Title

Diencephalic and white matter knock-on effects in hippocampal amnesia – why they matter

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Contributions

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Abstract

Studies of brain-behaviour relationships in hippocampal amnesia largely ignore the presence and explanatory potential of knock-on effects beyond the medial temporal lobes. In a large cohort of patients (n=38) with hippocampal damage due to autoimmune limbic encephalitis, we had reported evidence that extra-hippocampal structural and functional abnormalities in the broader "hippocampal-diencephalic-cingulate network" fully mediated the effects of hippocampal damage on several aspects of episodic memory. However, we had not examined the specific diencephalic nuclei affected or the white matter pathways that would help explain these remote effects. In this study, we used recently developed methods of automated segmentation of diencephalic nuclei, as well as a range of analyses of white matter integrity. As expected, we found atrophy in the anterior thalamic nuclei and in the mammillary bodies, but also in the laterodorsal, pulvinar, and dorsomedial nuclei. The extent of atrophy in some of these nuclei was comparable to, if not larger than that observed for the hippocampal formation, even though none of our patients' acute clinical scans disclosed thalamic damage. We also present evidence linking these volumes to patients' episodic memory impairment over and above any correlation with hippocampal/subicular subfield volumes. White matter integrity was strongly compromised in the hippocampal-diencephalic-cingulate network, and the volumetric relationship between the hippocampal formation and the mammillary bodies was at least partly mediated by the integrity of the fornix across patients, consistent with the assumption of Wallerian degeneration following focal medial temporal lobe damage. However, evidence for the specialisation of the "hippocampal-diencephalic-cingulate network" in recollection/recall was mixed, and white matter abnormalities extended to regions well beyond this network. Our findings highlight the need to longitudinally examine diencephalic and white matter integrity in cohorts of hippocampal damage with different aetiologies and update neuroanatomical models of this network.

Keywords

Hippocampus; thalamus; fornix; white matter; memory; amnesia

Introduction

Lesion studies in animal models of focal hippocampal damage have demonstrated widespread knock-on effects well beyond the medial temporal lobe (Machado et al., 2008; Meng et al., 2014, 2016). Despite the acknowledgment (Basile et al., 2020; Jonin et al., 2018) of the need to examine the integrity of the "extended hippocampal system" (Aggleton & Brown, 1999; also referred to as the "hippocampal-diencephalic-cingulate" network: Bubb et al., 2017) across patients with "focal" hippocampal damage, studies continue to examine memory deficits as a function of hippocampal damage per se (Dede, Frascino, et al., 2016; Gold et al., 2006; Miller et al., 2017; Patai et al., 2015; Wixted & Squire, 2004). While a substantial volume of literature has emphasised the importance of examining the functional dysconnectivity between the affected hippocampal formation (hippocampus proper, dentate gyrus, and subiculum) and the rest of the brain in explaining hippocampal amnesia (Hayes et al., 2012; Henson et al., 2016; Miller et al., 2020; Rudebeck et al., 2013), there remain very few studies that have investigated the significance of structural abnormalities beyond the medial temporal lobe (Argyropoulos et al., 2019; Harms et al., 2023). Identifying these relationships may help us explain the variability in performance in neuropsychological tests across different patient cohorts and resolve topics of debate in the literature, such as those pertaining to the contribution of the hippocampal formation to processing remote memories (Dede, Wixted, et al., 2016; Moscovitch et al., 2016; Squire & Bayley, 2007) or working memory (Squire, 2017; Yonelinas et al., 2024), or to material- (Kim et al., 2015; Lee et al., 2006, 2012; Maguire & Mullally, 2013; Urgolites et al., 2017) and/or process-specific roles of the hippocampal-diencephalic-cingulate network (Argyropoulos & Butler, 2020; Kafkas et al., 2017; Kopelman et al., 2007; Lee et al., 2006; Patai et al., 2015; Wixted & Squire, 2011). For instance, according to prominent dual-process frameworks (Aggleton et al., 2023; Aggleton & Brown, 1999; Montaldi & Mayes, 2010), damage in the hippocampal-diencephalic-cingulate network would predict the integrity of recollection (retrieval of specific details and context about a past event), which supports performance in tests of recall, but not familiarity (the sense of having encountered a stimulus before, without retrieval of specific details or context); the latter, along with recollection, supports performance in tests of recognition memory. Strong support for these models has been provided by evidence for a selective relationship between fornical damage and impaired recollection-recall (Carlesimo et al., 2007; Tsivilis et al., 2008; Vann et al., 2009). However, not all studies of fornical damage have showed a sparing of recognition (e.g., Calabrese et al., 1995; D'Esposito et al., 1995;

Park et al., 2000; Poreh et al., 2006), which has also been impaired in patients with relatively selective damage to the mammillary bodies and the anterior thalamic nuclei (Cipolotti et al., 2008; Gold & Squire, 2006). This wider perspective may thus also clarify the similarities and discrepancies observed in the neuropsychological profile of patients presenting with damage in hippocampal vs. extra-hippocampal (especially diencephalic) structures, and how the interactions of those areas support episodic memory (Aggleton et al., 2008; Aggleton & Brown, 1999; Gold & Squire, 2006; Kopelman et al., 2007; Winocur, 1985).

To a certain extent, this research gap could be explained by the secondary importance attributed to other structures relative to the hippocampal formation within the context of the traditional "Papez circuit", or, more subtly, in the term "extended hippocampal system" (Aggleton & Brown, 1999) - see discussion in Aggleton et al. (2022). Research is also impeded by several other factors, such as small sample sizes and the fact that very few neuroimaging studies have disclosed nucleus-specific evidence of thalamic lesions in humans (Segobin et al., 2019); reliance on clinical instead of research-dedicated MRI data, and the difficulties of quantifying individual diencephalic volumes (Annink et al., 2021; Dzieciol et al., 2017; Segobin et al., 2024). Moreover, certain neurological forms of hippocampal damage that appear focal within the medial temporal lobes, such as early hypoxia/ischaemia are likely associated with primary (i.e., not necessarily secondary) damage in diencephalic structures (Dzieciol et al., 2017; Meys et al., 2022).

In Argyropoulos et al. (2019), we examined the presence and explanatory potential of such knock-on effects in a large (n=38) cohort of patients who had been treated for autoimmune limbic encephalitis (aLE). This neurological condition is very often studied as a "human model" of hippocampal damage (Hassabis et al., 2007; Henson et al., 2016, 2017; Lad et al., 2019; Maguire et al., 2006; McCormick et al., 2016, 2018; Spanò, Weber, et al., 2020), primarily because, relative to other conditions that involve hippocampal damage, such as ischemia/anoxia (Heinz & Rollnik, 2015; Huang & Castillo, 2008) or other types of encephalitis (Damasio & Van Hoesen, 1985; Gitelman et al., 2001; Kelly et al., 2024; Raschilas et al., 2002), it involves focal damage in the hippocampal formation and the amygdala, as seen in post-mortem studies (Khan et al., 2009; Park et al., 2007) and animal model research (Tröscher et al., 2017). Consistent with the above, we previously reported bilateral atrophy in the hippocampal formation at the group level (Argyropoulos et al., 2019), which presented in a rather focal fashion within the medial temporal lobe (along with right

entorhinal volume reduction), with the temporal pole, the amygdala, and the perirhinal and parahippocampal cortices not showing group-level volume reductions. However, we also provided evidence for reduced thalamic volumes and reduced resting-state activity in the posterior cingulate cortex, which fully mediated the relationship of hippocampal formation volumes with remote autobiographical and anterograde memory, respectively.

Nevertheless, our analyses of thalamic volume had relied on whole-brain voxel-based morphometry of grey matter density and on whole-thalamus volumetry and, hence, did not suffice to identify the nuclei that drove the limited volume reduction in the thalamus (~5% relative to healthy controls). Since then, methods designed to overcome the difficulties posed by conventional MRI protocols in segmenting individual thalamic nuclei have become available (Tregidgo et al., 2023; Vidal et al., 2024). Moreover, we had not examined the integrity of white matter (WM) pathways in our patients, which would help explain their reduced resting-state activity and connectivity with the hippocampal formation across midline cortical structures (anterior cingulate and medial prefrontal cortex; posterior cingulate and retrosplenial cortex/precuneus).

In this study, we employed recently developed methods of automated segmentation of diencephalic nuclei, along with a series of analyses of WM structural integrity. We predicted that structural abnormalities beyond the hippocampal formation would be observed in the revised Papez circuit recently articulated in Aggleton et al. (2022), and would accordingly comprise the anterior thalamic nuclei, the mammillary bodies, along with the WM tracts connecting those – in particular, the fornix, the mammillothalamic tract, the cingulum, and the internal capsule. We hypothesised that compromised structural integrity of the fornix and the mammillary bodies would be causally secondary to hippocampal damage, given that: i) aLE is associated with selective hippocampal-amygdala damage (*supra*); ii) there is evidence for atrophy of the mammillary bodies following transections of the fornix (Loftus et al., 2000; Zola-Morgan et al., 1989), and evidence consistent with Wallerian degeneration of the fornix following hippocampal damage (Baldwin et al., 1994; Fernandez et al., 2022); iii) fornix damage does not produce retrograde degeneration in its fibers arising from the temporal lobe (Daitz & Powell, 1954; Saunders & Aggleton, 2007).

We also sought to determine whether any of the diencephalic and WM abnormalities seen in our patient cohort could be attributable to heterogeneity in the aLE antibody profile. Of our

38 patients, 14 had tested positive for anti-leucine-rich glioma inactivated (anti-LGI-1). Studies of hippocampal damage often focus on patients with this type of aLE (Lad et al., 2019; Spanò, Pizzamiglio, et al., 2020; Spanò, Weber, et al., 2020), as they has been argued to homogeneously present with limbic symptoms (Bastiaansen et al., 2017; van Sonderen et al., 2016, 2017). Of the remaining 24 patients in our cohort, 10 were reported as seronegative, but may have had LGI-1 aLE, despite that anti-LGI-1 was not detectable in routine clinical practice at the time of screening. Two were positive for anti-glutamic acid decarboxylase autoantibody. One presented with autoantibodies characteristic of paraneoplastic encephalitis. Four presented with dual seropositive antibodies of contactin-associated protein-like 2 and LGI-1, and seven were found positive for antibodies targeting the voltage-gated potassium channel complex, with no further information on the specific antibodies (Table 2 in Argyropoulos et al., 2019).

We further hypothesised that volumes of the affected diencephalic nuclei and measures of the integrity of the affected WM might be better predictors of episodic memory impairment relative to even finer-grained measures of hippocampal and subicular subfield volumes. Finally, we sought to examine whether abnormalities in the diencephalon and the fornix are predictive of our patients' recall vs. recognition memory performance. According to the aforementioned dual-process frameworks of the extended hippocampal system, damage in the anterior thalamic nuclei, the mammillary bodies, and the fornix would predict impairment in recall, but not recognition memory performance.

Methods

Participants and MRI data acquisition

Structural MRI

As previously reported (Argyropoulos et al., 2019), all 38 aLE patients (26M:12F; age at imaging: mean = 61.39; SD = 13.91 years) underwent structural brain imaging, along with 67 healthy controls (40M:27F; age at imaging: mean = 61.23; SD = 13.57 years; controls vs. patients: M:F ratio: $\chi^2 = 0.79$, p=0.374; age at imaging: t(103) = -0.06, p = 0.954). 3D T1-weighted images were acquired using a Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequence (echo time = 4.7 ms, repetition time = 2040 ms, 8° flip angle, field of view = 192 mm, voxel size = 1×1×1 mm). All 38 patients and 35/67 controls were recruited by the Memory and Amnesia Project (Nuffield Department of Clinical Neurosciences, University of Oxford). An additional 32 T1-weighted structural MRI datasets of healthy controls were made available through the Oxford Project To Investigate Memory and Aging. Although the acquisition protocols did not differ (Zamboni et al., 2013), our volumetric comparisons between all controls and patients reported below have included scan source as a covariate of no interest.

Diffusion MRI

All diffusion MRI data were acquired within the context of our Memory and Amnesia Project, involving 35/35 controls (age at imaging: mean = 55.14; SD = 14.04 years; 25M:10F), and 37/38 patients (age at imaging: mean = 61.14; SD = 14.01 years; 26M:11F; controls vs. patients: M:F ratio: $\chi^2 = 0.01$, p=0.914; age at imaging: t(70) = 1.81, p = 0.074). We used a single-shot echo planar imaging sequence (64 slices; slice thickness = 2 mm, 0 gap; axially acquired; 64 directions at b = 1,500 s/mm^2, repetition time = 8,900 ms; echo time = 94.8 ms; voxel size = 2 × 2 × 2 mm; field of view = 192 × 192 mm). One no-diffusion-weighted image at b = 0 s/mm^2 was also acquired.

Data preprocessing and analyses

Diencephalic volumetry

We first compared controls and patients on the volumes of the thalamic segmentations derived from HIPS-THOMAS (Vidal et al., 2024), and the HypothalamicSubunits tool (Billot et al., 2020) for hypothalamic nuclei. HIPS-THOMAS (https://github.com/thalamicseg/thomas_new) is a variant of the THalamus Optimized Multi Atlas Segmentation method (Su et al., 2019). It involves a HIstogram-based Polynomial Synthesis as a preprocessing step, which outputs WM-nulled-like image contrast from standard T_1-weighted structural MRI, by means of polynomial approximation. It is motivated by the observation that WM-nulled-MPRAGE images provide higher intra-thalamic contrast (Su et al., 2019) and generate more accurate segmentation (Umapathy et al. 2021) relative to T_1-weighted MRIs. HIPS-THOMAS has been shown to surpass the T_1-based FreeSurfer segmentations (Iglesias et al., 2018) in accuracy (Williams et al., 2024). The segmented thalamic nuclei comprise the anteroventral, ventral anterior, ventral lateral anterior, ventral lateral posterior, ventral posterolateral, pulvinar, lateral geniculate, medial geniculate, centromedian, mediodorsal-parafascicular, and habenular nuclei (output resolution: 1 × 1 × 1 mm). We used the "-B" option, which is recommended for cases with enlarged ventricles, given the age of our participants. As HIPS-THOMAS relies exclusively on T1-weighted MRIs, it enabled us to estimate volumes of thalamic nuclei from all 38/38 of our patients and 67/67 of our controls. We also used the HypothalamicSubunits tool (Billot et al., 2020) (https://surfer.nmr.mgh.harvard.edu/fswiki/HypothalamicSubunits), which segments the hypothalamus and its associated subunits in 3D T1-weighted scans, producing segmentation maps (output resolution: 1 × 1 × 1 mm) for the left/right inferior and superior tubular, anterior-inferior, anterior superior, and posterior hypothalamus (wherein the mammillary bodies reside). We used age, sex, FreeSurfer's estimated total intracranial volume, and scan source ("Memory and Amnesia Project", or "Oxford Project To Investigate Memory and Aging") as covariates of no interest in a series of ANCOVAs (independent variable: Group; dependent variable: raw volume). We used the Holm-Bonferroni sequential correction method (Holm, 1979) to correct ("p-corr") for the number of multiple comparisons made (n=16; henceforth, "p-corr(16)").

In order to examine the volumes of more thalamic nuclei (and their subdivisions), we then used the convolutional neural network tool developed in FreeSurfer – henceforth 'FreeSurfer-

CNN' (Tregidgo et al., 2023) (https://surfer.nmr.mgh.harvard.edu/fswiki/ThalamicNucleiDTI), which uses information from both diffusion and T1-weighted MRI (72 subjects with diffusion and structural T1-weighted MRI data, all from the "Memory and Amnesia Project") with an output resolution of 0.7 × 0.7 × 0.7 mm. Using FreeSurfer 7.4.1, we first produced a bias-corrected, whole-brain structural T_1-weighted MRI image ("norm.mgz"), a whole-brain segmentation ("aseg.mgz") using FreeSurfer's "recon-all" stream, and a T_1-based FreeSurfer segmentation (Iglesias et al., 2018), using "segmentThalamicNuclei.sh" (https://freesurfer.net/fswiki/ThalamicNuclei). We then used "TRActs Constrained by UnderLying Anatomy" (Maffei et al., 2021; Yendiki et al., 2011) to derive a fractional anisotropy volume ("dtifit_FA.nii.gz") and a 4D volume containing the principal direction vector for each DTI voxel ("dtifit_V1.nii.gz"). The segmented nuclei comprise the central lateral, central medial, centromedian, lateral geniculate, lateral posterior, laterodorsal, limitans (suprageniculate), medial geniculate, mediodorsal lateral (parvocellular), mediodorsal medial (magnocellular), parafascicular, pulvinar anterior, pulvinar inferior, pulvinar lateral, pulvinar medial (medial segment – henceforth, "m"; lateral segment – henceforth, "l"), reuniens (medial ventral), ventral anterior, ventral anterior magnocellular, ventral lateral anterior, ventral lateral posterior, ventral posterolateral nuclei, along with an "anteroventral" segmentation, which, however, includes the anterior medial and anterior dorsal nuclei (Iglesias et al., 2018) – we will thus refer to this segmentation as the "principal anterior nuclei" instead. We also segmented the mammillary bodies using FreeSurfer-ScLimbic ("mri_sclimbic_seg" in FreeSurfer https://surfer.nmr.mgh.harvard.edu/fswiki/ScLimbic) (105 subjects with T1-weighted MRI data) to derive segmentations of the left and right mammillary bodies (output resolution: 1 × 1 × 1 mm) (Greve et al., 2021). We then conducted a series of ANCOVAs (independent variable: Group; dependent variable: raw volume), using, as between-subjects covariates, age, sex, and FreeSurfer's estimated total intracranial volume, and adding scan source as a further covariate of no interest for the mammillary body volumes. As above, we corrected for the number of multiple comparisons made - p-corr(24). As the data for the majority of our variables were normally distributed (Shapiro-Wilk tests: $p < 0.05$), we retained parametric tests, and, whenever that was not the case, we examined whether any significant differences observed retained their significance after iterating the analyses with non-parametric equivalents (e.g., Quade non-parametric ANCOVA). We also iterated these ANCOVAs, comparing our subgroup (n=14) of LGI1-aLE patients (Argyropoulos et al., 2019; Table 2)

with the healthy controls, in order to examine whether the abnormalities observed could be attributed to the heterogeneity of our cohort with respect to the aLE types involved.

Hippocampal-subicular subfield volumetry

In a previous study (Argyropoulos et al., 2019), we assessed relationships between episodic memory scores and volumes of the hippocampal formation (total, anterior, posterior). The latter was quantified using gold-standard manual segmentation, along with the average grey matter density values from voxel-based morphometry clusters that reflected significant grey matter volume reduction in this aLE cohort relative to their controls. However, a question remained whether volumes of specific hippocampal-subicular subfields would show stronger relationships with episodic memory performance across patients, such that these would be unmediated by any extra-hippocampal structural/functional abnormalities. We thus employed the "Subregions Segmentation" tool (segment_subregions) in FreeSurfer (Iglesias et al., 2015) (https://surfer.nmr.mgh.harvard.edu/fswiki/SubregionSegmentation), which is used for segmentation of MR images pre-processed through the FreeSurfer "recon-all" pipeline, and outputs segmentations for the right/left hippocampal formation: amygdala transition area, CA1/CA3/CA4 head/body, subiculum head/body, presubiculum head/body, molecular layer head/body, granule cell and molecular layer of the dentate gyrus head/body, hippocampal fissure, parasubiculum, tail, and fimbria. Approximately 95% of subfield segmentations have been found to have "excellent" numerical reliability (Kahhale et al., 2023). With the exclusion of the fimbria (WM), the rest of the segmentations were included in our volumetric comparisons between controls and patients. We then corrected for the number of multiple comparisons made - p-corr(18).

WM integrity

We used fixel-based analysis to assess WM structural integrity and supplemented this with another two automated methods of identifying WM abnormalities across the whole brain: voxel-based morphometry (Supplementary Figure 1), and tract-based spatial statistics (Supplementary Figure 2). Driven by our a priori hypotheses on WM abnormalities in the hippocampal-diencephalic-cingulate network, as well as the findings disclosed by fixel-based analysis, voxel-based morphometry, and tract-based spatial statistics, we also used deterministic tractography to manually reconstruct the fornix, the dorsal and the ventral

cingulum, portions of the corona radiata, and the anterior thalamic radiation, especially since it comprises fibres from the principal anterior nuclei, as well as from the mediodorsal nuclei (Parent, 1996) (Supplementary Figure 3).

Fixel-based analysis has been developed to address challenges faced by tract-based spatial statistics and other voxel-based analyses of WM integrity, such as the lack of specificity of individual fibre populations within each voxel, or the fact that traditional measures (e.g., fractional anisotropy) are difficult to interpret in regions involving crossing fibres (Raffelt et al., 2015, 2017). Unlike voxels, "fixels" reflect an individual fibre population within a voxel, and directly relate to the underlying WM anatomy. They are typically derived from WM fibre orientation distributions, which are computed by constrained spherical deconvolution techniques (Tournier et al., 2007). Fixel-based analysis thus enables the identification of specific fiber pathways, even within regions that contain crossing fibers. By enabling the estimation of the number of axons and the axon diameter within a voxel, the inferences drawn from these analyses may be more biologically meaningful (Raffelt et al., 2017). We used the two most typical measures in fixel-based analysis, namely: i) apparent fibre density, also referred to as "neurite density" (Zhang et al., 2012) or "axonal density" (Assaf et al., 2008), reflecting intra-axonal volume, a microstructural property (Raffelt et al., 2012). ii) fibre-bundle cross-section, which captures macroscopic differences by describing the axon diameter or the number of voxels that the bundle occupies (Raffelt et al., 2017). Preprocessing, whole-brain fixel-based analysis, and visualisations were performed in MRtrix3 (Tournier et al., 2019). A standard preprocessing pipeline for single-shell single-tissue constrained spherical deconvolution was followed (as outlined in https://mrtrix.readthedocs.io/en/dev/fixel_based_analysis/st_fibre_density_cross-section.html), which involved: denoising and Gibbs ringing removal; correction for motion and eddy current-induced distortions; bias field correction to eliminate low frequency intensity inhomogeneities across the image; global intensity normalisation (Raffelt et al., 2017) in order for the absolute amplitudes of the fibre orientation distributions to be comparable between participants; computation of single-shell response functions representing single-fibre WM from the data, followed by a single *unique* (average) response function to perform spherical deconvolution of all subjects (Raffelt et al., 2012); upsampling to a recommended voxel size of 1.25 × 1.25 × 1.25 mm in order to increase anatomical contrast and improve downstream template building, registration, tractography and statistics; computation of upsampled brain mask images; Fibre Orientation Distribution estimation,

using constrained spherical deconvolution with the unique WM response function calculated above; generation of a study-specific unbiased template of Fibre Orientation Distribution, by averaging the fibre orientation distributions from 30/72 subjects (15 controls and the 15 patients that showed the smallest volume reduction in the thalamus and the hippocampal formation, in order to avoid patients with excessive abnormalities compared to the rest of the population, in keeping with the MRtrix3 instructions above); nonlinear registration of all subjects' fibre orientation distribution images to the template (Raffelt et al., 2011); warping all subject masks into template space and computing a template mask as the intersection of all subject masks in template space, to ensure analysis is confined to voxels that contain data from all subjects; segmentation of fixels from the template, resulting in a fixel mask defining the fixels on which statistical analysis will be conducted; warping fibre orientation distribution images to template space; segmentation of each lobe of fibre orientation distributions to estimate the number and orientation of fixels in each voxel and their apparent fibre density; re-orienting the fixels of all subjects in template space, using the local transformation at each voxel, determined by the warps above; assigning subject fixels to template fixels; computing the log of the fibre cross-section metric, to ensure that data are centred around zero and normally distributed; computation of a combined metric of fibre density and cross-section (Raffelt et al., 2017); whole-brain fibre tractography on the fibre orientation distribution template, which involves statistical analysis using connectivity-based fixel enhancement, which exploits local connectivity information derived from probabilistic fibre tractography (20 million streamlines), which acts as a neighbourhood definition for a threshold-free cluster-enhancement; applying "Spherical-deconvolution-Informed Filtering of Tractograms" (Smith et al., 2013) to reduce biases in the tractogram densities and the number of streamlines to 2 million; generation of a fixel-to-fixel connectivity matrix, based on the whole-brain streamlines tractogram; smoothing of fixel data based on the sparse fixel-to-fixel connectivity matrix. A General Linear Model was used for the statistical analysis of fibre density and cross-section for the contrast "Controls > Patients", including age at scanning and sex as covariates of no interest. As in other recent studies (Andica et al., 2021; Zarkali et al., 2020), we selected fibre density and cross-section as the measure of interest, on the grounds that it is likely to be the most sensitive of the three fixel metrics, since it is a combined metric of both microstructural and macrostructural changes representing the overall ability to relay information (Raffelt et al., 2017). Connectivity-based fixel enhancement (a threshold-free cluster-enhancement-like approach; Smith & Nichols, 2009) was involved, which used probabilistic tractography to identify structurally connected fixels that share

underlying anatomy. FWE-corrected *p*-values (< 0.05) were then assigned to each fixel using non-parametric permutation testing (5,000 permutations). The resulting significant fixels were displayed at a p-FWE < 0.05 threshold in the "mrview" tool in MRtrix3.

For the purposes of examining structure-structure/behaviour relationships (*infra*), we used a tract-of-interest analysis. Major tracts (n=33, excluding the inferior cerebellar peduncle, as inferior cerebellar slices were clipped from the field of view; Supplementary Table 12) were automatically delineated on the WM fibre orientation distribution template using TractSeg (Wasserthal et al., 2018). Delineated fibre tracts were then converted into fixel masks using the "tck2fixel" command in MRtrix3 (Tournier et al., 2019), and subsequently thresholding this fixel image to create a binary tract fixel mask. The mean fibre density and cross-section value across all fixels within each tract-of-interest was computed for each participant. These were entered in a series of univariate ANOVAs comparing controls and patients (covariates: age, sex). The mean fibre density and cross-section values of tracts that showed significant (p-corr < 0.05) reduction in patients relative to controls were regressed against age and sex, to derive standardised residuals, and were entered in a series of bivariate correlational analyses with (age-scaled, standardised) memory scores (*infra*).

Structure-structure/behaviour relationships

In a series of correlational analyses, we examined the relationship of patients' impaired episodic memory with the diencephalic segmentations that showed volume reduction and the WM tracts that showed reduction in fibre density and cross-section. We used the composite scores for visual/verbal recall/recognition, visual forgetting, and remote autobiographical memory, as reported in Argyropoulos et al. (2019): these were derived from the following (sub)tests, on all of which the patient cohort showed impairment: i) visual recall: Doors and People - Shapes (Baddeley et al., 1994), Rey-Osterrieth Complex Figure Copying Test (Rey, 1959) Immediate and Delayed Recall; ii) visual recognition: Doors and People – Doors (Baddeley et al., 1994), Warrington Topographical Memory test (Warrington, 1996); iii) verbal recall: Wechsler Memory Scale III – Logical Memory I/II, Word List I/II (Wechsler, 1997), Doors and People – People (Baddeley et al., 1994); iv) verbal recognition: Doors and People – Names (Baddeley et al., 1994), Wechsler Memory Scale III – Word List II Recognition (Wechsler, 1997), Warrington Recognition Memory Tests - words (Warrington, 1984); v) visual forgetting: Doors and People – visual forgetting (Baddeley et al., 1994); vi)

remote autobiographical memory: Autobiographical Memory Interview (Kopelman et al., 1989) – autobiographical memory scores for Childhood and Early Adulthood.

At uncorrected levels, we further conducted correlations with: i) patients' Doors and People (Baddeley et al., 1994) subtest scores, given the widespread use of this test in exploring brain-behaviour relationships in hippocampal-diencephalic damage (Dzieciol et al., 2017; Manns & Squire, 1999; Patai et al., 2015; Tsivilis et al., 2008; Vann et al., 2009), and its advantage of matching recall and recognition tasks for difficulty – although it has been commented that the norms for its visual recall subtest indicate ceiling effects in healthy participants (Germine et al., 2011); ii) the performance of a subset of aLE patients (n=8) on two custom-made recognition memory tasks that dissociated familiarity from recollection (Argyropoulos et al., 2022).

Moreover, we examined whether these diencephalic nuclei and WM tracts were associated with hippocampal-subicular volumes, and whether any relationships observed between these volumes and episodic memory scores were mediated by the affected diencephalic volumes across patients. To do so, we employed a series of mediation analyses (predictor: hippocampal-subicular volumes; mediator: diencephalic volumes; outcomes: episodic memory scores), relying on the assumption of causality between the independent variable (damage in the hippocampal formation) and the mediator variable (diencephalic damage) (Baron & Kenny, 1986; Judd & Kenny, 1981; MacKinnon et al., 2007). These analyses were conducted using estimated subfield volumes, to examine whether enhancing the granularity in the segmentation of the hippocampal formation reveals direct volumetric relationships with episodic memory. We deliberately examined hippocampal/subicular-memory correlations at uncorrected levels, and diencephalic-memory correlations at corrected levels (Holm, 1979), in order to highlight cases wherein strong diencephalic-memory relationships held over and above any hippocampal/subicular-memory relationships, even when the latter were only observed at uncorrected levels. We also conducted a mediation analysis among total hippocampal formation volumes (predictor), mean fornical fibre density and cross-section (mediator), and total mammillary body volumes (outcome), to assess our hypothesis that any reduction in the volume of mammillary bodies would follow as a knock-on effect of damage in the hippocampal formation and subsequently in the fornix. All correlational and mediation analyses reported below were conducted on patient data separately from those of healthy controls. For key structure-behaviour and structure-structure relationships, we also report

comparisons of correlation coefficients between healthy controls and aLE patients, using a Fisher r-to-z transformation.

Results

Diencephalic volumetry

Using HIPS-THOMAS and FreeSurfer's "HypothalamicSubunits", we observed reduction for the anteroventral (mean volume reduction relative to controls: 22%; η^2_p =0.24), mediodorsal-parafascicular (10%; η^2_p =0.17), pulvinar (10%; η^2_p = 0.19; Figure 1a), and the posterior hypothalamic segmentations (10%; η^2_p = 0.09; Figure 1b; Supplementary Table 1), where the mammillary bodies reside. The FreeSurfer-CNN segmentation of thalamic volumes and the ScLimbic segmentation of the mammillary bodies were strongly consistent with the above, further identifying subdivisions of some of these nuclei along with further nuclei that are not currently covered by HIPS-THOMAS. In particular, these segmentations disclosed volume reduction in the mammillary bodies (7%; η^2_p = 0.09; Figure 1c), along with pronounced volume reduction in the principal anterior nuclei (36%; η^2_p = 0.33), in the medial (m) (31%; η^2_p = 0.32) and lateral pulvinar (13%; η^2_p = 0.15), in the medial mediodorsal (22%; η^2_p = 0.23) and lateral mediodorsal nuclei (22%; η^2_p = 0.19), but also in the laterodorsal (21%; η^2_p = 0.17) and in the limitans-suprageniculate segmentation (20%; η^2_p = 0.14; Figure 1d; Supplementary Table 2; all ANCOVAs: p-corr(24) < 0.05). Among these thalamic nuclei, the extent of volume reduction was not homogeneous, with the principal anterior, medial (m) pulvinar and medial mediodorsal nuclei showing significantly more pronounced reduction than the lateral pulvinar, laterodorsal, and limitans-suprageniculate nuclei (mixed ANCOVAs: Group*Nucleus interactions: p-corr(21) $\leq$ 0.041; $\eta^2_p \geq$ 0.11; Supplementary Table 3).

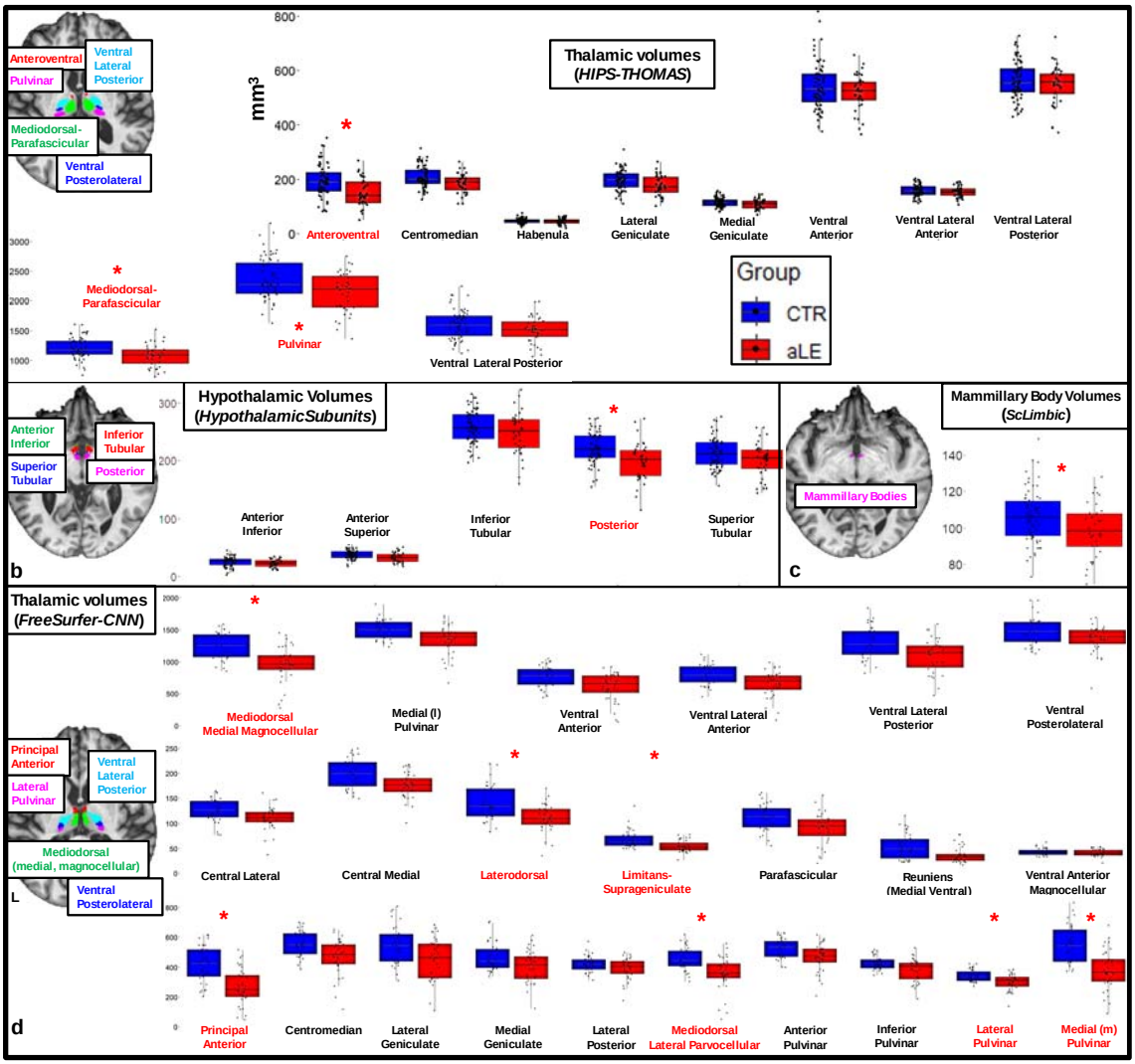

Figure 1: volumes of thalamic and hypothalamic nuclei in controls and patients in native space; **a:** thalamic segmentations (HIPS-THOMAS); **b:** hypothalamic volumes (FreeSurfer-HypothalamicSubunits); **c:** mammillary body segmentations (FreeSurfer-ScLimbic); **d:** FreeSurfer-CNN thalamic segmentations; **key:** line within each boxplot = median value; bottom of box = 25th %ile; top of box = 75th %ile; upper and lower whiskers = scores outside the middle 50; whiskers = 1.5 * interquartile range; *: p-corr < .05 for a series of ANCOVAs: IV: Group(2); for (a-c): 67 controls vs. 38 patients with T1-weighted structural MRI (covariates of ANCOVA: age, sex, intracranial volume, scanning protocol): for (d) : 35 controls vs. 37 patients with T1-weighted structural MRI and diffusion MRI data (covariates: age, sex, intracranial volume); aLE: autoimmune limbic encephalitis; CTR: healthy controls; DTI: Diffusion Tensor Imaging; L: Left (Hemisphere); p-corr: p values adjusted using the Holm-Bonferroni sequential correction method (Holm, 1979); R:

Right (Hemisphere); z-res: volumes residualised against age, sex, FreeSurfer's estimated total intracranial volume (a-d), and scan source (a-c).

Volumetric relationships with the hippocampal formation

Out of the diencephalic nuclei that showed significant volume reduction (n=8), it was the laterodorsal (r = 0.49, p-corr(8) = 0.016), the medial (m) pulvinar (r = 0.47, p-corr(8) = 0.016), and the mammillary bodies (r = 0.52, p-corr(8) = 0.007) that correlated significantly with the total volume of the manually delineated hippocampal formation across patients (Figure 2). We then examined relationships between these volumes and those of hippocampal-subicular subfields. All subfields other than the parasubiculum and the hippocampal fissure (hippocampal tail, molecular layer/presubiculum/subiculum/CA1/CA2-3/CA4/dentate gyrus head/body, and hippocampal-amygdalar transition area) showed volume reduction (15%-26%) across patients (p-corr (18) < 0.05; η^2_p = 0.11-0.36; Supplementary Table 4). Correlations between the subfield volumes (n=16) that showed reduction in patients and the 8 diencephalic nuclei of interest replicated strong relationships for the medial (m) pulvinar and the laterodorsal nucleus with several subfields (r = 0.56-0.66; p-corr(128) ≤ 0.035), but also disclosed a significant correlation between the volume of the principal anterior segmentation and the head of the presubiculum (r = 0.57, p-corr(128) = 0.026). No relationships between individual subfield volumes and those of the mammillary bodies survived correction for multiple testing (r ≤ 0.51; p-corr(128) ≥ 0.119; Supplementary Table 5). Similar relationships between the volume of the hippocampal formation and those of the diencephalic nuclei were also observed across healthy controls, at uncorrected levels (e.g., with laterodorsal nucleus: r = 0.34, p = 0.044; vs. patients: z = -0.71, p = 0.478; with medial (m) pulvinar: r = 0.46, p = 0.005; vs. patients: z = -0.33, p = 0.741; with mammillary bodies: r = 0.36, p = 0.003; vs. patients: z = -0.66, p = 0.509).

Volumetric relationships with episodic memory

We examined the relationship of the diencephalic segmentations that showed volume reduction (n=8) in aLE patients with their impaired episodic memory, as reflected in verbal recall, visual recall, verbal recognition, visual recognition, visual forgetting, and remote autobiographical memory (n=6; p-corr(48); Supplementary Tables 6-7). We also examined the relationship of these scores with the volumes of hippocampal-subicular subfields that showed significant reduction in patients (n=16; Supplementary Tables 8-9) at uncorrected

levels (p), as well as whether these correlations held over and above those with diencephalic volumes, and whether the subfield-memory relationships were mediated by the diencephalic volumes.

Overall, we observed that patients' reduced diencephalic volumes predicted their performance in verbal recognition, visual recognition, and remote autobiographical memory, over and above hippocampal-subicular subfield volumes, moreover, mediating hippocampal-memory relationships, which were only observed at uncorrected levels.

For **verbal recognition memory**, we observed a significant correlation with the volume of the mammillary bodies ($r = 0.54$, p-corr(48) = 0.025; rest of volumes: $r \leq 0.39$; p-corr(48) $\geq$ 0.634). This was driven by the volume of the left mammillary body ($r = 0.61$, p-corr(96) = 0.007; figure 2a; right: $r = 0.36$, p-corr(96) $\geq$ 0.999; rest of volumes: $r \leq 0.43$; p-corr(96) $\geq$ 0.629). Since this volume correlated, at uncorrected levels, with other scores of anterograde retrieval (verbal recall: $r = 0.53$, $p < 0.001$, p-corr(96) = 0.065; visual recall: $r = 0.41$, $p = 0.012$, p-corr(96) = 0.893; visual recognition: $r = 0.48$, $p = 0.003$, p-corr(96) = 0.251), we conducted a series of partial correlation analyses, which disclosed that its relationship with verbal recognition held over and above those with visual recall ($r = 0.45$, $p = 0.008$) and visual recognition (0.41, $p = 0.016$), but only marginally over and above that with verbal recall ($r = 0.30$, $p = 0.075$).

Among the relationships between hippocampal-subicular subfield volumes and memory scores (n=96), the strongest one with verbal recognition memory was that with the head of the subiculum, observed only at uncorrected levels ($r = 0.36$, $p = 0.028$; p-corr(96) $\geq$ 0.999; rest of correlations: $r \leq 0.34$; $p \geq 0.043$; p-corr(96) $\geq$ 0.999). While this volume also correlated, at uncorrected levels, with that of the mammillary bodies ($r = 0.45$, $p = 0.005$, p-corr(128) = 0.311), the mammillary body volumes correlated with verbal recognition memory scores over and above their relationship with the head of the subiculum (partial correlation: $r = 0.46$; $p = 0.005$), and they also fully mediated this hippocampal-memory relationship (indirect effect: $z = 2.09$, $p = 0.037$; direct effect: $z = 1.11$, $p = 0.267$; Figure 2a). A similar pattern was observed when hippocampal volumes were examined separately for each hemisphere (Supplementary Table 10).

For **visual recognition memory**, we observed a significant correlation with the volume of the laterodorsal nucleus ($r = 0.58$, p-corr(48) = 0.011), and a marginal one with medial (m) pulvinar volumes ($r= 0.51$, p-corr(48) = 0.079; rest of volumes: $r \leq 0.49$, p-corr(48) ≥ 0.107). However, the relationship with the laterodorsal nucleus held over and above that with the medial (m) pulvinar (partial correlation: $r = 0.35$, $p = 0.040$). This relationship was driven by the left laterodorsal nucleus ($r = 0.60$, p-corr(96) = 0.015; right: $r = 0.52$, p-corr(96) = 0.130; rest of volumes: $r \leq 0.50$, p-corr(96) ≥ 0.191). While this volume also correlated, at uncorrected levels, with other scores of anterograde retrieval (visual recall: $r = 0.45$, $p = 0.006$; verbal recall: $r = 0.51$, $p = 0.001$; verbal recognition: $r = 0.43$, $p = 0.008$), a series of partial correlation analyses disclosed that its links with visual recognition held over and above the rest (controlling for visual recall: $r = 0.44$, $p = 0.009$; for verbal recall: $r = 0.40$, $p = 0.019$; for verbal recognition: $r = 0.46$, $p = 0.006$).

Among the relationships between hippocampal-subicular subfield volumes and memory scores, the head of CA4 showed numerically the highest correlation with visual recognition memory, albeit observed at uncorrected levels ($r = 0.45$, $p = 0.005$; p-corr(96) = 0.482; rest of correlations: $r \leq 0.45$, $p \geq 0.006$, p-corr(96) ≥ 0.515). While this volume correlated strongly with that of the laterodorsal nucleus ($r = 0.60$, $p < 0.001$, p-corr(128)= 0.010), the laterodorsal volumes correlated with verbal recognition memory scores over and above their relationship with the head of CA4 (partial correlation: $r = 0.45$; $p = 0.008$), and they also fully mediated this hippocampal-memory relationship (indirect effect: $z = 2.49$, $p = 0.013$; direct effect: $z = 0.70$, $p = 0.483$; Figure 2b). A similar pattern was observed when hippocampal volumes were examined separately for each hemisphere (Supplementary Table 10).

Remote autobiographical memory scores correlated across patients with the volume of the medial (m) pulvinar ($r = 0.62$, p-corr(48) = 0.005), the laterodorsal nucleus ($r = 0.56$, p-corr(48) = 0.032), and the limitans-suprageniculate ($r = 0.59$, p-corr(48) = 0.015). Importantly, none of these thalamic volumes was associated with the semantic aspect of remote memories (all three correlations: $r \leq 0.18$; $p \geq 0.339$). This pattern was driven by the left medial (m) pulvinar ($r=0.65$, p-corr(96) = 0.005; left limitans-suprageniculate: $r=0.58$, p-corr(96)= 0.037; right medial (m) pulvinar: $r = 0.57$, p-corr(96) = 0.056; left laterodorsal nucleus: $r = 0.55$, p-corr(96) = 0.091; rest of correlations: $r \leq 0.52$, p-corr(96) ≥ 0.160). Its link with remote autobiographical memory held over and above its relationship with these volumes (all partial correlations: $r \geq 0.38$; $p \leq 0.033$).

Among the relationships between hippocampal-subicular subfield volumes and memory scores, the body of the subiculum showed numerically the highest correlation with remote autobiographical memory, albeit at uncorrected levels ($r = 0.53$, $p = 0.001$; p-corr(96) = 0.124). This volume correlated strongly with that of the medial (m) pulvinar ($r = 0.58$, $p < 0.001$; p-corr(128) = 0.017). However, the medial (m) pulvinar volumes correlated with remote autobiographical memory scores over and above the relationship with the volumes of the body of the subiculum (partial correlation: $r = 0.47$, $p = 0.006$), and they also fully mediated this hippocampal-memory relationship (indirect effect: $z = 2.44$, $p = 0.015$; direct effect: $z = 1.37$, $p = 0.170$; Figure 2c). A similar pattern was observed when hippocampal volumes were examined separately for each hemisphere (Supplementary Table 10).

Verbal recall correlated only at marginal (corrected) levels with the mammillary bodies. This held over and above relationships with hippocampal-subicular subfield volumes (Supplementary Table 10), but no evidence for mediation of the hippocampal-memory relationship was found. No correlations of total or hemisphere-specific diencephalic volumes with **visual recall** scores survived correction for multiple testing. At uncorrected levels, the volume of the left laterodorsal nucleus correlated with visual recall over and above the strongest relationship noted with subfield volumes, but did not mediate the hippocampal-memory relationship (Supplementary Table 10), which was only disclosed at uncorrected levels. For **visual forgetting scores**, the strongest relationship was that with the left mammillary body, yet only observed at uncorrected levels, and not holding over and above the relationship with the total volume of the manually delineated right hippocampus (Supplementary Table 10) - reported in Argyropoulos et al. (2019). The above relationships among diencephalic volumes and memory scores were not observed across healthy controls (laterodorsal nucleus and visual recognition memory: $r = -0.03$, $p = 0.864$; vs. patients: $z = -2.66$, $p = 0.008$; mammillary bodies and verbal recognition memory: $r = 0.25$, $p = 0.198$; vs. patients: $z = -1.35$, $p = 0.177$; medial (m) pulvinar and remote autobiographical memory: $r = -0.17$, $p = 0.395$; vs. patients: $z = -3.29$, $p = 0.001$).

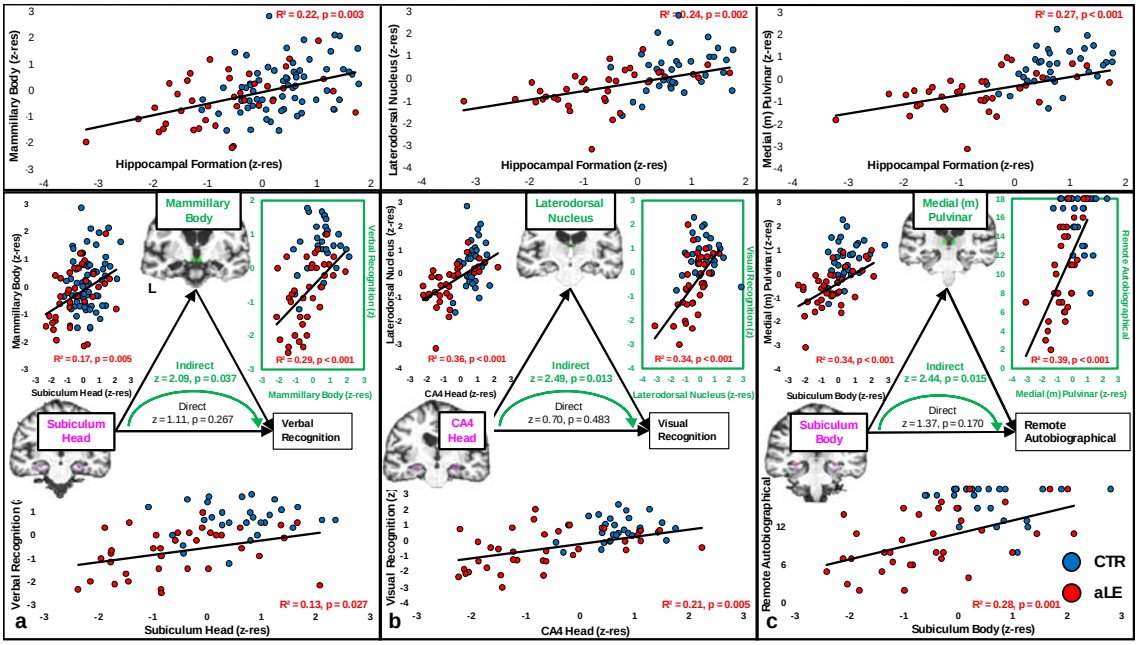

Figure 2: relationships among patients' reduced episodic memory scores, hippocampal-subicular volumes, and reduced thalamic/hypothalamic volumes – (a) mammillary bodies, (b) laterodorsal nuclei, and (c) medial (m) pulvinar volumes; data from healthy controls are only illustrated for display purposes and are not used in the calculation of the R^2 reported; **a:** verbal recognition memory scores – subiculum (head) volume – mammillary body volume; **b:** visual recognition memory scores – CA4 (head) volume – laterodorsal nucleus volume; **c:** remote autobiographical memory scores – subiculum (body) volume – medial (m) pulvinar volume; **key:** aLE: autoimmune limbic encephalitis patients; CTR: healthy controls; z-res: hippocampal-subicular subfield and mammillary body volumes are residualised against age, sex, intracranial volume, and scan source; thalamic volumes are residualised against age, sex, and intracranial volume.

In an exploratory fashion, we also examined, at uncorrected levels, relationships between these diencephalic volumes and Doors and People scores across patients, given that this test has been broadly used to examine structure-behaviour relationships across patient cohorts with diencephalic and/or medial temporal lobe damage (*supra*). The total volumes of the laterodorsal, lateral pulvinar, and medial (m) pulvinar segmentations were strongly associated with visual memory scores (all rs, $|r| \geq 0.46$; all ps, $p \leq 0.007$), but not verbal memory scores (all rs, $|r| \leq 0.29$; all ps, $p \geq 0.092$), showing significant relationships with visual-verbal discrepancy scores (all rs, $|r| \geq 0.35$; all ps, $p \leq 0.042$; Supplementary Figure 5). When

iterated on left vs. right volumes, these relationships were seen to hold in a broadly bilateral fashion (Supplementary Table 11).

Regarding recall vs. recognition in the Doors and People, the total ($r = 0.36$, $p = 0.039$) and left ($r = 0.36$, $p = 0.034$) mammillary body volumes were the only ones to show a relationship, at uncorrected levels, with recall ($p < 0.05$; left laterodorsal: $r = 0.33$, $p = 0.058$; rest of ps: $p \geq 0.117$), although the volumes for mammillary bodies, medial (m) pulvinar and laterodorsal nuclei also showed significant relationships with recognition memory performance (all rs, $r \geq 0.36$, $p \leq 0.039$), with no volume (left, right, or total) correlating with recall-recognition discrepancy scores (all rs, $|r| \leq 0.25$; all ps, $p \geq 0.157$; Supplementary Table 11).

Moving beyond recall vs. recognition, we also explored the presence of any relationships between these volumes and the recollection vs. familiarity estimates derived from the custom-made recognition memory tasks reported in a previous study (Argyropoulos et al., 2022) for the n=8 aLE patients in that study. While no (left, right, total) volume's relationship with familiarity estimates approached $p = 0.05$ (all ps, $p \geq 0.206$), only the right mammillary body volumes showed a significant (uncorrected for multiple testing) relationship with recollection ($r = 0.72$, $p = 0.045$; right medial mediodorsal nucleus: $r = 0.70$, $p = 0.051$; rest of ps, $p \geq 0.119$).

WM Abnormalities

Fixel-based analysis disclosed low fibre density and cross-section in the patients' fornix, cingulum, mammillothalamic tract, and internal capsule. However, there were clear abnormalities beyond the "extended hippocampal system" – in particular, the anterior commissure, the corpus callosum and its radiations, and the superior cerebellar peduncle (figure 3a; Supplementary Figure 4). Most of these abnormalities were replicated with voxel-based morphometry (reflecting reduced volume; Supplementary Figure 1), tract-based spatial statistics (reflecting reduced fractional anisotropy or increased axial or radial diffusivity; Supplementary Figure 2), and in the manually reconstructed tracts using deterministic tractography (Supplementary Figure 3; Supplementary Table 15).

Of the 25 tracts that showed significant mean fibre density and cross-section reduction in patients relative to controls (Supplementary Table 12), the volume of the hippocampal formation was only associated with the integrity of the fornix ($r = 0.57$, p-corr(25) = 0.006; anterior commissure: $r = 0.48$, p-corr(25) = 0.066; rest: $|r| \leq 0.35$; p-corr(25) ≥ 0.784). Likewise, mammillary body volumes were only associated with the integrity of the fornix ($r = 0.52$, p-corr(25) = 0.024; rest: $|r| \leq 0.27$, p-corr(25) ≥ 0.999). We found that the volumetric relationship between the hippocampal formation and the mammillary bodies across patients was at least partly mediated by the integrity of their fornix (figure 3b). At uncorrected levels, similar trends were observed across healthy controls: the volume of the hippocampal formation correlated with that of the mammillary bodies ($r = 0.36$, $p = 0.003$; vs. patients: $z = -0.66$, $p = 0.509$) and the integrity of the fornix ($r = 0.35$, $p = 0.038$; vs. patients: $z = -1.14$, $p = 0.254$), and there was a non-significant trend for a relationship between the volume of the mammillary bodies and the integrity of the fornix ($r = 0.25$, $p = 0.152$; vs. patients: $z = -1.31$, $p = 0.190$).

At uncorrected levels, the average fibre density and cross-section metric of the fornix was associated, across the patient cohort, with recognition memory scores and Doors and People recognition scores (Argyropoulos et al., 2019), as well as with the familiarity estimates for the 8 patients previously reported (see Argyropoulos et al., 2022) (figure 3c; Supplementary Tables 13-4).

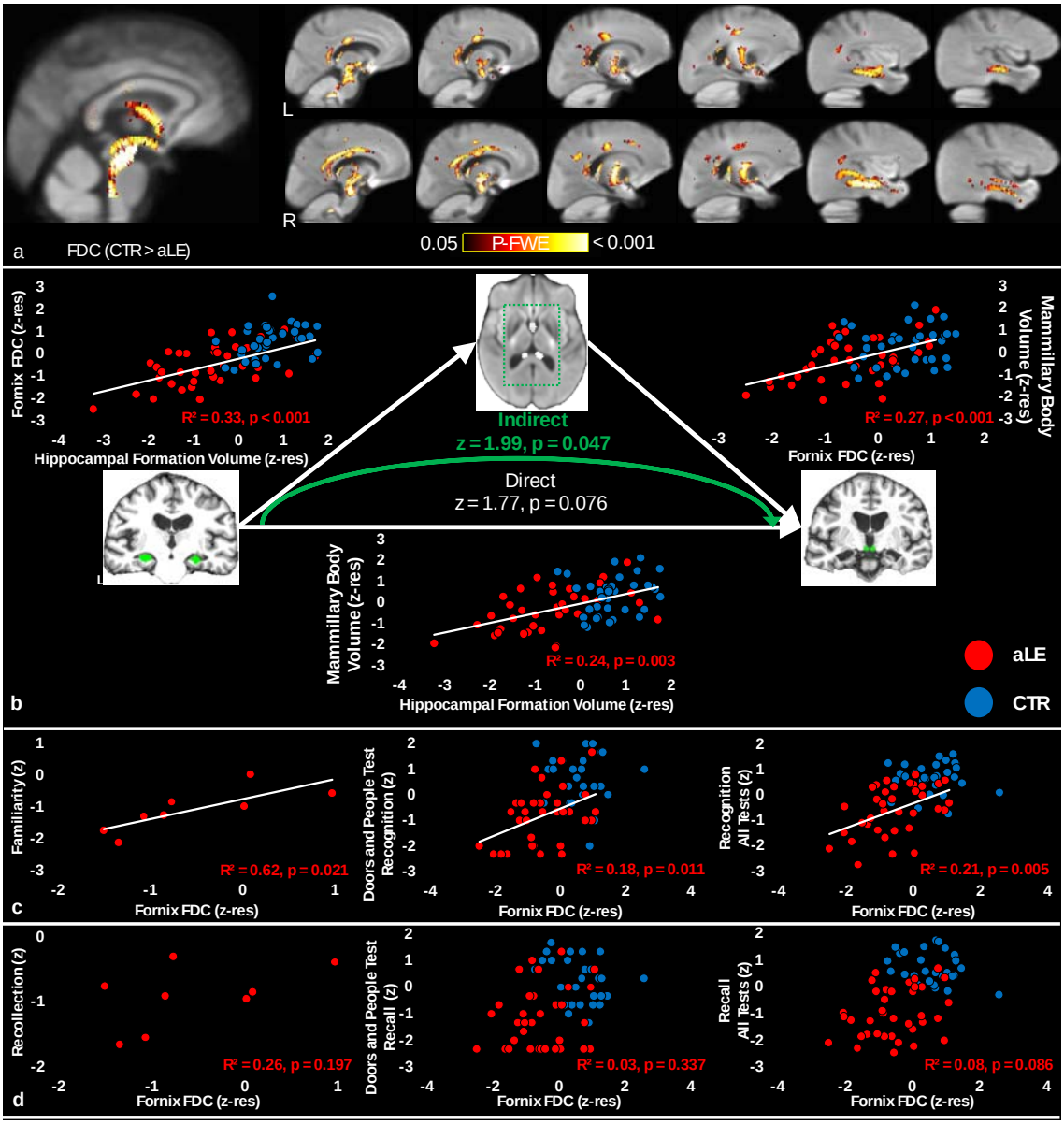

Figure 3: a: Fixel-based analysis comparisons (covariates of no interest: age, sex) between controls and patients on WM integrity (FDC), using a custom-made template based on 30 subjects. All clusters survive whole-brain a threshold-free cluster-enhancement-correction (p-FWE < .05); **b:** mediation analysis among the total volume of the hippocampal formation (predictor; volume residualised against age, sex, intracranial volume, and scan source), fornical integrity (mediator; mean FDC, residualised against age and sex), and total mammillary bodies volume (outcome variable; volumes residualised against age, sex, total intracranial volume, and scan source); **c:** relationship of the mean fornical FDC across patients with their recognition/recall memory composite scores, their recognition/recall scores (Argyropoulos et al., 2019) on the Doors and People test (Baddeley et al., 1994), and the

recollection and familiarity estimates on our custom-made recognition memory tasks for the 8 aLE patients reported in (Argyropoulos et al., 2022); b-d: data from healthy controls are only illustrated for display purposes and are not used in the calculation of the R^2 reported; **key:** aLE: autoimmune Limbic Encephalitis; CTR: healthy controls; FDC: Fiber Density and Cross-section; L: left hemisphere; p-FWE: all clusters survive whole-brain threshold-free cluster enhancement correction; R: right hemisphere; WM: white matter; z-res: standardised residuals.

LGI-1 aLE abnormalities

We also iterated the aforementioned ANCOVAs on diencephalic volumes and WM integrity, comparing our subgroup (n=14) of LGI1-aLE patients (Argyropoulos et al., 2019; Table 2) with healthy controls, in order to establish whether these abnormalities should be attributed to the heterogeneity of our cohort with respect to the autoantibodies involved. Consistent with the whole cohort's (n=38) profile, LGI1-aLE patients showed pronounced volume reduction in the anteroventral / principal anterior nuclei, the medial and the lateral mediodorsal nuclei, the medial pulvinar, along with compromised WM integrity in the fornix and beyond (Supplementary Tables 16-8). Likewise, the atrophy in the hippocampal formation was not (hippocampal/subicular) subfield-specific (Supplementary Table 19). We highlight that comparisons between this subgroup and the rest (n=24) of the patient cohort would not be informative, given that: i) 10 patients that were reported as seronegative may have had LGI-1 aLE, despite that anti-LGI-1 was not detectable in routine clinical practice at the time of screening; ii) only 2 patients were positive for anti-glutamic acid decarboxylase autoantibody, iii) 1 presented with autoantibodies characteristic of paraneoplastic encephalitis, iv) 4 presented with dual seropositive antibodies of contactin-associated protein-like 2 and LGI-1, and v) 7 were found positive for antibodies targeting the voltage-gated potassium channel complex, although there was no further information on the particular antibodies.

Discussion

Research on brain-behaviour relationships in hippocampal amnesia has rarely considered the knock-on effects that damage in the hippocampal formation has on the rest of the brain (e.g., Argyropoulos et al., 2019; Harms et al., 2023). A few other studies (e.g., Dzieciol et al., 2017) that have examined the explanatory significance of damage beyond the medial temporal lobe cannot establish whether such damage is acute or a secondary effect. Meanwhile, most of the studies of structural abnormalities beyond the medial temporal lobe in relatively "focal" hippocampal damage pertain to temporal lobe epilepsy (Cormack et al., 2005; Morgan et al., 2015; Mueller et al., 2010; Romeo et al., 2019; Rosenberg et al., 2006; Tung et al., 2022), with little insight into whether such damage explains these patients' deficits.

Thalamic nuclei

In an earlier study (Argyropoulos et al., 2019), we presented a large (n=38) cohort of patients with residual hippocampal amnesia due to aLE. This is a disease that is traditionally held to involve focal damage in the hippocampus and the amygdala, as seen in animal model research (Tröscher et al., 2017) and post-mortem studies (Khan et al., 2009; Park et al., 2007). Our patients' group-level atrophy in the hippocampal formation (which, beyond the mild volume reduction in the right entorhinal cortex, was focal within the medial temporal lobe) was accompanied by mild thalamic volume reduction, and reduced resting-state activity and hippocampal connectivity across midline cortical structures, from the medial prefrontal cortex and the anterior cingulate to the posterior cingulate cortex and the precuneus. Neuroradiological examinations of our patients' acute clinical scans (Argyropoulos et al., 2019) had disclosed very few abnormalities beyond the medial temporal lobes (bright caudate in one patient, mild, ageing-related microangiopathic changes in four others), with no abnormalities in the thalami. However, we do acknowledge that the cross-sectional nature of our study prevents us from directly establishing whether the extra-hippocampal structural and functional abnormalities reported occur subsequently to focal hippocampal damage. Longitudinal volumetric approaches, such as those reported in Harms et al. (2023), would provide stronger evidence in the future. Although Harms et al. (2023) did not examine the thalamus, we do note that a longitudinal whole-brain voxel-based morphometric analysis on 18 aLE patients (Wagner et al., 2015) had reported grey matter volume reduction in the chronic relative to the acute stage of the illness in the medial temporal lobe, the basal ganglia,

but also the thalamus, albeit with no further details or discussion. Moreover, we are not aware of reports of thalamic damage in the acute stage of aLE, in contrast to reports of significant thalamic injury in other conditions of hippocampal damage, such as acute neonatal/perinatal hypoxic-ischaemic encephalopathy (Eicke et al., 1992; Latchaw & Truwit, 1995).

Here, we identified the specific thalamic nuclei driving the whole-thalamus volume reduction we had previously reported (Argyropoulos et al., 2019), the integrity of hypothalamic nuclei, the relationship of these volumes with the atrophic hippocampal formation, as well as with patients' impaired episodic memory. This is the first study to examine individual diencephalic nuclei in aLE and to combine recently developed advanced methods of segmentation (Billot et al., 2020; Greve et al., 2021; Tregidgo et al., 2023; Vidal et al., 2024). Importantly, we found that such abnormalities were present even across our subset of patients with LGI-1 aLE – the type of aLE patients that comprise the cohorts of many recent studies of "focal" hippocampal damage (Lad et al., 2019; Miller et al., 2020; Spanò, Pizzamiglio, et al., 2020; Spanò, Weber, et al., 2020).

Principal anterior nuclei

Based on the revised articulation of Papez circuit (Aggleton et al., 2022), we would expect our patient cohort to disclose thalamic knock-on effects by means of volume reduction in the anterior thalamic nuclei. Indeed, we observed pronounced atrophy in the anteroventral nucleus (HIPS-THOMAS) and in the principal anterior nuclei as a whole (FreeSurfer-CNN), with its extent (estimated mean reduction between ~21% and ~36% for the whole cohort; ~26% and ~43% for the LGI-1 aLE subset) being comparable, if not larger than that reported for the volumes of our patients' manually delineated hippocampal formation (~22%-25%) (Argyropoulos et al., 2019), or any of the individual, automatically segmented hippocampal-subicular subfield volumes that we reported here (~15%-26% for the whole cohort; ~11%-20% for the LGI-1 aLE subset). Consistent with the strong projections of the anterior nuclei to the presubiculum in the rodent brain (e.g., Thompson & Robertson, 1987), the only volumetric relationship of the anterior thalamic segmentation with hippocampal-subicular subfields to survive correction for multiple testing was that with the head of the presubiculum.

Atrophy in the principal anterior thalamic nuclei has been reported in medial temporal lobe epilepsy, in relation to the hippocampal damage involved (Mueller et al., 2010; Tung et al., 2022). Surprisingly, though, despite the evidence linking the anterior thalamic region with episodic memory (Dzieciol et al., 2017; Segobin et al., 2019; for further references and discussion: Aggleton et al., 2022), no relationships survived correction for multiple testing. We cannot establish whether this should be attributed to false negatives due to stringent correction for multiple correlations, or to the lack of granularity in the automated segmentation of the anterior principal nuclei and, potentially, the stronger involvement of other principal anterior nuclei (anteromedial, anterodorsal) in episodic memory (which these segmentations do not cover): as noted earlier, for example, the FreeSurfer pipelines include the anterior medial and anterior dorsal nuclei into their "anteroventral" segmentation (Iglesias et al., 2018). Moreover, the manifestation of these knock-on effects may go beyond volume reduction, such as hypometabolism and reduced resting-state activity (Argyropoulos et al., 2019; Juhász et al., 1999), and such measures may be shown to predict episodic memory impairment. Even so, we observed pronounced volume reduction in other thalamic nuclei, along with strong structure-behaviour relationships, which we discuss below.

Mediodorsal nuclei

Both methods of thalamic segmentation disclosed volume reduction in the mediodorsal nuclei (HIPS-THOMAS mediodorsal-parafascicular segmentation: ~10%; FreeSurfer-CNN segmentation of both magnocellular and parvocellular divisions of the mediodorsal nuclei: ~22%). Findings of atrophy in the mediodorsal nuclei are consistent with literature on temporal lobe epilepsy. In patients, for instance, this nucleus has shown hypometabolism ipsilateral to the seizure focus (Juhász et al., 1999). In animal models of limbic seizures, prolonged seizures have been shown to trigger abnormalities in this nucleus (Shimosaka et al., 1992; Turski et al., 1986).

Nevertheless, we did not find strong evidence linking the volumes of either the medial or the lateral mediodorsal nuclei with memory scores. The contributions of these nuclei to episodic memory remain unclear. Evidence for the existence of fibers from the perirhinal cortex (and the adjacent amygdala) to this nucleus (Graff-Radford et al., 1990; Parkin et al., 1994), as well as task-based fMRI studies (Kafkas & Montaldi, 2014) and neuropsychological research

on thalamic amnesia (see Carlesimo et al., 2011 for references and discussion) have supported dissociations between the mediodorsal and the anterior nuclei in supporting familiarity and recollection processes, respectively. There has also been discussion of the possibility of dissociating between the medial magnocellular portion and the lateral parvocellular one in supporting familiarity vs. recollection processes, respectively (see review in Carlesimo et al., 2015). While there is some evidence for a causal link between damage in the mediodorsal nuclei and episodic memory impairment (Victor et al., 1971), these relationships have since been elusive (Harding et al., 2000), and there is growing recognition that the mediodorsal nucleus primarily supports executive functions by influencing prefrontal circuits (Wolff & Halassa, 2024). Consistent with the suggestion that this nucleus may support "executive" aspects of memory (Mair et al., 2015), the magnocellular mediodorsal nucleus has been more recently discussed as necessary for rapidly updating and optimising behavioural responses on the basis of recent choice outcomes, while the parvocellular part has been associated with decision making and response selection (Perry et al., 2021).

Custom-made memory tasks that involve larger demands on executive processes may thus highlight links that were not captured by our standardised neuropsychological tests. Likewise, since standardised tests of recognition memory cannot separately assess recollection and familiarity processes underlying recognition memory, custom-made tests should instead be used to assess any relationship between the mediodorsal nucleus and specific memory processes. The weak evidence we found for a relationship between the right medial mediodorsal nucleus and the recollection estimates across the 8 aLE patients who had completed the custom-made recognition memory tasks we previously reported (Argyropoulos et al., 2022) may point in this direction.

Laterodorsal nucleus

The Freesurfer-CNN segmentation disclosed reduction in the laterodorsal nuclei (~21%). While we highlight that this finding could only be seen with FreeSurfer-CNN (since HIPS-THOMAS does not involve segmentation of this nucleus), we believe that this volume reduction is highly consistent with the known connectivity of this nucleus. Characteristically, it has been often assigned to the anterior thalamic nuclear complex (Krauth et al., 2010; Morel et al., 1997), primarily because of the similarities in its neocortical connectivity with the anterior thalamic nuclei (Jones, 2012; Robertson & Kaitz, 1981). Consistent with its strong volumetric relationship with the hippocampal formation across our patients, this

nucleus is known to have direct interconnections with the hippocampal formation (Aggleton et al., 1986; Van Groen & Wyss, 1992; Varela et al., 2014; Vertes et al., 2007), and, like the anterior nuclei (Taube, 1995), it contains head direction cells, such that the activity of hippocampal head direction cells may depend on its integrity (Mizumori et al., 1994). In fact, along with the anterior-dorsal nucleus, it is considered to be the primary source of thalamic head direction signals to the hippocampal formation (Wilton et al., 2001). Moreover, there is evidence for reciprocal anatomical connections between the posterior cingulate (wherein we had shown reduced resting-state activity in our patients: Argyropoulos et al., 2019) and the laterodorsal and anterior thalamic nuclei (Aggleton et al., 2014; Horikawa et al., 1988).

Across our patients, the integrity of this nucleus predicted patients' visual recognition memory (and, at uncorrected levels, visual recall, over and above any relationships with hippocampal-subicular volumes). This is strongly consistent with their proposed involvement in learning and memory, particularly of spatial tasks, via their interactions with the hippocampus (Shibata, 2000; Shibata & Naito, 2005). Nevertheless, it has been highlighted (Perry & Mitchell, 2019) that the contribution of this nucleus to spatial memory has thus far been explicitly examined in very few studies in animals (Mizumori et al., 1994; van Groen et al., 2002; Warburton et al., 1997; Wilton et al., 2001). Crucially, far less is known about this nucleus in humans (Cipolotti et al., 2008; Saunders et al., 2005), and discussion on its role within the recollection-specific extended hippocampal system has been limited (Aggleton et al., 2010, 2022; Aggleton & Brown, 1999).

It is difficult to interpret the evidence on its relationship with visual recognition memory over and above that with visual recall. On the one hand, our findings are consistent with those of Cipolotti et al. (2008), who examined two case studies of patients with thalamic damage, and concluded that (contra the literature on the specialisation of the extended hippocampal system in recollection), if anything, the laterodorsal nucleus would make a contribution to familiarity. On the other hand, we note that the material involved to assess visual recognition involved photographs of doors (Doors subtest of the Doors and People test; Baddeley et al., 1994) and topographical scenes (Camden Memory Tests; Warrington, 1996), whereas the stimuli for visual recall were simple, arbitrary shapes (Rey-Osterrieth Complex Figure Test: Rey, 1959; Shapes subtest from the Doors and People test: Baddeley et al., 1994). It is thus plausible that the relationship observed does not reflect process-specificity, but, instead, stronger engagement in memory for more complex visual stimuli. This was supported by the

significant correlation between these volumes and the visual-verbal discrepancy scores in the Doors and People test.

Pulvinar

The HIPS-THOMAS segmentation disclosed whole-pulvinar volume reduction (~10%), and the FreeSurfer-CNN segmentation clarified that this was driven by the medial (m) pulvinar (~31% mean volume reduction), and, to a lesser extent, the lateral pulvinar (~13%). Whereas the anterior, inferior, and lateral subdivisions of the pulvinar are known to be connected with the parietal and occipital lobes (for review, see Gutierrez et al., 2000), the medial pulvinar is reciprocally connected with the temporal lobe, including the entorhinal area, the parahippocampal gyrus, and its associative neocortical areas (Baleydier & Morel, 1992; Burton & Jones, 1976; Insausti et al., 1987; Mauguière & Baleydier, 1978; Webster et al., 1993; Yeterian & Pandya, 1985). Apart from perirhinal and entorhinal projections to the medial pulvinar via the temporopulvinar bundle (Saunders et al., 2005), the non-fornical projection (sublenticular limb of the internal capsule, bundle of Arnold) from the subicular cortex to the laterodorsal nucleus has been shown to pass through the medial pulvinar, with some additional termination in this nucleus (Aggleton et al., 1986). Moreover, in a study of structural and diffusion MRI (Barron et al., 2014), probabilistic tractography between the thalamus and medial temporal lobe structures disclosed that the medial pulvinar had the highest connection density with the hippocampus in both healthy controls and patients with medial temporal lobe epilepsy and hippocampal sclerosis (see also Segobin et al., 2019). In the same neurological condition, the medial pulvinar is one of the most commonly reported thalamic nuclei to show pathological changes (Capecchi et al., 2020; Guye et al., 2006; Morgan et al., 2015; Rosenberg et al., 2006; Soulier et al., 2023; Voets et al., 2015; Zheng et al., 2018), and depth stimulation studies in epileptic patients have highlighted the functional connectivity between the hippocampus and the medial pulvinar (Catenoix et al., 2011; Rosenberg et al., 2009). There is also anatomical evidence for reciprocal medial pulvinar connections with the posterior cingulate cortex (Baleydier & Mauguiere, 1985; Parvizi et al., 2006; Shibata & Yukie, 2003), wherein we had previously shown reduced resting-state activity in our patients (Argyropoulos et al., 2019).

In this study, we observed a strong link between the left medial (m) pulvinar with remote autobiographical memory, clarifying our previous findings (Argyropoulos et al., 2019), where

we had reported a correlation between the left whole-thalamic volumes and these scores. In both cases, this held over and above the volumes of the hippocampal formation (fully mediating their relationship with remote autobiographical memory). However, despite the anatomical connectivity of the medial pulvinar with the medial temporal lobe and the posterior cingulate, we are not aware of any patient studies implicating this nucleus in autobiographical (or episodic, in general) memory. Likewise, there is very little evidence on the pulvinar in general from functional neuroimaging studies of episodic memory (Kraut et al., 2003; Levine et al., 2004). The relationship observed could be interpreted within the context of a causal link between the integrity of the default-mode network and autobiographical retrieval (Philippi et al., 2015), and the fact that the medial pulvinar is one of the thalamic nuclei embedded within the default-mode network (Li et al., 2021).

Limitans-suprageniculate and medioventral-reuniens segmentations

The volume reduction in the limitans-suprageniculate segmentation in the face of the absence of such reduction in the medioventral-reuniens segmentation is harder to interpret. Given the small volumes of these segmentations, and the fact that they have only been generated with FreeSurfer-CNN, replication is required in other cohorts of aLE patients. A recent study in patients with temporal lobe epilepsy and hippocampal sclerosis (Lee et al., 2020) disclosed a significant increase in these volumes for patients relative to healthy controls. We note, however, that this study involved the T_1-based FreeSurfer segmentations (Iglesias et al., 2018), which HIPS-THOMAS and FreeSurfer-CNN have been designed to surpass in accuracy and reliability. While there is evidence for anatomical connectivity of the limitans and suprageniculate nuclei with the prefrontal cortex (Burman et al., 2011; Preuss & Goldman-Rakic, 1987) and with the perirhinal cortex (Kimura et al., 2003; Tomás Pereira et al., 2016), we are aware of very little information on these nuclei regarding their involvement in memory processes (Kim et al., 2020), and we note that the relationship of remote autobiographical memory with the medial (m) pulvinar held over and above that with the limitans-suprageniculate segmentation.

Arguing on the grounds of anatomical connectivity with the hippocampus, one would expect the medial ventral – reuniens segmentation to have disclosed significant volume reduction in patients. The anatomical connectivity of the reuniens and rhomboid nuclei in the human brain is relatively unknown (Dolleman-van der Weel & Witter, 2020). In rodents and cats, however, these nuclei have dense reciprocal connections with both the prefrontal cortex and

the hippocampal formation (Vertes, 2006; Vertes et al., 2007; Yanagihara et al., 1985), and some cells in the reuniens can directly coordinate activity in these structures (Varela et al., 2014).

Fornix and Mammillary bodies

Knock-on effects of hippocampal damage would also be expected in the mammillary bodies. Indeed, the volume reduction in the posterior hypothalamus, and, in particular, the mammillary bodies, was significant, but much more limited (~ 10% and ~7%, respectively) relative to that for the thalamic nuclei (*supra*). Consistent with our hypothesis that hippocampal damage precedes the deterioration of the integrity of the fornix and the mammillary bodies, our mediation analysis provided evidence for a causal link, whereby hippocampal damage compromises the integrity of the fornix, which in turn compromises that of the mammillary bodies. Out of the 25 WM tracts whose integrity was compromised, the mammillary bodies only showed a volumetric relationship with the fornix. This is consistent with the use of the integrity of the mammillary bodies as a proxy of fornical integrity (e.g., Tsivilis et al., 2008; Vann et al., 2009).

Despite their limited reduction across patients, the volumes of the mammillary bodies correlated strongly with verbal recognition (and marginally with verbal recall), over and above any relationship with hippocampal volumes, corroborating our earlier findings (Argyropoulos et al., 2019) on the explanatory importance of knock-on effects following hippocampal damage. The fact that the relationship between the left mammillary body volume and verbal recognition (which relies on both recollection and familiarity processes) held only marginally over and above that for verbal recall (which relies only on recollection) makes it difficult to argue that our findings are consistent with those supporting a selective role of the extended hippocampal system in recollection relative to familiarity processes (Carlesimo et al., 2007; Tsivilis et al., 2008; Vann et al., 2009). Likewise, total mammillary body volumes correlated with both the recognition and the recall memory composite scores in the Doors and People test.

Some weak evidence favouring the extended hippocampal system's proposed specialisation in recollection processes was reflected in that the volume of the right mammillary body was the only one to show a relationship (at uncorrected levels) with the recollection estimates of our custom-made recognition memory tasks reported in (Argyropoulos et al., 2022),

completed by a subset (n=8) of our patient cohort. Even so, it is worth noting that impaired recognition memory has also been reported in patients with relatively selective damage to the mammillary bodies and the anterior thalamic nuclei (Cipolotti et al., 2008; Gold & Squire, 2006). Likewise, not all studies of fornical damage have showed a sparing of recognition (e.g., Calabrese et al., 1995; D'Esposito et al., 1995; Park et al., 2000; Poreh et al., 2006). This dovetails with our observations on the integrity (mean fibre density and cross-section) of the fornix per se, which correlated, at uncorrected levels, with our recognition memory composite scores but not those for recall (Argyropoulos et al., 2019). This pattern was replicated when we focused on the equivalent composite scores of the Doors and People test, which matches recognition and recall tasks on difficulty and on the delay between the study/encoding and test/retrieval for immediate recall/recognition (Baddeley et al., 1994). This was further corroborated by the relationship observed between fornical integrity and familiarity, but not recollection, in the small subset (n=8) of aLE patients that completed our custom-made recognition memory tasks reported in (Argyropoulos et al., 2022). As such, our findings are not consistent with those linking (in healthy participants) fornical integrity with recall performance (Coad et al., 2020; Hartopp et al., 2019; Metzler-Baddeley et al., 2019; Nestor et al., 2007) or the recollection processes supporting recognition memory (Rudebeck et al., 2009). Nevertheless, it is important to clarify that our findings here should not be misinterpreted as a failure to conceptually replicate those of the aforementioned patient studies, given the substantial differences in the profiles (aetiological, neuropathological) of the patient cohorts involved.

Other WM abnormalities

To investigate WM abnormalities in our cohort, we combined three whole-brain methods of assessing WM integrity (voxel-based morphometry, tract-based spatial statistics, and fixel-based analysis), accompanied by manual reconstruction of fiber tracts using deterministic tractography. To the best of our knowledge, this is one of the very few studies to have done so for any neurological condition.

Within the framework of the extended hippocampal system, one would expect that knock-on effects on the integrity of WM following hippocampal damage would be limited to the fornix, the mammillothalamic tract, the cingulum, and the internal capsule (Aggleton et al., 2022). All four methods used consistently disclosed abnormalities in the fornix and the cingulum.

The abnormalities in the fornix complement the volume reduction observed in the mammillary bodies and the principal anterior nuclei, since projections to the latter almost exclusively involve the fornix (Saunders et al., 2005). Likewise, those in the cingulum are consistent with the atrophy in the principal anterior nuclei, since the cingulum involves projections of anterior thalamic nuclei to the hippocampal formation (Aggleton et al., 2022). Abnormalities in the cingulum also dovetail with the reduced resting-state activity and hippocampal connectivity we had observed in the cingulate and retrosplenial cortices in our cohort (Argyropoulos et al., 2019), since the cingulum comprises reciprocal connections between the anterior thalamic nuclei and the cingulate and retrosplenial cortices (Bubb et al., 2018, 2020; Domesick, 1970; Heilbronner & Haber, 2014; Shibata, 1993b, 1993a).

Abnormalities in the mammillothalamic tract and the internal capsule were captured by tract-based spatial statistics and fixel-based analysis. The internal capsule has been found to carry hippocampal (e.g., subiculum, post-subiculum, pre-subiculum) and entorhinal projections to thalamic nuclei (e.g., lighter ones to the principal anterior nuclei, and more pronounced to the laterodorsal nuclei; Aggleton et al., 1986; Dillingham et al., 2015; Saunders et al., 2005). Moreover, the cortico-thalamic projections targeting the anterior thalamic nuclei often enter the internal capsule, as do the fibres leaving the thalamus via the anterior thalamic radiation (Bubb et al., 2020; Domesick, 1969).

However, there were clear abnormalities beyond the “extended hippocampal system”, in agreement with recently reported work (Krohn et al., 2024) showing that, in the post-acute phase, LGI1-aLE appears as a “network disease”, characterised by reduced whole-brain structural connectivity. In particular, all four of our methods disclosed abnormalities in the corpus callosum and its radiations. Tract-based spatial statistics and fixel-based analysis showed abnormalities in the superior cerebellar peduncle, and tract-based spatial statistics also showed abnormalities in the external capsule.

Evidence for the last two tracts may be seen as consistent with the volume reduction we observed in the mediodorsal thalamic nuclei. The lateral cerebellar nucleus reaches the lateral mediodorsal nucleus via the superior cerebellar peduncle (Çavdar et al., 2014), and the external capsule carries projections of the entorhinal and perirhinal cortices to the mediodorsal nuclei (Saunders et al., 2005). Evidence for callosal abnormalities following focal hippocampal damage has been disclosed in non-human primates (Meng et al., 2014;

Payne et al., 2017). Callosal damage has also been disclosed in a fixel-based analysis study in patients with unilateral temporal lobe epilepsy with hippocampal sclerosis (n=26) (Raffelt et al., 2017). Although the hippocampus does not send inter-hemispheric projections directly via the corpus callosum, the cortical regions that are interconnected with the hippocampus have dense interhemispheric connectivity via the corpus callosum (Meng et al., 2014, 2018).

Nevertheless, it is particularly difficult to associate significant differences between controls and patients in the measures we examined (voxel-based morphometry: reduced volume; tract-based spatial statistics and deterministic tractography: reduced fractional anisotropy or increased axial or radial diffusivity; fixel-based analysis: reduced fibre density and cross-section, fibre density or fibre cross-section) with abnormalities in microstructural properties. For instance, fractional anisotropy is influenced by several properties (e.g., myelination, axon density) in different ways across WM tracts (Friedrich et al., 2020). Likewise, while abnormalities in axial diffusivity have been associated with axon injury (Song et al., 2003) and those in radial diffusivity with demyelination (Baijot et al., 2022; Song et al., 2003), drawing conclusions without examining further mathematical/geometrical information has been discouraged (Wheeler-Kingshott & Cercignani, 2009). Regarding apparent fibre density, we note that the assumption that it is approximately proportional to the total amount of axonal intracellular volume is only valid at higher *b*-values of $b \geq 3000$ s/mm^2 (Genc et al., 2020) – ours was 1,500s/mm^2. For these reasons, our discussion below abstains from attributing the abnormalities observed to specific processes that may have compromised WM microstructural integrity.

Hippocampal volumes and memory

The relationships between diencephalic volumes and episodic memory scores (in particular, verbal/visual recognition and remote autobiographical memory) held over and above those seen with hippocampal-subicular subfield volumes. This corroborates the findings in Argyropoulos et al. (2019), wherein patients' manually delineated whole-hippocampal volumes and hippocampal voxel-based morphometry clusters of reduced grey matter volume were poor predictors of memory scores. Our findings thus show that increasing the granularity of hippocampal volumetry by examining individual subfield volumes does not disclose any stronger evidence for a direct link between hippocampal damage per se and hippocampal amnesia. The only exception to this, as seen previously (Argyropoulos et al.,

2019), was that for visual forgetting: none of the diencephalic volumes that showed reduction in patients was a significant predictor of their scores, which instead strongly correlated with the manually delineated right hippocampal volumes, albeit with no specific subfield volume driving this relationship. While we do acknowledge that manually delineated hippocampal and/or subicular subfield volumes on higher-resolution MRIs acquired at higher field strength would be more accurate, our results thus far (based on manually delineated right/left anterior/posterior/total hippocampal volumes, mean grey matter density from hippocampal voxel-based morphometry clusters, and automatically segmented hippocampal-subicular subfield volumes) do not support the presence of direct links between hippocampal damage per se and impaired remote autobiographical memory or (anterograde) visual/verbal recall/recognition.

Regarding the atrophy within the hippocampal formation (no evidence for subfield-specific atrophy, either in the whole cohort or in the subset of LGI-1 aLE patients), our findings deviate from those in (Miller et al., 2017, 2020), who reported focal CA3 volume reduction. This discrepancy may be attributed to the fact that we used automated (see discussion in Kahhale et al., 2023), instead of manual, segmentation of images acquired at lower field strength (3T vs. 7T), although others have also failed to find subfield-specific atrophy (Hanert et al., 2019).

Conclusion

Our study highlights the importance of examining the remote knock-on effects of hippocampal damage in establishing brain-behaviour relationships. Using novel methods of automated segmentation, we identified diencephalic nuclei that showed volume reduction that was as (if not more) pronounced as that in the hippocampal formation. These volumes explained substantial aspects of patients' episodic memory impairment, over and above hippocampal-subicular subfield volumes. However, some of the diencephalic nuclei and WM tracts affected went beyond those acknowledged as key components of the "extended hippocampal system". A key priority for future research would be to longitudinally examine diencephalic and white matter integrity in cohorts of hippocampal damage with different aetiologies and update neuroanatomical models of this system. Findings like ours may help resolve the debates on the hippocampal and diencephalic contributions to episodic memory, as well as identify further key components within the hippocampal-diencephalic-cingulate circuitry.

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Competing interests

- No competing interests declared

Ethics

Human subjects: All participants provided written informed consent according to the Declaration of Helsinki. Ethical approval was received from South Central Oxford Research Ethics Committee (REC no: 08/H0606/133).

Data availability

Demographic, behavioural, and volumetric data are publicly available at https://osf.io/5ybnk/

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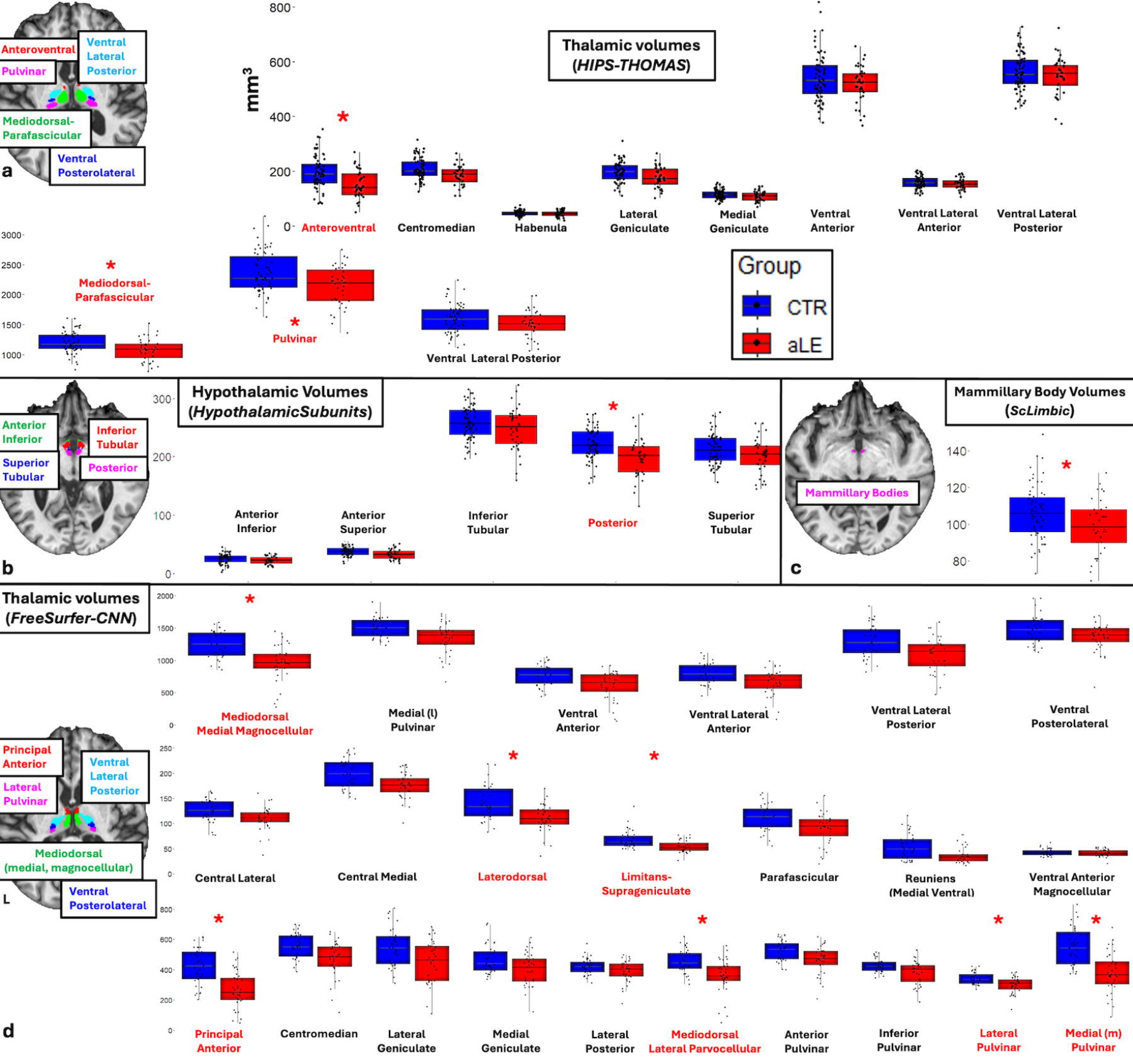
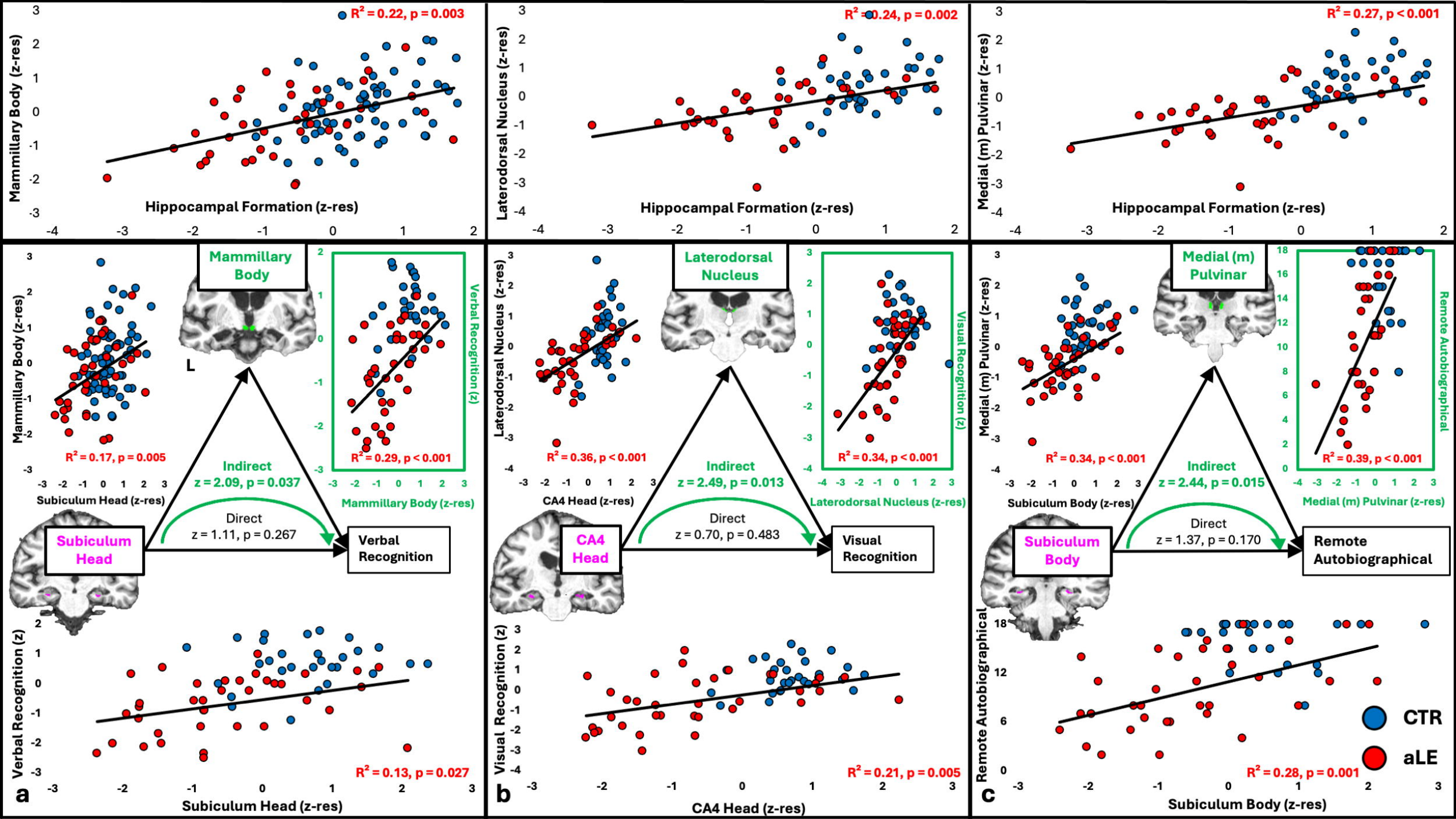
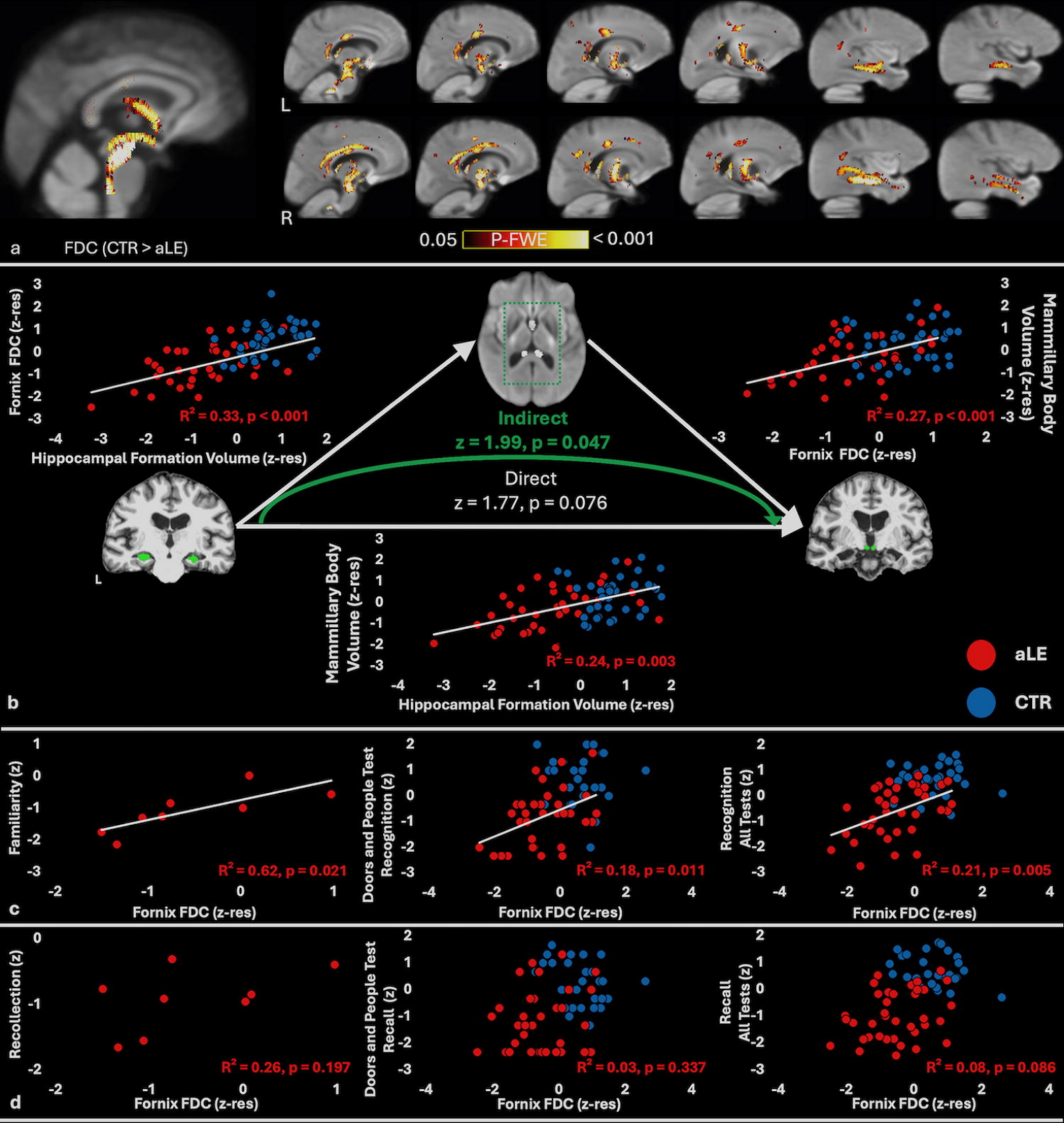

Thalamic volumes
(HIPS-THOMAS)
mm3
Anteroventral
Ventral Lateral Posterior
Pulvinar
Mediodorsal-Parafascicular
Ventral Posterolateral
a
Anteroventral
Centromedian
Habenula
Lateral Geniculate
Medial Geniculate
Ventral Anterior
Ventral Lateral Anterior
Ventral Lateral Posterior
Mediodorsal-Parafascicular
Pulvinar
Ventral Lateral Posterior
Group
CTR
aLE
Hypothalamic Volumes
(HypothalamicSubunits)
Anterior Inferior
Inferior Tubular
Superior Tubular
Posterior
b
Anterior Inferior
Anterior Superior
Inferior Tubular
Posterior
Superior Tubular
Mammillary Body Volumes
(ScLimbic)
Mammillary Bodies
c
Thalamic volumes
(FreeSurfer-CNN)
Principal Anterior
Ventral Lateral Posterior
Lateral Pulvinar
Mediodorsal (medial, magnocellular)
Ventral Posterolateral
L
d
Mediodorsal Medial Magnocellular
Medial (l) Pulvinar
Ventral Anterior
Ventral Lateral Anterior
Ventral Lateral Posterior
Ventral Posterolateral
Central Lateral
Central Medial
Laterodorsal
Limitans-Suprageniculate
Parafascicular
Reuniens (Medial Ventral)
Ventral Anterior Magnocellular
Principal Anterior
Centromedian
Lateral Geniculate
Medial Geniculate
Lateral Posterior
Mediodorsal Lateral Parvocellular
Anterior Pulvinar
Inferior Pulvinar
Lateral Pulvinar
Medial (m) Pulvinar


R² = 0.22, p = 0.003
Mammillary Body (z-res)
Hippocampal Formation (z-res)
R² = 0.24, p = 0.002
Laterodorsal Nucleus (z-res)
Hippocampal Formation (z-res)
R² = 0.27, p < 0.001
Medial (m) Pulvinar (z-res)
Hippocampal Formation (z-res)
Mammillary Body
L
Mammillary Body (z-res)
R² = 0.17, p = 0.005
Subiculum Head (z-res)
Verbal Recognition (z)
R² = 0.29, p < 0.001
Mammillary Body (z-res)
Indirect
z = 2.09, p = 0.037
Direct
z = 1.11, p = 0.267
Subiculum Head
Verbal Recognition
Verbal Recognition (z)
R² = 0.13, p = 0.027
Subiculum Head (z-res)
a
Laterodorsal Nucleus
Laterodorsal Nucleus (z-res)
R² = 0.36, p < 0.001
CA4 Head (z-res)
Visual Recognition (z)
R² = 0.34, p < 0.001
Laterodorsal Nucleus (z-res)
Indirect
z = 2.49, p = 0.013
Direct
z = 0.70, p = 0.483
CA4 Head
Visual Recognition
Visual Recognition (z)
R² = 0.21, p = 0.005
CA4 Head (z-res)
b
Medial (m) Pulvinar
Medial (m) Pulvinar (z-res)
R² = 0.34, p < 0.001
Subiculum Body (z-res)
Remote Autobiographical
R² = 0.39, p < 0.001
Medial (m) Pulvinar (z-res)
Indirect
z = 2.44, p = 0.015
Direct
z = 1.37, p = 0.170
Subiculum Body
Remote Autobiographical
Remote Autobiographical
R² = 0.28, p = 0.001
Subiculum Body (z-res)
CTR
aLE
c


L
R
a
FDC (CTR > aLE)
0.05
P-FWE
< 0.001
Fornix FDC (z-res)
Hippocampal Formation Volume (z-res)
R² = 0.33, p < 0.001
Indirect
z = 1.99, p = 0.047
Direct
z = 1.77, p = 0.076
Mammillary Body Volume (z-res)
Fornix FDC (z-res)
R² = 0.27, p < 0.001
L
Mammillary Body Volume (z-res)
Hippocampal Formation Volume (z-res)
R² = 0.24, p = 0.003
aLE
CTR
b
Familiarity (z)
Fornix FDC (z-res)
R² = 0.62, p = 0.021
Doors and People Test Recognition (z)
Fornix FDC (z-res)
R² = 0.18, p = 0.011
Recognition All Tests (z)
Fornix FDC (z-res)
R² = 0.21, p = 0.005
c
Recollection (z)
Fornix FDC (z-res)
R² = 0.26, p = 0.197
Doors and People Test Recall (z)
Fornix FDC (z-res)
R² = 0.03, p = 0.337
Recall All Tests (z)
Fornix FDC (z-res)
R² = 0.08, p = 0.086
d