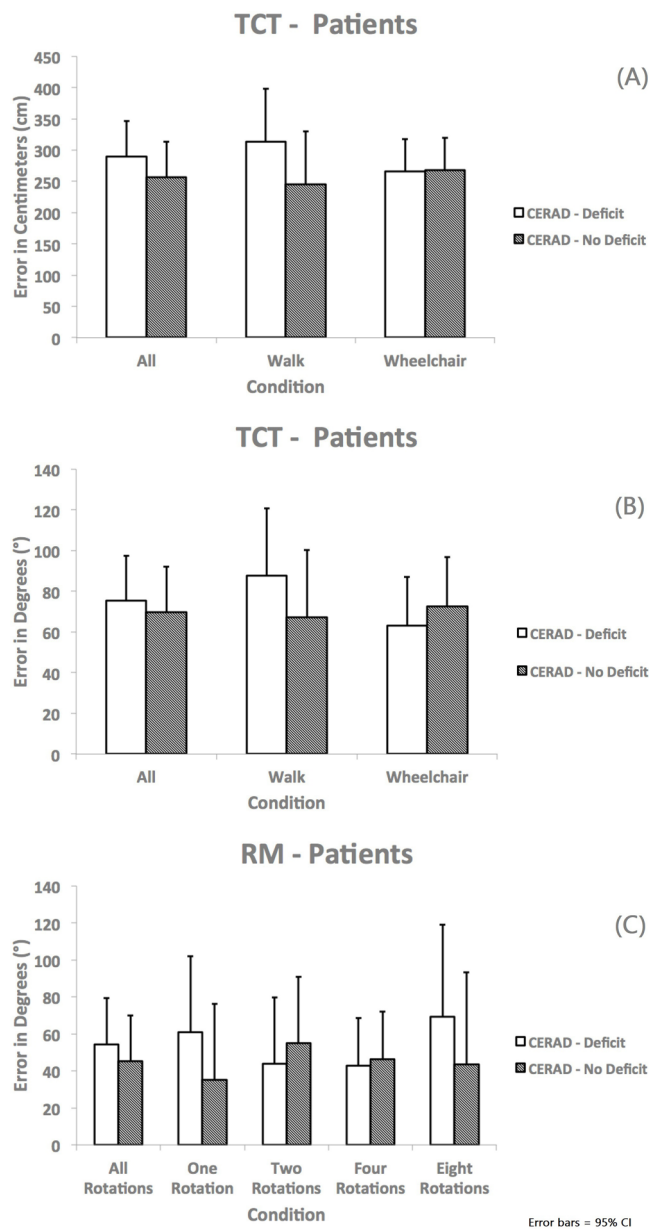


Figure 2 Errors on TCT (A and B) and RM (C) on all conditions for two groups of patients (grouped by CERAD score). CERAD, Consortium to Establish a Registry for Alzheimer's Disease; RM, rotational memory test; TCT, triangle completion test.

the current data suggest that the patients' disruption of the MTL led to vestibular deficits.

The concept of interdependency between the vestibular system and the MTL, particularly the hippocampus, has been well described by earlier studies on animals^{1 28 29} and humans.^{2 4-6 30-32} Since deficits in patients with TLE, with no known vestibular disorders (eg, vestibulopathy), in each of the appointed vestibular-dependent tasks (TCT, RM, CBT) were observed in this study, their impaired performance may be attributed to distorted processing of vestibular inputs by spatial orientation centres, located in the hippocampus and surrounding regions. This is in accordance with studies on patients with temporal

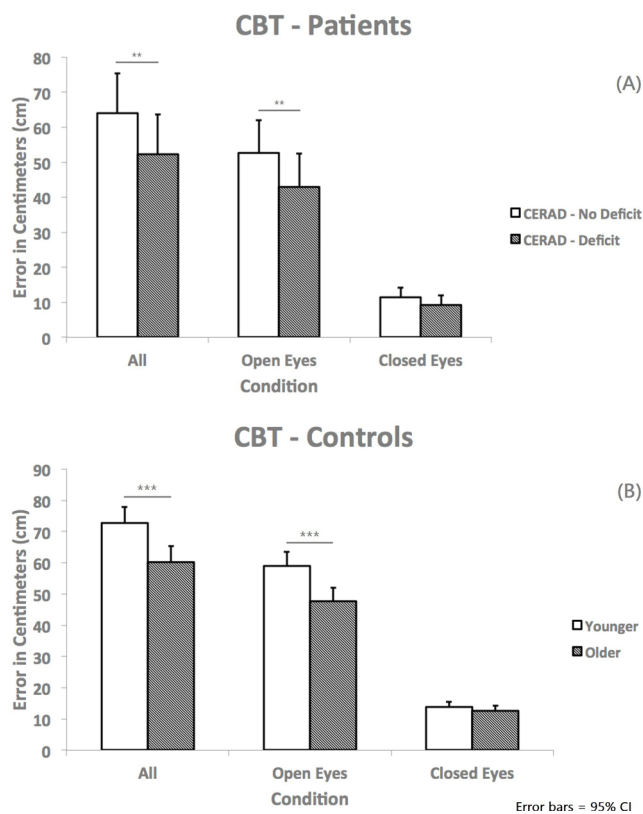


Figure 3 Score on CBT on all conditions for two groups of patients (grouped by CERAD score) and controls (grouped by age); ** $p < 0.01$, *** $p < 0.001$. CBT, clinical balance test; CERAD, Consortium to Establish a Registry for Alzheimer's Disease.

lobectomy.^{14 15} However, unlike these studies, we could not find any structural brain changes nor did we notice a performance differences between operated and non-operated TLE patients.

The rotatory chair test has been successfully applied in a number of studies on various patient groups and healthy participants.³³⁻³⁶ Vestibular inputs play a critical role in human angular orientation by providing inertial cues of self-motion; the brain must then convert motion information to distance information, a process which is known to rely on the temporal lobe and associated regions.³⁵ Temporal lobe regions, primarily the hippocampus and the medial entorhinal cortex, also encode spatial information.³⁶⁻³⁹ Furthermore, it has already been shown that spatial memory becomes impaired in patients with hippocampal atrophy.² Also, earlier studies could demonstrate a relationship between vestibular function and topographical/spatial memory, centred in the hippocampus.³⁶⁻⁴⁰ However, there is a major lack of information on RM abilities in humans, thus preventing us to make a direct comparison. In our still unpublished work, we could observe a better performance on this test by ballet dancers, who use their vestibular system very frequently. This was also true for participants who underwent a 1-month slackline training with closed eyes. Our current study is the first one to report a decrement in RM abilities of patients with TLE, allowing us to speculate about a

possible influence of a functional deficit due to TLE itself or alterations of temporal structures due to the epileptogenic lesion on this ability. This may also indicate that relevant temporal structures have lost their capacity to process and store vestibular inputs, signifying limitations in vestibulo-MTL function or impairments in the vestibulo-MTL axis.

There are very few studies on balancing abilities of patients with TLE and none of them used a clinically validated balance test for assessment. One study on drug-resistant TLE reported postural control abnormalities in the patients.⁴¹ Moreover, vestibular dysfunction may lead to a deterioration in short-term visuospatial memory, whereby the involved pathways include the hippocampus, among other cortical regions.⁴² Vice versa, balance training in healthy adults has positive effects on memory and spatial cognition, and an improvement in cardiorespiratory fitness does not seem to be necessary for these cognitive effects to take place.⁴³ Our study results are also in favour of this interdependency between the MTL and balancing skills, with patients with TLE performing much worse on all conditions of the CBT compared with healthy controls. Although we found a significant difference in balancing abilities between the patients with and without cognitive deficits, our data also indicated that one source of this difference might be the age difference between these two groups, which is in accordance with previous studies investigating the effects of age on clinical balancing abilities.²⁷ Neurocognitive and memory deficits are well-accepted impairments especially in patients with TLE. The current results also have direct clinical consequences as they imply that patients with TLE are also at increased risk of vestibular dysfunction, which could result in falls. This assumption needs further investigation since even in neurological wards this deficit may be overlooked.

The question remains what pathology induced the behavioural deficits in the patients. Using VBM we could not find any significant differences between (non-operated) patients with TLE and healthy controls. Also, the patients who had undergone surgery did not perform differently from the non-operated ones. Together, these observations rather speak for a functional than a structural alteration in these patients. Of course alternative explanations for the null results regarding observable anatomical changes need to be considered. First, the sample size was small consisting of only 11 subjects per group. Previous studies on a much larger sample were able to detect volumetric differences between patients with TLE and controls.^{44 45} Another limitation is heterogeneity of the sample, consisting of patients with and without hippocampal sclerosis, as well as of those who have and who have not undergone a temporal lobectomy. In only four of our non-operated patients, a hippocampal sclerosis was diagnosed—earlier research has demonstrated that VBM-based differences may highly depend on the extent of hippocampal sclerosis.^{8 45} The remaining task of future studies is to attempt to confirm our findings

on a larger and more homogeneous sample. Nevertheless, functional differences on all three behavioural tests were found despite the shortage of volumetric effects, speaking for a dissociation between structural and functional alterations in patients with TLE.

In conclusion, this study provides a set of evidence of functional interdependency between the vestibular system and brain regions responsible for processing of vestibular inputs, located in the hippocampus and surrounding MTL areas. Patients with TLE, which we had chosen to test our hypotheses, performed significantly worse than healthy controls on all three tasks known to, at least partially, depend on intact inputs from the vestibular system—namely RM, path integration (triangle completion) and CBTs. On the contrary, no significant volumetric brain differences (as seen by VBM) could be detected between the two groups, which might be due to a small and heterogeneous sample. Nevertheless, since behavioural deficits arose despite the absence of structural changes, there could be a dissociation between the two in patients with TLE. For the purpose of simplicity and effortless understanding of similar structural and functional effects anywhere on the pathway between the vestibular system and MTL, we proposed the concept of a ‘vestibulo-MTL’ axis—based on this concept, alterations in one structure should entail disturbances in the other.

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Patient consent for publication Not required.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available.

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