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# Differential reorganization of episodic and semantic memory systems in epilepsy-related mesiotemporal pathology

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Declarative memory encompasses episodic and semantic divisions. Episodic memory captures singular events with specific spatiotemporal relationships, whereas semantic memory houses context-independent knowledge. Behavioural and functional neuroimaging studies have revealed common and distinct neural substrates of both memory systems, implicating mesiotemporal lobe (MTL) regions such as the hippocampus and distributed neocortices. Here, we explored declarative memory system reorganization in patients with unilateral temporal lobe epilepsy (TLE) as a human disease model to test the impact of variable degrees of MTL pathology on memory function.

Our cohort included 31 patients with TLE and 60 age- and sex-matched healthy controls, and all participants underwent episodic and semantic retrieval tasks during a multimodal MRI session. The functional MRI tasks were closely matched in terms of stimuli and trial design. Capitalizing on non-linear connectome gradient-mapping techniques, we derived task-based functional topographies during episodic and semantic memory states, in both the MTL and neocortical networks.

Comparing neocortical and hippocampal functional gradients between TLE patients and healthy controls, we observed a marked topographic reorganization of both neocortical and MTL systems during episodic memory states. Neocortical alterations were characterized by reduced functional differentiation in TLE across lateral temporal and midline parietal cortices in both hemispheres. In the MTL, in contrast, patients presented with a more marked functional differentiation of posterior and anterior hippocampal segments ipsilateral to the seizure focus and pathological core, indicating perturbed intrahippocampal connectivity. Semantic memory reorganization was also found in bilateral lateral temporal and ipsilateral angular regions, whereas hippocampal functional topographies were unaffected. Furthermore, leveraging MRI proxies of MTL pathology, we observed alterations in hippocampal microstructure and morphology that were associated with TLE-related functional reorganization during episodic memory. Moreover, correlation analysis and statistical mediation models revealed that these functional alterations contributed to behavioural deficits in episodic memory, but again not in semantic memory in patients.

Altogether, our findings suggest that semantic processes rely on distributed neocortical networks, whereas episodic processes are supported by a network involving both the hippocampus and the neocortex. Alterations of such networks can provide a compact signature of state-dependent reorganization in conditions associated with MTL damage, such as TLE.

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## Introduction

Declarative memory is commonly divided into episodic and semantic memory components. Episodic memories are unique events with specific spatiotemporal associations, whereas semantic memory refers to context-invariant knowledge and facts about the world.[1-3] The relationship between both forms of memory is complex, with behavioural and neuroimaging studies suggesting shared and distinct substrates. Behavioural studies have shown a synergistic interplay between both memory types, whereby episodic memory for events and words processed with semantic categorization exceeds that from non-semantic tasks.[4-6] Functional and structural neuroimaging evidence in healthy populations supports this finding, suggesting shared neural substrates across both memory types. Shared key networks are situated in the medial and lateral temporal lobes,[7-18] alongside posterior parietal regions.[19-21] More broadly, networks involved in both memory types have been shown to engage similar intrinsic functional systems, notably the frontoparietal network[22-24] and the default mode network.[10,25,26] As such, behavioural and neural evidence collectively implicates shared processes in both forms of declarative memory. Nonetheless, findings also point to divergences. Generally, episodic processes appear to rely more on medial temporal lobe (MTL) systems, whereas anterior temporal lobe (ATL) regions are more heavily implicated in semantic processing.[10,16] Likewise, prior work has suggested differential activations in middle frontal versus inferior temporal regions in episodic in comparison to semantic retrieval.[27] A neural divergence between both memory systems is supported by (i) the controlled semantic cognition framework, which stipulates that semantic representations within the ATL 'hub' and modality-specific 'spokes' interact with a 'semantic' control' system that dynamically supervises and adjusts semantic retrieval bilaterally[1,28-30]; and (ii) hippocampal–neocortical connectivity, such that the hippocampus interacts closely with other regions through process-specific alliances to support episodic memory.[13,31,32] A systematic investigation of neocortical and MTL networks will help us to understand substrates contributing to declarative memory function in the human brain.

Temporal lobe epilepsy (TLE) is a common pharmaco-resistant epilepsy in adults and can serve as a human disease model to probe declarative memory system reorganization in young and middle-aged adults.[32,33] Patients typically present with pathology of structures in the MTL, notably the hippocampus,[34-37] and prior research has demonstrated marked impairments in episodic memory in some patients even at a young age.[32,38-40] Episodic memory impairment has been related directly to degrees of hippocampal structural alterations,[41-46] together with widespread structural and functional imbalances in both temporal and extratemporal neocortical networks.[47,48] In contrast to the relatively consistent finding of episodic memory impairment in TLE, semantic memory has been studied less frequently, and reports remain mixed. Semantic memory function appears to be rather mildly affected,[46,49] even in TLE patients with pronounced MTL hypometabolism.[49] Moreover, and in contrast to the frequent finding of episodic memory disruptions in patients undergoing selective MTL resection,[50-52] there are less marked semantic memory impairments seen postsurgically.[53,54] Such resilience suggests a more distributed cortical control network substrate for semantic memory involving both hemispheres,[55,56] in contrast to MTL representations of episodic memory.[57,58] Individuals with TLE may, therefore, have difficulty recalling specific events or episodes from their past while retaining their general knowledge of the world. However, other studies have found significant semantic memory deficits in patients with TLE,[59-61] which have been associated with MTL[41] and ATL lesions.[62] Additionally, poor performance on semantic memory tasks has been demonstrated in TLE patients after unilateral ATL resection.[59,63,64] Nevertheless, given that impairments in declarative memory challenge the day-to-day patient functioning and well-being, it is crucial to derive more mechanistic insights into these memory types and their differential vulnerabilities in TLE.

Contemporary systems neuroscience has emphasized a key role for the spatial organization of macroscale functional networks in human cognition.[65-68] Recent analytical and conceptual advances have notably emphasized the existence and utility of spatial gradients[65,68-71] as low-dimensional axes of cortical organization, often reflective of established principles of cortical topography and

hierarchy.[65,72,73] At the level of intrinsic functional connectivity derived from task-free functional MRI (fMRI), the first/principal gradient anchors primary sensory and motor areas at one end and transmodal association systems, such as the frontoparietal network and default mode network, at the other end, whereas a second gradient differentiates visual and somatosensory/motor areas.[65] Gradients also describe subregional hippocampal organization in a compact manner, with a first gradient differentiating anterior–posterior (long-axis) segments and a second gradient the proximal–distal arrangement of different subfields along the infolding of this allocortical structure.[74-77] Beyond the application of gradient-mapping techniques to study healthy brain organization,[65,76,78-85] recent studies have interrogated gradient alterations in diseased cohorts, including TLE patients.[86,87] A recent study from our group demonstrated microstructural gradient contractions in TLE in the neocortex, which were localized primarily in temporolimbic systems and found to track deficits in episodic memory recall accuracy.[87] Another study demonstrated functional gradient expansion in subcortical structures during resting conditions, with notable differences in ipsilateral hippocampal gradient deviations between left- and right-lateralized TLE.[86] Additionally, patterns of cortical asymmetry and atrophy were shown to reflect microstructural and functional gradients distinctively.[88] Gradient mapping, therefore, offers a framework within which to interrogate global memory network topographies and their association with cognition in both health and disease.

In the present study, we investigated declarative memory network organization in healthy individuals and in a cohort of TLE patients presenting with variable degrees of MTL pathology. All participants underwent episodic and semantic retrieval tasks inside the MRI scanner, with both tasks being matched closely for stimulus presentation, task design and task structure.[32,46] For each of the declarative memory states, we mapped spatial gradients of memory state connectivity, both within the MTL and in macroscale neocortical networks. By adopting gradients as an analytical and conceptual framework for task-derived fMRI data in TLE, we were able to determine: (i) whether networks subserving episodic versus semantic memory in patients undergo a shared or selective reorganization relative to controls; (ii) whether memory network reorganization reflects TLE-related structural alterations in the MTL, capitalizing on established *in vivo* proxies of mesiotemporal pathology[35,89-91]; and (iii) whether these findings reflect behavioural impairment in relational memory seen in patients.

# Materials and methods

## Participants

We studied 31 patients with pharmaco-resistant TLE (17 females, age = 35 ± 11.59 years, left/right-handed = 1/30) and 60 healthy controls (30 males, age = 33 ± 8 years, left/right-handed = 2/58). All participants were recruited between May 2018 and March 2023 at the Montreal Neurological Institute (MNI). Controls met the following inclusion criteria: (i) age between 18 and 65 years; (ii) no neurological or psychiatric illness; (iii) no MRI contraindication; (iv) no drug/alcohol abuse problem; and (v) no history of brain injury and surgery. Patient demographics and clinical features were obtained through interviews with patients and their relatives. Seizure focus lateralization was determined through a comprehensive evaluation of medical history, neurological examination, seizure semiology, video-EEG and clinical neuroimaging. Detailed clinical data, including preoperative MRI findings and information on hippocampal asymmetry/atrophy, in addition to Engel outcome, are available in Supplementary Table 1. Twenty-one patients were diagnosed with left-sided TLE. The mean age of seizure onset was 20.42 ± 10.22 years (range = 2–49 years), with a mean epilepsy duration of 14.20 ± 10.97 years (range = 1–45 years). Eight patients (26%) had a history of childhood febrile convulsion. At the time of the study, most patients were treated with multiple anti-seizure medications (range = 1–4), with differing dosage. Based on quantitative hippocampal MRI volumetry,[92] 20/31 patients (65%) showed marked hippocampal atrophy ipsilateral to the focus (i.e. absolute ipsilateral–contralateral asymmetry z-score > 1.5 and/or ipsilateral volume z-score < –1.5; Supplementary Table 1). At the time of the study, 14/31 patients underwent resective temporal lobe surgeries. In those, postsurgical seizure outcome was assessed using Engel's modified classification,[93] with an average follow-up duration of 23 ± 15.50 months. Postsurgery, nine patients (64%) achieved complete seizure freedom (Engel-I), and five patients (36%) had recurrent seizures. A total of nine specimens were available for histopathological analysis. Here, four patients showed mesiotemporal/hippocampal sclerosis, one patient had evidence of mesiotemporal ganglioglioma, and four had evidence of mild dysplasia in the mesiotemporal structures. There were no significant differences in males/females ($\chi^2 = 0.20$, $P = 0.66$), and there were no significant differences in age ($t = -1.01$, $P = 0.32$) between patients and controls. The study was conducted in accordance with the Declaration of Helsinki, and the MRI data-acquisition protocols were approved by the Research Ethics Board of the Montreal Neurological Institute and Hospital. All participants provided informed consent.

## Declarative memory paradigm

All participants underwent episodic and semantic retrieval fMRI tasks (Fig. 1). These tasks were carefully designed to be closely matched, i.e. they were based on: (i) equivalent symbolic stimuli to accommodate a bilingual participant pool in the Montreal area; (ii) the same number of trials that were presented in a pseudo-randomized manner; (iii) an identical task structure with three alternative forced choice responses at the retrieval phases; and (iv) two difficulty levels.

### Episodic memory

The task had two phases. During the encoding phase, participants were shown paired images of objects and asked to memorize them. To ensure that the images were well matched, we used the University of Maryland, Baltimore County similarity index[93] to control for semantic relatedness. Specifically, we selected items where the similarity score remained below 0.3 on a scale of zero to one. The task comprised 56 pseudo-randomized trials, with 28 difficult trials (with paired images shown only once) and 28 easy trials (paired images shown twice). During the retrieval phase, which took place after several minutes of delay, participants were presented with an image of an object at the top of the screen ('prime') and three different objects at the bottom. From these choices, subjects were asked to identify the 'target' that was paired with the prime during encoding. We analysed data only from the retrieval phase.

### Semantic memory

The semantic task involved a retrieval phase only. In each trial, participants were presented with an image of an object at the top of the

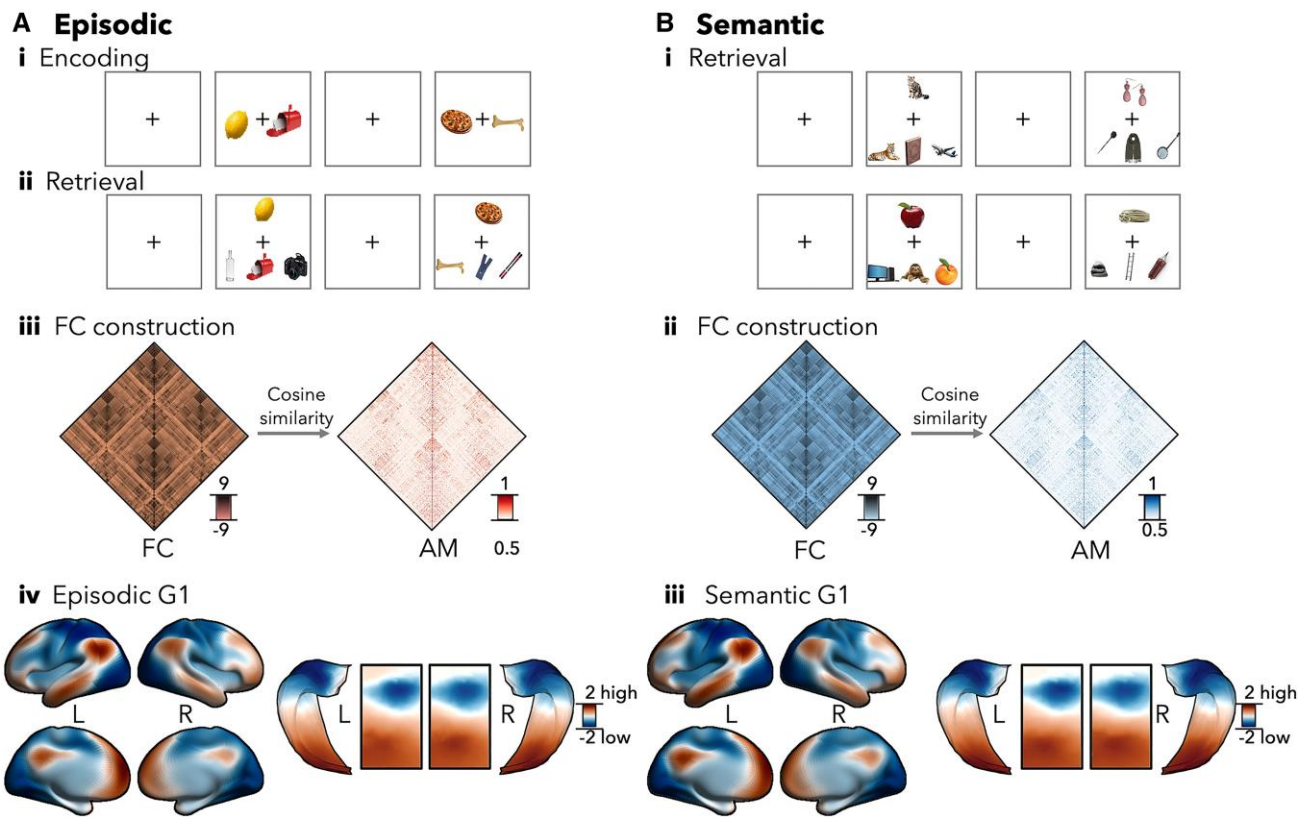


**Figure 1 Episodic and semantic memory tasks.** (**A**) The episodic memory task included encoding [**A(i)**] and retrieval [**A(ii)**] phases. (**B**) In contrast, the semantic memory task included only a retrieval phase [**B(i)**]. Both tasks were matched in terms of stimuli, number of trials, difficulty levels and task structure, such that retrieval phases included three alternative forced-choice responses. Functional connectomes [FC; **A(iii)** and **B(ii)**] were derived independently from episodic and semantic task FC, and affinity matrices (AM) were built based on cosine similarity, followed by gradient decomposition. [**A(iv)** and **B(iii)**]. Neocortical and hippocampal principal gradients (G1) projected to the corresponding surfaces. L = left; R = right.

screen (prime) and three different objects at the bottom (one target and two 'foils'). From these choices, subjects were asked to identify the item (target) that was most conceptually related to the prime. The 56 pseudo-randomized trials were also modulated for difficulty (i.e. there were 28 difficult trials where prime/target shared a similarity index ≥0.7, and prime/foils shared a similarity between 0.3 and 0.7, in addition to 28 easy trials, where prime/target shared a similarity ≥0.7 and prime/foils shared a similarity between 0 and 0.3).

### Performance metrics

Individual episodic and semantic performance was computed by averaging the scores in the difficult and easy trials. We also averaged reaction time. Additionally, we computed performance scores on the mnemonic similarity task[32] (Supplementary material), an alternative test for episodic memory.

## Additional screening for executive function and general cognitive impairment

Participants also completed the Montreal Cognitive Assessment (MoCA)[94] tests outside the scanner. The paradigm has been developed to detect mild cognitive impairment and dementia.

## MRI acquisition

MRI data were acquired on a 3 T Siemens Magnetom Prisma-Fit with the 64-channel head coil. $T_1$-weighted scans were acquired with a 3D-magnetization-prepared rapid gradient-echo sequence [MPRAGE; 0.8 mm isovoxels, matrix = 320 × 320, 224 sagittal slices, repetition time (TR) = 2300 ms, echo time (TE) = 3.14 ms, inversion time (TI) = 900 ms, flip angle = 9°, iPAT = 2, partial Fourier = 6/8, field of view (FOV) = 256 mm × 256 mm]. The diffusion-weighted imaging (DWI) data were obtained with a two-dimensional spin-echo echo-planar imaging sequence with multi-band acceleration and consists of three distinct shells, each with different b-values of 300, 700 and 2000 s/mm$^2$, with each shell acquired with 10, 40 and 90 diffusion weighting directions, respectively (1.6 mm isotropic voxels, TR = 3500 ms, TE = 64.40 ms, flip angle = 90°, refocusing flip angle = 180°, FOV = 224 mm × 224 mm, slice thickness = 1.6 mm, multi-band factor = 3, echo spacing = 0.76 ms). All fMRI were acquired with a 2D/blood oxygenation level-dependent echo-planar imaging sequence (3.0 mm isovoxels, matrix = 80 × 80, 48 slices oriented to AC-PC-30°, TR = 600 ms, TE = 30 ms, flip angle = 50°, FOV = 240 mm × 240 mm, slice thickness = 3 mm, multi-band factor = 6, echo spacing = 0.54 ms). During the resting-state functional MRI (rs-fMRI), participants were instructed to fixate on a grey cross and not to think of anything. All fMRI scans were presented via a back-projection system, and responses were recorded using an MRI-compatible four-button box. The episodic and semantic retrievals both lasted ~6 min.

## MRI processing

Scans were preprocessed using *micapipe*[95] v.0.2.2 (https://github.com/MICA-MNI/micapipe), an open-access multimodal preprocessing,

surface-mapping and data fusion software. $T_1$-weighted data were de-obliqued and reoriented to ensure a consistent orientation across images. Next, linear co-registration, intensity non-uniformity correction and skull stripping were applied. DWI data underwent denoizing, eddy current-induced distortion correction and motion correction, in addition to non-uniformity bias field adjustment. Corrected DWI data were fitted with a diffusion tensor model[96] to compute the mean diffusivity (MD) images.[97] Cortical surfaces were extracted with FreeSurfer v.6.0 from each $T_1$-weighted scan, followed by manual surface generation. Resting-state and task-fMRI were preprocessed using a combination of FSL[98] v.6.0, ANTs[99] v.2.3.4 and AFNI[100] v.20.3.0 software, which involved the following steps: (i) removal of the first five TRs; (ii) image reorientation; (iii) motion correction; (iv) distortion correction based on AP-PA blip field maps; (v) high-pass filtering to be >0.01 Hz; (vi) MELODIC decomposition; (vii) linear/non-linear co-registration to the $T_1$-weighted scans; (viii) nuisance signal regression with FMRIB's ICA-based Xnoiseifier[101] (ICA-FIX); (ix) native cortical surface registration; (x) surface-based registration to the Conte69 surface template with 32k surface points (henceforth, vertices) per hemisphere; (xi) surface-based smoothing with a Gaussian diffusion kernel with a full-width at half-maximum of 10 mm; and (xii) statistical regression of motion spikes. The hippocampus and surrounding structures were automatically segmented using *HippUnfold*[92] v.1.0.0 (https://hippunfold.readthedocs.io/). Task-fMRI and MD data were sampled along the hippocampal midthickness surface, and full-width at half-maximum = 2 mm surface smoothing was applied.

## Gradient identification and alignment

For computational efficiency, surface-mapped neocortical time series were downsampled to a mesh with 10k vertices using *connectome workbench*.[102] Intrahemispheric neocortical functional connectomes were generated for each functional state (episodic, semantic and rest) by calculating Pearson correlations between the time series for all vertices for each participant, resulting in a 5k × 5k connectome per hemisphere (Fig. 1). In this study, the anterior and posterior hippocampus were defined as a continuous span using measures provided by *HippUnfold*.[92] This measure considers the geodesic distance from the hippocampal–amygdalar transition area to the posterior terminus of the indusium griseum. We used a Laplace field ranging from zero to one across the hippocampal grey matter, with zero representing the anterior boundary and one the posterior boundary. As in the neocortex, internal hippocampal connectomes were generated from the extracted time series, resulting in a 419 × 419 functional connectivity matrix per hippocampus. We applied Fisher *r*-to-*z* transformations to neocortical and hippocampal functional connectomes and retained the top 10% of row-wise connections. We constructed affinity matrices using a cosine similarity kernel to measure the similarity of connectivity patterns between regions. Diffusion map embedding,[65,103] a non-linear dimensionality reduction technique implemented in *Brainspace*[104] v.0.1.3 (https://brainspace.readthedocs.io/; Fig. 1), was applied to identify low-dimensional eigenvectors (i.e. gradients) that accounted for the variance in neocortical and hippocampal connectomes. Diffusion mapping is a powerful and efficient tool to compress large-scale datasets. This algorithm uses the diffusion operator $P\alpha$ to create a new representation of data and is guided by two key parameters: $\alpha$, which controls the influence of sampling point density on the manifold, and $t$, which represents the scale of the data. To maintain global connections among data points in the embedded space, $\alpha$ was set to 0.5 ($\alpha = 0$, maximal influence, $\alpha = 1$ no influence), and $t$ was set at 0, consistent with previous studies.[65,104] In contrast to previous work that derived functional gradients mainly from rs-fMRI data,[65,70] our study used multi-task profiling of gradients in TLE. Nevertheless, to ensure consistency with prior literature, we generated intrahemispheric template gradients from group-average rs-fMRI connectomes of both TLE and healthy control participants. We aligned these group-level gradients to a normative gradient template derived from the rs-fMRI data of the Human Connectome Project,[105] a recognized source for constructing reference templates for gradient alignment.[65,104] Procrustes rotations aligned individual and state-specific task-fMRI gradients with these normative reference gradients, ensuring that gradients were consistent in ordering and polarity across participants and memory states.[106] Similar procedures were performed to align hippocampal gradients. Finally, we normalized state- and subject-specific neocortical and hippocampal gradient scores using *z*-transformations relative to the distribution in our healthy control cohort. After normalization, we sorted the data from the TLE patients based on the laterality of the epileptogenic focus by flipping the hemispheric data in right-lateralized TLE, as in prior work.[87]

## Statistical analysis

After gradient alignment, we inferred between-group differences using surface-based linear models implemented in *Brainstat*[107] v.0.4.2 (https://brainstat.readthedocs.io). We additionally controlled for age and sex and corrected for vertex-wise multiple comparisons using random field theory for non-isotropic imaging,[108] at a set family-wise error (FWE) of $P_{FWE} < 0.05$. We also examined gradient alterations in left and right TLE patients separately. We computed the association between gradient scores in regions showing significant between-group differences and cognitive scores. We also investigated the association between gradients and memory while controlling for MoCA scores to ensure that results were not influenced by other neurological disorders. Finally, statistical mediation analyses tested whether the association between group and episodic memory performance was transmitted via gradients.

## Morphological and microstructural substrate analysis

To assess structural substrates of functional network changes, we also compared neocortical and hippocampal thickness and mean diffusivity (MD) between controls and TLE patients. These features have been used previously to demonstrate hippocampal and neocortical structural alterations in TLE.[35,109,110] Neocortical thickness was quantified as the Euclidian distance between corresponding pial and white matter vertices, and we used mid-thickness surfaces to sample MD from co-registered diffusion MRI data. To establish spatial correspondence, cortical thickness and MD maps were registered to the Conte69 surface template and were subsequently downsampled from 32k vertices to 5k vertices/hemisphere. Hippocampal thickness and hippocampal MD were measured using hippocampal surface meshes derived with *HippUnfold*[92] v.1.0.3 (https://hippunfold.readthedocs.io/). Multivariate surface-based linear models assessed morphological and microstructural differences between patients and controls in both hippocampal and neocortical regions, while controlling for effects of age and sex. Finally, we investigated the association between atypical morphology patterns and microstructure and observed

TLE-related gradient alterations. Specifically, we computed the mean thickness and MD scores in regions showing significant functional Gradient 1 (G1) differences between controls and TLE patients and correlated these measures with G1 changes.

### Functional decoding via task-based meta-analysis

We conducted a functional decoding analysis based on Neurosynth[26] (https://neurosynth.org/), a platform for large-scale *ad hoc* meta-analysis of task-based fMRI data. We studied spatial associations between TLE-related functional gradient changes and previously published fMRI activations to identify cognitive terms that elicit similar activation patterns.

## Results

Hippocampal and neocortical surface models for each participant were generated using automatic segmentation[92,95] procedures based on $T_1$-weighted MRI. Functional data were co-registered to these surfaces, and the resulting neocortical and hippocampal time series were used to derive functional connectomes for resting, episodic and semantic memory states for each participant. Diffusion map embedding,[104] a non-linear dimensionality reduction technique, was applied to estimate low-dimensional eigenvectors explaining spatial gradients of connectivity variance. For consistency, reference gradients were derived from rs-fMRI data,[105] and subject- and state-specific neocortical and hippocampal gradients were aligned to these using Procrustes rotations, as in previous work[104,106] (for pre-alignment gradient patterns, see Supplementary Fig. 1).

### Declarative memory topographies

Studying neocortical connectivity in healthy individuals, we derived the first eigenvectors (G1) during both episodic and semantic states separately (for findings of subsequent gradients, please see Supplementary Fig. 2). In episodic/semantic states, G1 explained 22%/21% of functional connectome variance and described a sensory-to-transmodal neocortical gradient, as expected from previous work in healthy adults based on rs-fMRI connectivity.[65] Studying hippocampal networks in controls, we also derived the first eigenvectors in episodic and semantic memory states (Fig. 1). In episodic/semantic states, G1 accounted for 40%/38% of functional connectome variance and described a canonical postero-anterior spatial pattern.[76] State-specific neocortical and hippocampal gradients were spatially correlated in healthy controls ($r = 0.99$, $P = 0$, $n_{permutations} = 1000$), suggesting that both memory systems were captured by both sensory–transmodal neocortical and posterior–anterior MTL trends.

### Atypical task-based gradients in patients with MTL pathology

Comparing neocortical topographies in TLE patients with controls, we found reduced G1 scores in the episodic memory state in patients ($P_{FWE} < 0.05$, mean effect sizes in significant regions $d > 0.50$; Fig. 2A). Functional G1 alterations were localized primarily in the ipsilateral lateral temporal and bilateral posterior cingulate regions. Between-group differences were also seen in the semantic memory state (Fig. 2B), localized in the bilateral lateral temporal and ipsilateral angular gyrus. The TLE-related functional G1 contractions are indicative of a functional dedifferentiation between these unimodal and transmodal systems. Consistent with this finding, the histogram depicting overall mean gradient scores showed an overall reduction in the spread of gradient scores in TLE patients relative to controls (Fig. 2). *Post hoc* analyses revealed relatively consistent effects in clusters of significant gradient alterations in both left ($d = -0.47$) and right ($d = -0.53$) TLE patients for episodic memory and for semantic memory ($d = -0.46$ for left, $d = -0.54$ for right). Moreover, direct comparison between both TLE subgroups did not result in noteworthy differences in both episodic memory ($t = -0.57$, $P = 0.57$, $d = -0.09$) and semantic memory ($t = -0.29$, $P = 0.77$, $d = -0.05$). Considering the hippocampus, conversely, we observed an expansion of G1 scores in the episodic memory state when comparing patients with controls, which was particularly significant in anterior divisions ipsilaterally ($P_{FWE} < 0.05$, $d = -0.84$). The expanded functional G1 in the anterior portions reflects increased connectivity profile variability in TLE, indicating a great intrahippocampal functional disconnection. In other words, the anterior hippocampal gradient scores in TLE are shifted away from the gradient midpoint, further increasing inter-regional differentiation with the posterior hippocampus. Although gradient alterations appeared nominally stronger when comparing left TLE with controls ($d = -0.85$) than when comparing right TLE with controls ($d = -0.32$), no differences in episodic gradient mean values were observed when comparing both TLE subgroups directly, as in the neocortex ($t = -1.35$, $P = 0.69$, $d = -0.22$). These findings, thus, suggest that functional alterations in memory networks remained relatively consistent irrespective of seizure focus lateralization. Using measures provided by *HippUnfold*,[92] we subdivided the significant cluster of TLE-related gradient expansion into subfields. The cluster encompassed subregions in the cornu ammonis 1 (CA1) ($d = -0.82$), CA2 ($d = -0.83$) and CA3 ($d = -90$). Although semantic G1 expansion was also observed in TLE, no vertices survived multiple comparison correction.

### Relationship to temporolimbic structural alterations

An additional analysis explored how proxies of TLE-related structural pathology[35] contribute to episodic functional memory network reorganization. Proxies were derived from neocortical and hippocampal MRI measures of grey matter (i.e. cortical thickness) and diffusion parameters (i.e. cortical mean diffusivity, MD). Comparing patients and controls using multivariate models based on these parameters, significant alterations were observed in patients ($P < 0.05$; Fig. 3A and B; for univariate findings, see Supplementary Fig. 3), mainly localized in ipsilateral temporolimbic areas and anterior regions of the ipsilateral hippocampus. We next examined whether these structural disruptions are associated with previously observed functional alterations (Fig. 3C). To this end, we computed overall temporolimbic structural changes in TLE patients and controls, for both the neocortex and the hippocampus, and conducted a correlation analysis. This analysis revealed an association between overall episodic functional G1 changes and structural alterations ($r = -0.22$, $P_{FDR} = 0.03$). Further tests showed a slightly more selective association with hippocampal ($r = -0.22$, $P_{FDR} = 0.04$) than with neocortical functional G1 measures ($r = 0.19$, $P_{FDR} = 0.08$; for gradient differences after controlling for structural alterations, see Supplementary Fig. 4).

### Relationship to behavioural indices of declarative memory

We examined the relationships between the behavioural performance of participants and their functional memory network reorganization. Behaviourally, patients showed markedly reduced episodic

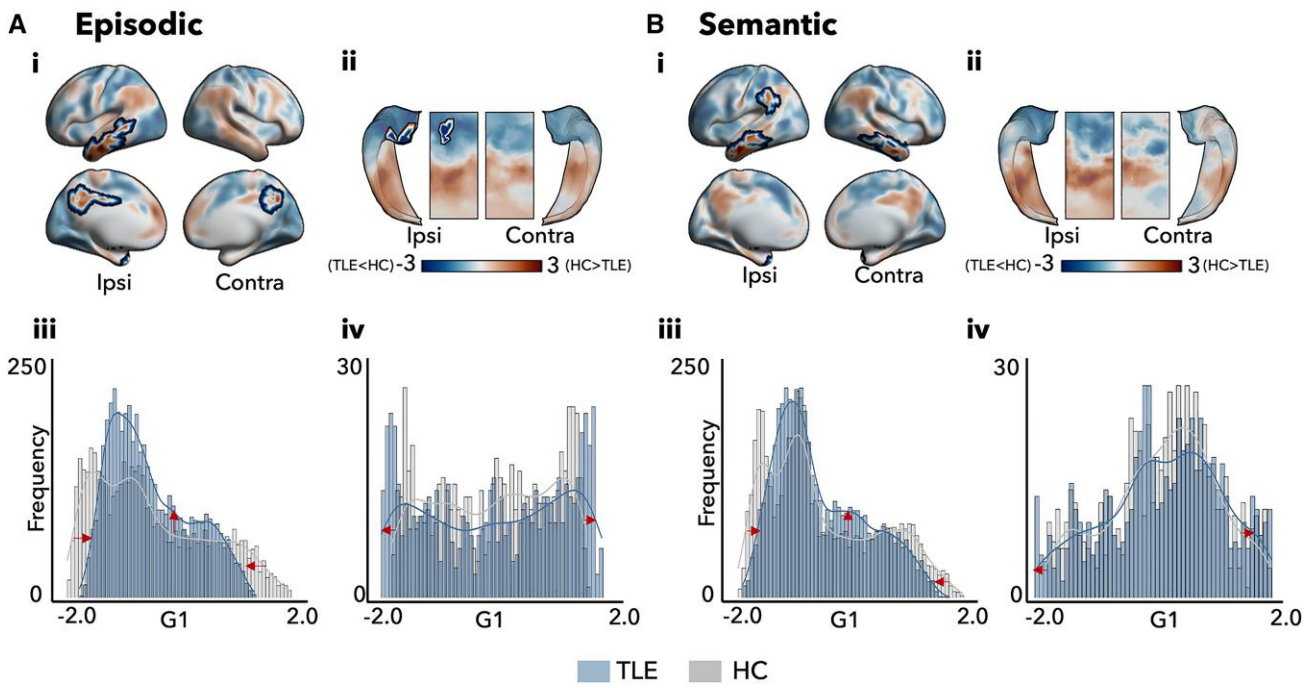


**Figure 2 Gradient alterations in patients with mesiotemporal lobe pathology.** Group differences in neocortical [**A(i)** and **B(i)**] and hippocampal [**A(ii)** and **B(ii)**] gradient scores for episodic (**A**) and semantic (**B**) states. Significant *P*-values were highlighted after correcting for multiple comparisons ($P_{FWE} < 0.05$, black outlines). Histogram plots of neocortical gradient contractions [**A(iii)** and **B(iii)**] and hippocampal gradient expansions [**A(iv)** and **B(iv)**] in TLE patients relative to controls in episodic and semantic states, respectively. Contra = contralateral; G1 = gradient 1; G2 = gradient 2; HC = healthy controls; Ipsi = ipsilateral; TLE = temporal lobe epilepsy.

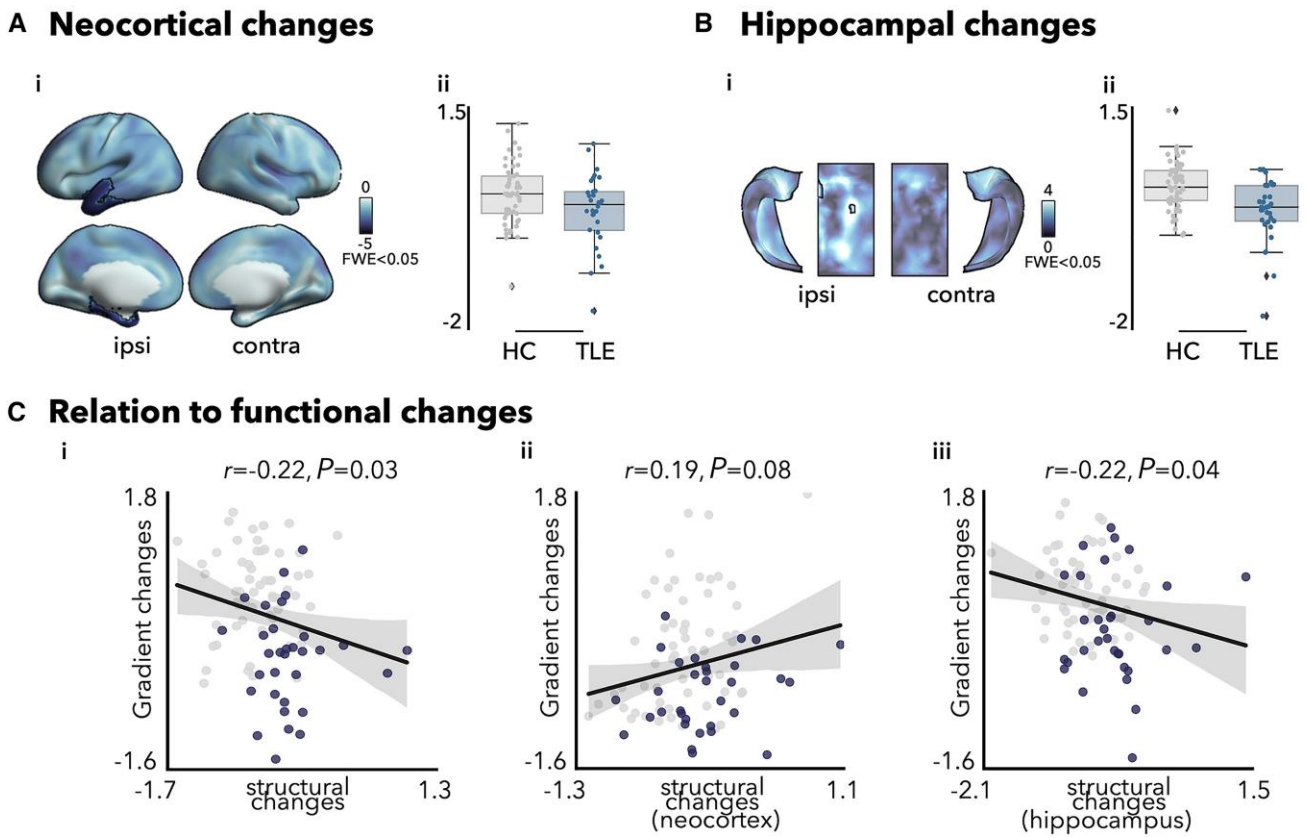


**Figure 3 Associations with temporolimbic pathology.** (**A** and **B**) Differences in neocortical [**A(i)**] and hippocampal [**B(i)**] MRI proxies of pathology (using a multivariate aggregate of cortical thickness and mean diffusivity) between TLE patients and controls. Regions showing alterations in TLE are highlighted ($P_{FWE} < 0.05$, black outline), with mean values represented in **A(ii)** and **B(ii)**. (**C**) False-discovery rate-corrected relationship between overall episodic changes to overall structural changes (**i**) and to structural changes in the neocortex (**ii**) and hippocampus (**iii**) (HC = grey; TLE = dark purple). contra = contralateral; HC = healthy controls; ipsi = ipsilateral; TLE = temporal lobe epilepsy.

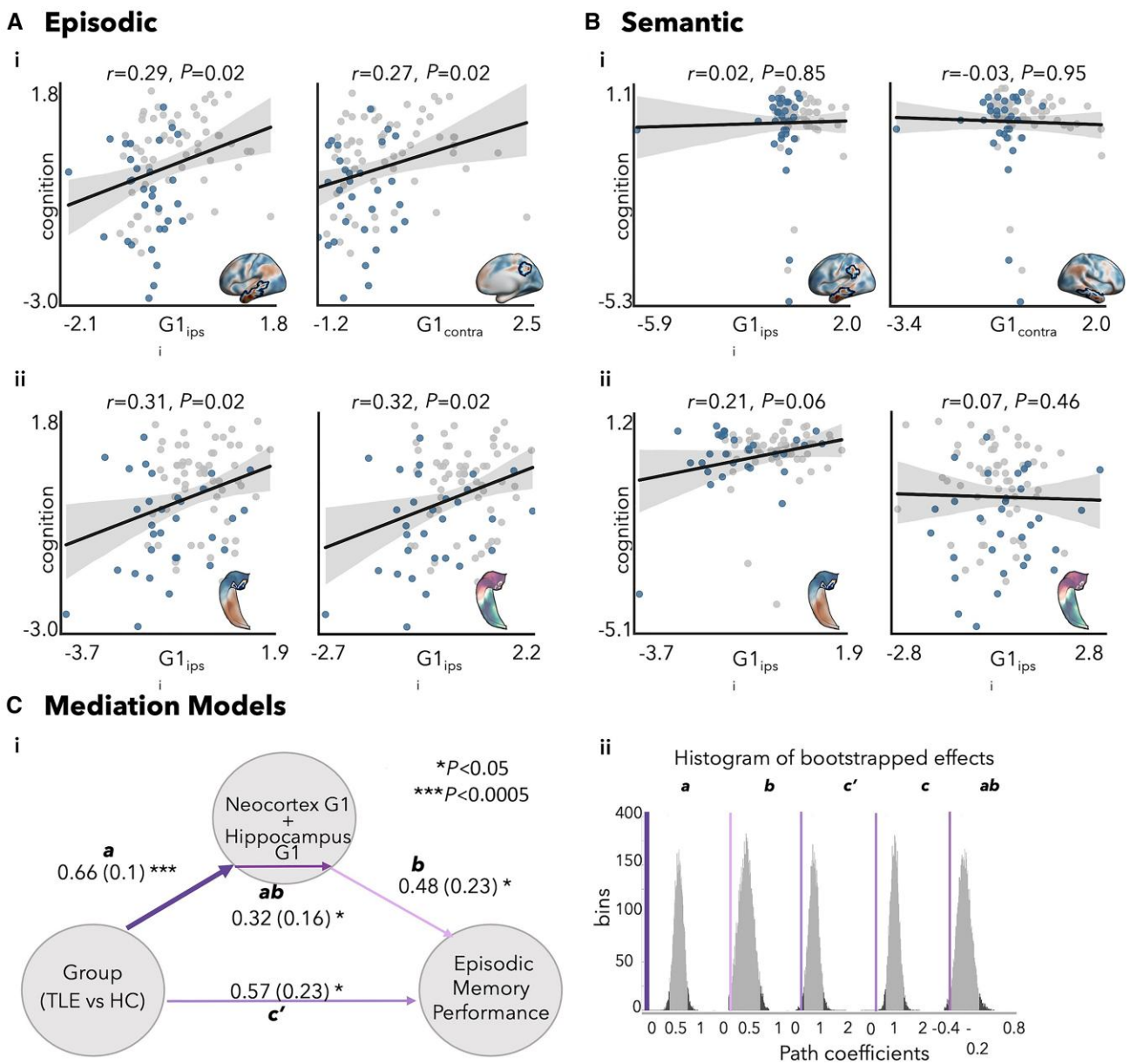


**Figure 4 Behavioural associations.** Mean G1 scores of regions showing significant case–control differences in the ipsilateral and contralateral hemispheres for neocortical and hippocampal G1 in episodic (**A**) and semantic (**B**) memory states, correlated with overall behavioural performance. Controlling for the aggregate effects of morphology and superficial white matter properties (mean diffusivity), hippocampal episodic G1 [**A(ii)**, *right panel*] was correlated significantly with task performance, whereas the hippocampal semantic G1 [**B(ii)**, *right panel*] correlation with memory performance disappeared (HC = grey; TLE = blue). (**C**) Statistical mediation analysis revealed the relationship between the group and episodic memory performance, transmitted via overall neocortical G1 + hippocampal $G1_{ipsi}$ (**i**) scores. (**ii**) Histogram of effects (nboot = 1000). a = Group ~ Gradient scores; ab = mediation effect; b = Gradient scores ~ Episodic memory performance; c' = Group ~ Episodic memory performance(residual); Contra = contralateral; G1 = gradient 1; HC = healthy controls; Ipsi = ipsilateral; TLE = temporal lobe epilepsy.

memory accuracy relative to controls ($t = -4.40$, $P < 0.001$, $d = -0.97$) and only subthreshold impairment in semantic memory ($t = -1.42$, $P = 0.16$, $d = -0.31$). Likewise, we observed faster reaction times for accurate recall in controls relative to patients (Supplementary Fig. 5). Notably, functional G1 scores in both neocortical clusters ($r_{ipsi} = 0.29$, $P_{FDR} = 0.02$; $r_{contra} = 0.27$, $P_{FDR} = 0.02$) and hippocampal clusters ($r_{ipsi} = 0.29$, $P_{FDR} = 0.02$) of significant between-group differences (see Fig. 2) were correlated with episodic memory performance (Fig. 4A). *Ad hoc* meta-analytical decoding[26] confirmed that TLE-related gradient contractions in the episodic state were enriched for memory-related terms, supporting the behavioural associations (Supplementary Fig. 6). In semantic memory states, hippocampal functional G1 ($r_{ipsi} = 0.21$, $P_{FDR} = 0.06$) was correlated with semantic task performance at trend levels, but neocortical functional G1 was not ($r_{ipsi} = 0.02$, $P_{FDR} = 0.85$; $r_{contra} = -0.03$, $P_{FDR} = 0.95$; Fig. 4B). To assess specificity, we also administered the MoCA test to probe mild cognitive dysfunction. Patients with TLE showed reduced MoCA ($t = -3.37$, $P = 0.001$, $d = -0.74$) scores relative to controls. Controlling for individual MoCA scores, significant functional G1 changes persisted in our cohort, in both the hippocampus ($P_{FWE} < 0.05$, $d = -0.80$, 4% increase in mean effect size) and the neocortex ($P_{FWE} < 0.05$, $d = -0.50$).

In a final analysis, we assessed whether functional G1 alterations mediated the relationship between group (TLE versus controls) and episodic memory performance (Fig. 4C; for individual mediation, see Supplementary Table 2). To this end, we first computed overall episodic alterations by averaging G1 scores in significant regions and submitted this to a statistical mediation analysis. Group and functional G1 alterations were correlated strongly (a, $P < 0.0005$), as were functional G1 alterations and episodic memory performance (b, $P < 0.05$), and group and episodic memory performance (c', $P < 0.05$). Importantly, functional G1 alterations in hippocampal and neocortical regions mediated the relationship between group and episodic memory performance (ab, $P < 0.05$). Overall, our statistical mediation analysis, thus, revealed that the relationship between group and episodic memory performance is transmitted via neocortical and hippocampal functional gradients. The robustness of our neural–behavioural correlations and mediation analysis was supported by a consistent correlation between mnemonic similarity task and functional reorganization during episodic but not semantic state (Supplementary Fig. 7).

## Discussion

This study demonstrated: (i) a selective reorganization of both neocortical and hippocampal episodic functional memory networks in patients with TLE; (ii) a close association between functional reorganization and hippocampal, but not neocortical *in vivo* proxies of MTL pathology; and (iii) a contribution of atypical temporolimbic functional organization to behavioural deficits in TLE patients. Our study harnessed several innovative elements, notably the closely matched fMRI tasks of episodic and semantic memory administered in TLE patients and controls, state-of-the-art MRI segmentation and multimodal image preprocessing methods, in addition to connectivity gradient-mapping techniques to identify functional topographies in a data-driven manner. These techniques were applied to a cohort of TLE patients with variable degrees of MTL pathology and memory impairment, allowing for the study of structure–function relationships in declarative memory systems in the human brain. By identifying the functional topographic alterations of episodic memory networks in TLE that mediate cognitive impairment and their structural underpinnings, our work emphasizes a key role of the MTL in episodic over semantic memory processes.

The segregation of episodic and semantic memory systems,[3] supported by our findings, is in line with foundational neuropsychological investigations dissociating list recall performance for episodic memory and picture naming for semantic memory.[38,60,61] Moreover, task-based neuroimaging studies have pointed to distinct neural substrates of these task demands.[9,16] The memory tasks[46] we used were carefully designed to distinctly tap into episodic and semantic memory while being homogeneous in low-level task structure. A recent behavioural study from our group supported the utility of these tasks to assess cognition in both healthy and diseased cohorts, showing reduced episodic, but relatively preserved semantic recall in TLE.[46] Despite these potential differential impairments of TLE patients, mounting evidence suggests that episodic and semantic memory systems might, nevertheless, share overlapping neural correlates.[9,22,23] By capturing both distinctive features and potential overlaps in the neural underpinnings of episodic versus semantic memory, we adopted a data-driven approach that mapped functional topographic patterns associated with each of these processes. In particular, we analysed task-based fMRI data across both episodic and semantic memory states and mapped the resulting task-based connectomes into topographic connectivity gradients.[65,70] Gradient-mapping techniques have previously been applied to several modalities, in particular resting-state fMRI connectivity, in addition to structural and microstructural MRI measures.[65,70,72,82,111,112] Instead of performing a conventional functional gradient mapping across task-free fMRI sessions, the present study derived topographic gradients during episodic and semantic memory states separately and found that they largely followed similar intrinsic organizational axes irrespective of the choice of gradient alignment.[10,23,25] Specifically, gradients associated with both memory states followed a sensory–transmodal neocortical and posterior–anterior hippocampal pattern, in line with previous observations.[65,70,71,74-76] Transmodal core regions (i.e. the default mode network) are recognized to occupy a cortical territory that is maximally distant and separate from unimodal sensory systems, balancing segregated processing streams and integration.[65,66,68,113] This is suggested to help decouple cognition, for instance through self-generated thought processes and episodic representations, from salient sensory information of the immediate external environment.[114-119] Conversely, in the hippocampus, anterior segments are thought to have broader tuning properties and are suited to generalization, whereas posterior segments are more narrowly tuned and appear more suited to memorizing specific instances for contextualization.[120,121] This can be supported by the preferential coupling of anterior divisions of the MTL with transmodal systems such as the default mode network, whereas posterior segments become increasingly connected to unimodal and sensory–motor systems.[75,84,122,123] Together, our findings echo this unified account of large-scale hierarchical organization of the brain and bridge the dichotomy between different declarative memory systems with reliable correlates to behavioural phenotypes.[77,124,125]

In TLE, previous work has mainly reported impaired memory performance and atypical functional activation patterns in the MTL and beyond.[126,127] Here, we extend this literature by showing a marked reorganization of task-based functional network topographies during episodic and semantic retrieval states. Effects were strongest in bilateral neocortical regions for both memory states, with selective involvement of the MTL region ipsilateral to the seizure focus on episodic states. Importantly, findings within the main clusters were relatively consistent in both left and right TLE patients. Consistent with previous work in TLE based on rs-fMRI data,[126] we found neocortical gradient compressions in regions susceptible to TLE-related pathology.[126,128] Other rs-fMRI studies reported simultaneous increases in short-range connections and decreases in long-range connections in temporolimbic and dorsomedial regions in TLE.[126,127] Moreover, a large body of structural covariance and diffusion MRI studies has shown reduced connectivity of primarily the temporolimbic diseased epicentre, but also broader brain networks.[35,126] Studying the hippocampus using gradient-mapping techniques, we observed an extended episodic, but not semantic principal gradient in TLE patients relative to controls. These hippocampal gradient alterations are, thus, in an opposing direction to the neocortical findings in TLE. An expanded hippocampal gradient in TLE patients is readily interpretable as an increased functional differentiation between anterior and posterior segments, which could reflect reductions in intrahippocampal crosstalk along the long axis. In healthy individuals, long-axis organization of the hippocampus has previously been suggested to relate to hierarchy of gist- versus detail-oriented recollection.[125,129,130] Studies show that the anterior hippocampus acts as a hub, recruiting transmodal neocortical regions for schema

construction, evidenced by direct and reciprocal connections between anterior temporal and dorsal and ventromedial prefrontal cortices.[2,131,132] Furthermore, the coactivation of posterior hippocampal and unimodal sensory regions of the neocortex is thought to allow detailed elaborations.[132] In TLE patients, previous work indicates that patients exhibit a reduced capacity for recalling internal details of specific personal episodes but with relatively preserved narrative components,[133] suggesting that the hippocampus is essential for recollecting sensory perceptual aspects of previous experiences. As such, the increasing spatial disconnection between the anterior and posterior hippocampus observed in our TLE patients could reflect a compensatory retrieval process emphasizing key elements over extraneous details during the episodic memory task.[133] Together, our findings showing the co-occurrence of gradient contractions in neocortical systems with simultaneous gradient expansion of hippocampal subregions might represent a topographic mechanism of memory reorganization in TLE, compatible with atypical functional segregation in mesiotemporal and neocortical systems, respectively.[86,126] Accordingly, neocortical gradient contractions indicate that transmodal regions are relatively dedifferentiated from unimodal systems, probably stemming from imbalances in both local and distant connectivity. In contrast, expansions in hippocampal connectivity gradients are likely to be indicative of reductions in intrahippocampal connectivity, which would contribute to marked divergences in signalling between anterior and posterior divisions. As such, our findings echo task-fMRI studies showing widespread extratemporal connectivity reductions and intrinsic MTL connectivity increases,[47] and less concordant fMRI activations between hippocampal long-axis and sensory–transmodal gradients in TLE relative to controls.[32] Collectively, the neocortical gradient contraction and hippocampal gradient expansion reported here provide a compact signature of reorganization of declarative memory systems in TLE.

Prior studies have reported atypical microstructure and morphology in TLE in both the MTL and adjacent temporolimbic neocortical systems[34,35,47,89,90,134-136] and have suggested that such changes could alter the spatial configuration of functional networks and influence hierarchical organization supporting episodic memory function.[87] In line with previous work,[35,110,126] white matter disruptions and atrophy were observed in our TLE patients, with most marked findings in temporolimbic regions and hippocampal anterolateral regions ipsilateral to the seizure focus. These findings could reinforce earlier models that propose increased susceptibility of paralimbic regions to structural and functional changes, potentially owing to a greater capacity for plasticity and connectivity rearrangement.[88,137] Interestingly, although neocortical structural changes did not reflect functional changes, morphological and microstructural derangements of the hippocampus were correlated with episodic memory network reorganization. Previous studies have consistently revealed anterior hippocampal atrophy[138,139] and alterations in tissue microstructure[126] in TLE patients, aligning with marked neuronal loss in the anterior hippocampus.[140] Such structural damage in crucial hubs, such as the hippocampus, extends beyond localized effects and can compromise communication within the interconnected memory network.[138,141] The functional association with pathological markers selective to the hippocampus reported herein, therefore, provides specificity and reinforces the key role of hippocampal integrity in episodic memory network organization.[142,143]

Previous studies have also linked network alterations in TLE patients to cognitive impairment.[47,87,127,134,136] Consistent with a recent study from our group,[46] episodic task impairments were marked in TLE, whereas semantic task performance remained intact. Additionally, neocortical and hippocampal gradient alterations were found to relate to episodic impairments in TLE. Although we acknowledge that our conservative patient inclusion criteria resulted in a relatively modest sample size of 31 TLE patients, the observed memory deficits and functional perturbations were unlikely to be influenced by neurodegenerative disorders,[46,144] because functional alterations persisted even after controlling for overall measures of cognitive function (i.e. MoCA). Behavioural indices of cognitive impairment in TLE were mediated by functional changes, confirming the already well-established literature on episodic impairment in TLE. In line with the hierarchical models of memory,[145,146] our findings lend support to the idea that semantic memory relies more on extrahippocampal brain regions compared with hippocampus-dependent episodic systems. This is consistent with evidence from TLE patients who underwent anterior lobe resections[59] and corroborates the controlled semantic cognition framework with the ATL acting as a central semantic hub.[1,16,29] Additionally, our findings are accounted for by the complementary learning systems framework,[147,148] which stipulates that hippocampus-encoded semantic memories undergo a long-term consolidation process[149,150] that renders the memory trace independent from the hippocampus and thus more resilient to its structural pathology. Likewise, the multiple trace theory[57,58] specifies that episodic memories are mediated consistently by the hippocampus, allowing a vivid recollection of context-rich events,[58,151] and each instance of recalling an episodic memory triggers subsequent re-encoding, leading to the formation of multiple traces or engrams that are mediated by hippocamponeocortical neuron ensembles.[57,58,151-154] In contrast, successful semantic memory recall does not require rich contextual detail and can, therefore, be supported solely by extratemporal regions.[155]

Our TLE cohort was of modest size, which could have affected the sensitivity to detect subtle effects. For example, functional network reorganization was not as marked during the semantic state compared with the episodic state, in the hippocampus. Larger samples might potentially have enabled the identification of more widespread functional reorganization across both states. Nevertheless, it is important to emphasize that we observed a more pronounced association with behaviour during the episodic state and not the semantic state, which suggests different behavioural implications of the functional reorganization in both declarative systems in TLE. Previous studies have also highlighted histopathological heterogeneity in TLE, even in relatively well-defined candidates for TLE surgery.[36,156] In the hippocampal epicentre, this heterogeneity is mirrored in MRI volumetric variation, where patients fall on a spectrum running from normal volumetric findings to marked structural compromise.[35,139,157] As our results show, variations in imaging proxies of hippocampal pathology might, ultimately, relate to functional network alterations, which, in turn, affect behavioural outcomes. Future work could benefit from a more comprehensive profiling of distributed structural changes in individual patients, which might involve a more targeted assessment of regions that contribute to the aetiology of TLE in some patients, including anterior temporal and entorhinal regions together with temporal neocortices.[158] Additionally, previous studies show that various anti-seizure medications have diverse effects on language and memory networks[159-162] in individuals with epilepsy, with some showing decreasing effects on neuronal excitability, whereas others might improve cognitive performance.[163] Given that our TLE patients were mainly treated with multiple anti-seizure medications, it was difficult to control rigorously for medication effects. Notably, however, we still

observed a functional–behavioural difference in those neural changes in episodic but not in semantic memory states, correlated with behavioural performance. In future work, it will be important to establish the effect of different anti-seizure medication on different functionally relevant networks. In light of variable treatment regimens, such efforts clearly demand large-scale, multi-site studies.

## Conclusion

Collectively, our work presents a novel decomposition analysis of task-fMRI data revealing an atypical and state-dependent reorganization of declarative memory systems in TLE, with a consistent correlation with behavioural impairments and *in vivo* markers of hippocampal pathology. Our findings support a more selective role of the hippocampus in episodic processes, in line with the episodic theory of memory organization.[31,164] This study also provides insights into mechanisms of cognitive impairments in conditions associated with MTL pathology, showing an opposing pattern of decreased neocortical functional differentiation together with increased intrahippocampal differentiation. As many pharmacoresistant patients from this cohort undergo resective MTL surgery, future work could investigate whether gradient patterns will help to predict postoperative memory deficits, and thus enrich patient-specific clinical decision-making.

## Data availability

The Human Connectome Project dataset used for generating normative resting-state gradients is available at https://db.humanconnectome.org/. Our healthy control cohort is made up of a subset of participants from the MICA-MICs[165] dataset, which is openly available on the Canadian Open Neuroscience Platform data portal (https://portal.conp.ca/dataset?id=projects/mica-mics) and Open Science Framework (OSF, https://osf.io/j532r/). Functional connectome gradients are available on OSF (https://osf.io/e6jph/).

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## Competing interests

The authors report no competing interests.

## Supplementary material

Supplementary material is available at *Brain* online.

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