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Differential relational memory impairment in temporal lobe epilepsy

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ABSTRACT

Objective: Temporal lobe epilepsy (TLE) is typically associated with pathology of the hippocampus, a key structure involved in relational memory, including episodic, semantic, and spatial memory processes. While it is widely accepted that TLE-associated hippocampal alterations underlie memory deficits, it remains unclear whether impairments relate to a specific cognitive domain or multiple ones.
Methods: We administered a recently validated task paradigm to evaluate episodic, semantic, and spatial memory in 24 pharmacoresistant TLE patients and 50 age- and sex-matched healthy controls. We carried out two-way analyses of variance to identify memory deficits in individuals with TLE relative to controls across different relational memory domains, and used partial least squares correlation to identify factors contributing to variations in relational memory performance across both cohorts.
Results: Compared to controls, TLE patients showed marked impairments in episodic and spatial memory, with mixed findings in semantic memory. Even when additionally controlling for age, sex, and overall cognitive function, between-group differences persisted along episodic and spatial domains. Moreover, age, diagnostic group, and hippocampal volume were all associated with relational memory behavioral phenotypes.
Significance: Our behavioral findings show graded deficits across relational memory domains in people with TLE, which provides further insights into the complex pattern of cognitive impairment in the condition.

1. Introduction

Temporal lobe epilepsy (TLE) is the most common pharmacoresistant epilepsy in adults, and typically associated with pathology of the hippocampus [82,85,86], a key structure involved in the formation and retrieval of memories [97]. Hippocampal lesions are believed to disrupt mnemonic functions in individuals with TLE, which can sometimes impact their quality of life more than seizures [41,90]. To improve patient care, it is crucial to understand the full scope of TLE deficits by recognizing how hippocampal damage impacts various cognitive processes.

Relational memory encompasses several faculties that synthesize the

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elements of subjective experience into a coherent mental representation [6,26,63]. Relational memory domains include episodic, semantic, and spatial memory. Episodic memory integrates contiguous spatiotemporal events [88,89] into a self-referential abstraction known as an episode [25,27]. Semantic memory amalgamates notions and facts into a mental hierarchy of conceptual categories [21,38,80]. Spatial memory maps out and binds the locations of ambient objects into a mental feature space of the physical environment, also referred to as a cognitive map [61]. Recent studies point to some convergence of these relational domains in healthy individuals, both at the behavioral and neural level, generally supporting a key involvement of the hippocampus and associated neocortical networks [2,11,12,36,42,43,58,72,73]. In healthy controls (HC), we previously showed an association between semantic and spatial cognition based on behavioral performance scores obtained on different cognitive tests [84], which was reflected in similar profiles of intrinsic functional connectivity between the hippocampus and neocortex [81]. Other task-based investigations have uncovered patterns of brain activity that are compatible with neural representations for both semantic concepts as well as physical space [20,57].

Episodic memory impairment is well-established in TLE, backed up by ample behavioral [4,67,90] and neuroimaging [55,76,79] findings. On the other hand, and surprisingly, the literature on other relational memory domains remains scarce. With respect to spatial memory, findings are relatively limited, but suggest atypical behavioral phenotypes and neural representations [74,83]. Likewise, despite well-recognized impairments in language and naming performance in TLE [4,5,29], relational semantic memory has only sporadically been studied in TLE [38,48]. Notably, there have not been any integrated assessments of episodic, semantic, and spatial memory in the same patients. Examining patients and HC using a multidomain memory paradigm can help address the specificity of TLE-associated behavioral impairments across these different cognitive domains.

The current study investigated episodic, semantic, and spatial memory in TLE patients as well as HC using a recently developed, open-access behavioral battery (*integrated Relational Evaluation Paradigm*, iREP). The iREP combines three computerized and domain-specific modules (*i.e.*, Episodic, Semantic, and Spatial), each of which incorporates visual stimuli representing ordinary items, two levels of difficulty (Easy *vs.* Difficult), and a 3-alternative forced choice design. We first ran independent analyses in each cohort to confirm the difficulty manipulation across modules, and then performed an analysis of variance (ANOVA) to identify between-group behavioral differences in episodic, semantic, and spatial memory performance on the iREP. Finally, we implemented partial least squares (PLS) analysis, a multivariate associative technique, to identify how variations in clinical/demographic factors contribute to shared mnemonic phenotypes across memory domains. We hypothesize that TLE patients will present with altered in relational memory relative to HC, with most noticeable deficits along the episodic domain. We further anticipate hippocampal volume to covary with all performance measurements.

2. Methods

2.1. Participants

We studied 74 adult participants recruited between 2018 and 2022 at the Montreal Neurological Institute and Hospital, including a cohort of 24 pharmacoresistant TLE patients (12 women, mean age ± SD: 35.0 ± 11.5 years, range: 18–57, 2 ambidextrous) referred to our hospital for presurgical investigation, and 50 age- and sex-matched HC recruited via advertisement (20 women, 32.0 ± 7.8 years, range: 19–57 years, 5 left-handed). Epilepsy diagnosis and seizure focus lateralization were established following a comprehensive multidisciplinary assessment based on medical history, neurological and neuropsychological evaluation, video-electroencephalography telemetry, and magnetic resonance imaging (MRI). Fifteen patients had a left-sided seizure focus, and 9 had a right-sided focus. Based on ictal and interictal EEG data, 15 patients presented with medial/antero-medial seizure onset while the rest displayed a lateral/complex phenotype. Quantitative hippocampal MRI volumetry [22] also revealed that 15 patients (62.5 %) showed marked hippocampal atrophy ipsilateral to the focus (*i.e.*, absolute ipsilateral-contralateral asymmetry index > 1.5 and/or ipsilateral volume z-score < -1.5). Average age at seizure onset was 21.1 ± 10.8 years (range: 2–49 years), and average duration of epilepsy was 13.8 ± 10.9 years (range: 1–39 years). At the time of study, no patient had undergone resective surgery. Following an average time of 147 ± 98 days post-study, 9 patients underwent temporal lobe surgery, and 5 were rendered seizure free after a mean follow-up of 372 ± 329 days post-op. All participants had normal or corrected-to-normal vision. Our study was approved by the Research Ethics Committee of the Montreal Neurological Institute and Hospital, and all participants provided written and informed consent.

2.2. Relational memory phenotyping

The *integrated Relational Evaluation Paradigm* (iREP) is an open access, python-based cognitive assessment protocol (https://github.com/MICA-MNI/micaopen/tree/master/task-fMRI) [84]. It incorporates three memory domain specific modules: Episodic, Semantic, and Spatial. iREP administration is flexible. Modules can be completed in the laboratory or within varied neuroimaging platforms (*i.e.*, MRI scanner environment). Task instructions require verbal comprehension, but the task execution is non-verbal and homogenized via *(i)* the use of similar visual stimuli taken from a pooled custom-made and semantically-indexed library, *(ii)* the modulation of cognitive load across two conditions (*i.e.*, Easy *vs.* Difficult) with a pseudo-randomized trial presentation order, and *(iii)* the implementation of a 3-alternative forced choice trial-by-trial paradigm. Each module contains four distinct stimulus lists (*i.e.*, A, B, C, and D) for inter-individual counterbalancing and/or longitudinal administration. This allows for a combined evaluation of different forms of relational memory across two difficultly levels using a matched stimulus set and task structure. In the current study, all participants were tested on the iREP inside the MRI scanner, as part of a multimodal neuroimaging protocol described elsewhere [84]. Participants used an MRI-compatible response box to provide their answers. The neural responses recorded with functional MRI will be the focus of forthcoming projects.

(i) Episodic module. The episodic module is a symbolic version of an established lexicon-based episodic memory paradigm [65,81] that involves an encoding and a retrieval phase (Fig. 1**: top row**). In the encoding phase (~6 min), the participant memorizes a pair of unrelated objects presented simultaneously at each trial (*i.e.*, doorknob and ostrich). Half of the stimulus pairs is shown only once throughout the run for a total of 28 trials (*i.e.*, Difficult condition), and the other half is displayed twice to ensure more stable encoding for a combined 56 trials (*i.e.*, Easy condition), with a total of 84 trials for the entire task. The retrieval phase (~4.5 min) is administered after a 10-min interval. During each trial, one item is displayed at the top of the monitor (*i.e.*, doorknob) and three others, at the bottom (*i.e.*, shark, ostrich, and ladder). From the latter three options, the participant selects the object that was paired with the top item during the encoding phase. There are 56 pseudo-randomized trials in total with equal number of trials per condition (*i.e.*, 28 Difficult: Epi-D; 28 Easy: Epi-E).

(ii) Semantic module. The semantic module is a symbolic variant of an established lexicon-based semantic association protocol [81,92] (Fig. 1**: middle row**). This task consists of 56 pseudo-randomized trials (~4.5 min), with two conditions of equal length (*i.e.*, 28 Difficult: Sem-D; 28 Easy: Sem-E). At each trial, a reference item appears at the top of the monitor (*i.e.*, basketball) with three stimuli below (*i.e.*, soccer ball, above ground pool, can opener), exactly as described in the retrieval phase of the Episodic module. The participant selects the option that is conceptually most alike to the object presented at the top. Pairwise

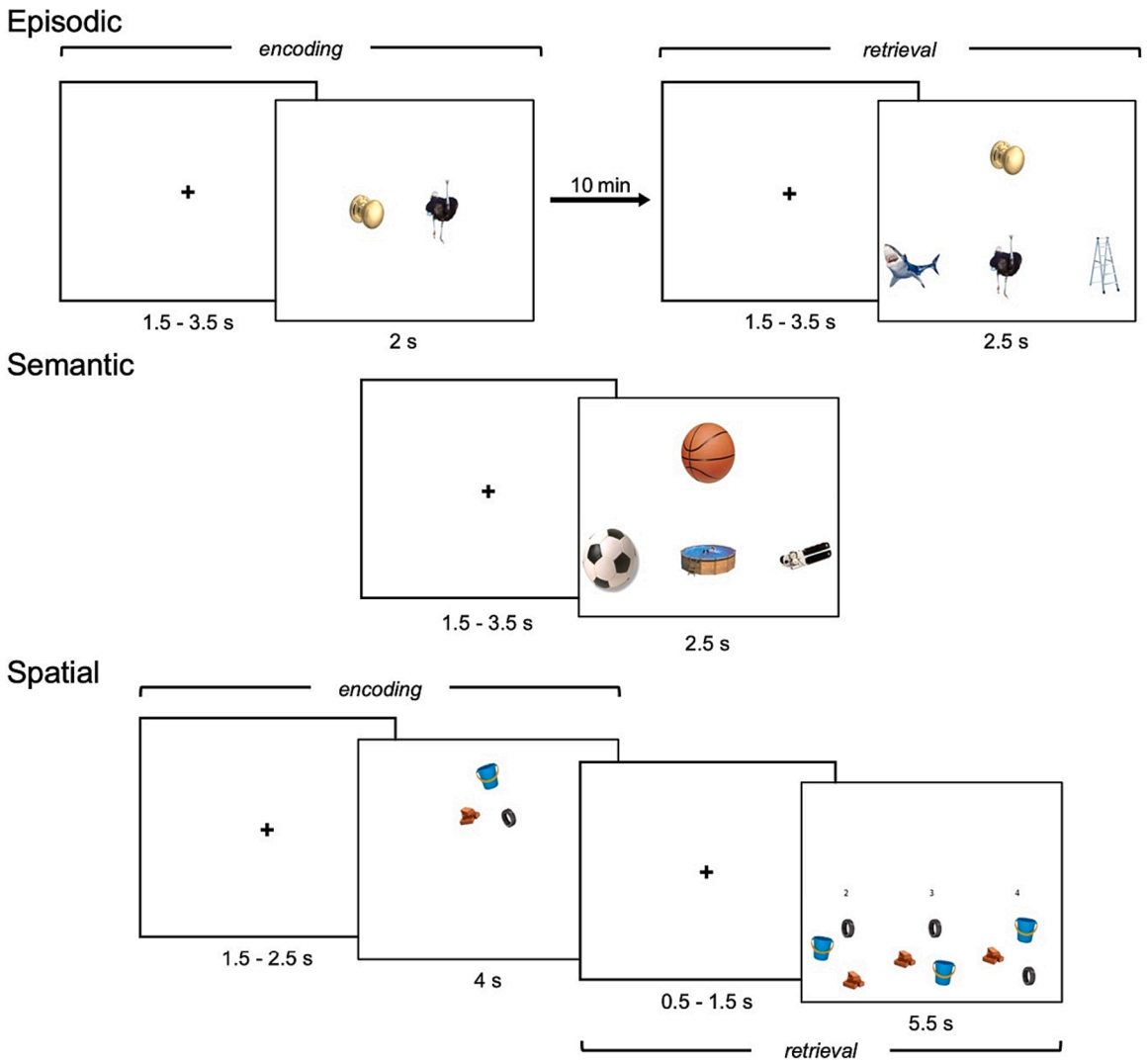

Fig. 1. Trial design for each iREP module. *(top row)* The Episodic task consists of two separate runs. During Encoding, object pairs must be memorized. After a 10-minute break during Retrieval, the item that was originally paired with the top image must be recalled among three options. *(middle row)* In the Semantic task, the item that is the most conceptually congruent with the top object must be selected out of three choices. *(bottom row)* During the Spatial task, the configuration of three items must initially be encoded (*encoding*). Within the same trial, the original spatial arrangement must be chosen out of three options (*retrieval*). Numbers are there to visually aid participants on which response key to press. Overall durations for stimuli and inter-stimulus intervals are shown for each module.

conceptual affinity indices (*cai*) were calculated using an algorithm that leverages internet-based lexical corpora [33], ranging from 0 to 1. In Sem-E trials, the correct response (*i.e.*, soccer ball) and the top image (*i.e.*, basketball) are related by $cai > 0.66$; in Sem-D trials, the similarity index is given by $0.33 \leq cai \leq 0.66$. Regardless of condition, the conceptual relatedness of the top stimulus and the foils (*i.e.*, above ground pool, can opener) is always $cai < 0.33$. Thus, the level of difficulty across conditions is a function of the semantic relationship between the top object and the correct response.

(iii) Spatial module. Spatial memory was assessed using a recently validated paradigm [84] (Fig. 1**: bottom row**). This module consists of 56 pseudo-randomized trials (~12.5 min), with two conditions (*i.e.*, 28 Difficult: Spa-D; 28 Easy: Spa-E). At each trial, the participant first memorizes the spatial configurations of three objects, and then selects the same arrangement among three options in a delayed-onset design. In Spa-D trials, the two distractor layouts are very similar to the target configuration as only the spacing between the objects has changed. In the Spa-E trials, in addition to the spacing, the relative position of each item within the configuration is also changed, thus making it easier to differentiate the correct arrangement from the two foils.

2.3. iREP scoring

For each participant, we computed six iREP accuracy scores (*i.e.*, Epi-E, Epi-D, Sem-E, Sem-D, Spa-E, and Spa-D): $accuracy = \frac{n_{Correct}}{n_{Trial}} * 100$, where $n_{Correct}$ is the number of correct responses and n_{Trial} is the number of trials, which is always 28.

2.4. Parallel assessment of executive and overall cognitive function

In addition to the iREP, we administered the EpiTrack and the Montreal Cognitive Assessment (MoCA) protocols to our participants to account for factors that could potentially affect the relationship between study cohorts and iREP outcome measures. Both tools are behavioral screening protocols for cognitive impairment. The EpiTrack is commonly used in patients with epilepsy to identify and monitor impairments in processing speed and attention [46,50], while the MoCA is used to detect mild cognitive impairment and dementia [60].

2.5. Hippocampal atrophy determination

We acquired MRI data on a 3 T Siemens Magnetom Prisma-Fit with a

64-channel head coil. Two T1-weighted scans with identical parameters were performed with a 3D-MPRAGE sequence (0.8 mm isotropic voxels, matrix = 320 × 320, 224 sagittal slices, TR = 2300 ms, TE = 3.14 ms, TI = 900 ms, flip angle = 9°, iPAT = 2). We used HippUnfold [22] to segment the left and right hippocampi in each participant, and to estimate their volumes. HippUnfold implements a U-Net deep convolutional neural network to automate detailed hippocampal tissue segmentations. Grey matter data are then mapped onto to the resulting "unfolded" hippocampal space, with distinct subregional features. In the current work, we only examined whole hippocampal grey matter volumes, restricting analyses to MNI152-derived metrics to account for interindividual variability in intracranial volume (see Supplemental Figure for subfield analyses). To compute the absolute ipsilateral-contralateral asymmetry index, we first calculated non-normalized left–right asymmetry scores for controls and patients as follows: $\frac{Hipp_L - Hipp_R}{(Hipp_L + Hipp_R)/2}$, where $Hipp_L$ ($Hipp_R$) is the volumes of the left (right) hippocampus in MNI152 space. We normalized patient asymmetry scores with respect to those of controls, and thresholded indices at *abs(index)* > 1.5. To calculate patient ipsilateral volume z-scores, we normalized left and right volumes for patients with respect to corresponding volumes for controls, and thresholded ipsilateral values at $z_{ipsi} < -1.5$. Criteria for atrophy were met if either measure was satisfied.

2.6. Statistical analysis

(i) Analysis of variance (ANOVA). We ran a 2 × 6 repeated measures mixed ANOVA which comprised one between-group factor with two levels (*i.e.*, group: HC, TLE) and one within-group factor with six levels (*i.e.*, iREP: Epi-E, Epi-D, Sem-E, Sem-D, Spa-E, Spa-D), with individual identifiers for each participant (*i.e.*, id):

$$accuracy \quad 1 + group^{*}iREP + Error(id/iREP) \tag{1}$$

(ii) Control analyses. To assess whether significant between-group differences in relational memory performance were seen above and beyond differences in socio-demographic factors (age, sex) as well as impairments in executive function and overall cognitive ability (EpiTrack, MoCA), we regressed out the effects of covariates of interest and refit the model using the residual scores. This step ensures that differences in behavioral accuracies between groups are not driven solely by extraneous cognitive phenotypes:

$$accuracy \quad 1 + covariate + Error \rightarrow residual\ accuracy \tag{2}$$

$$residual\ accuracy \quad 1 + group^{*}iREP + Error(id/iREP) \tag{3}$$

(iii) Partial least squares (PLS). We also used multivariate models to complement the above case-control method from a data-driven perspective. PLS is a multivariate associative technique that maximizes the covariance between two datasets by decomposing their cross-correlation matrix and deriving optimal linear combinations of the original datasets known as latent variables (LV) [44,56]. Unlike the factorial nature of ANOVA, which seeks to detect significant effects among the various levels of predetermined variables, PLS aims to generate a lower-dimensional manifold of these factors that effectively recapitulates their raw information content. In this way, PLS offers a flexible and complementary mode of analysis. We computed the cross-correlation matrix between five clinical/demographic features (*i.e.*, age, sex, group, hippocampal volume) and six iREP measurements (*i.e.*, Epi-E, Epi-D, Sem-E, Sem-D, Spa-E, Spa-D). Hippocampal volume was normalized with respect to healthy controls, averaged across hemispheres in HC, and ipsilateral to epileptogenic focus in TLE patients. We decomposed the cross-correlation matrix via singular value decomposition, which resulted in a vector of left singular values (*i.e.*, clinical saliences) characterizing a distinct phenotypic pattern for each LV, a diagonal eigenvalue (*i.e.*, singular value) matrix reflecting the covariance explained by each LV, and a vector of right singular values (*i.e.*, iREP saliences) describing a particular iREP pattern for each LV. Subject-specific composite scores were computed by projecting their original clinical and iREP data onto their respective saliences. To test for the significance of each LV, we ran 5,000 permutation tests by resampling the iREP dataset *without* replacement while iteratively realigning permuted saliences to the original ones using Procrustes rotation to obtain a distribution of null singular values. We interpreted LVs by calculating clinical and iREP loadings, which are product moment correlation coefficients between original clinical or iREP values with their corresponding composite scores (*i.e.*, linear projections of original values onto corresponding saliences). To assess the reliability of significant LVs' loadings, we applied a bootstrapping procedure with 5,000 iterations by resampling the iREP dataset *with* replacement and realigning bootstrapped saliences to the originals using Procrustes transform. We then computed *z*-scores for each variable loading by dividing the loading coefficient by its estimated standard error, which is the standard deviation of the bootstrapped distribution. Finally, we converted *z*-scores into FDR-adjusted [7] *p*-values ($\alpha_{FDR} = 0.05$) to determine coefficient significance.

All data and codes used in this work are openly available at: https://github.com/MICA-MNI/micaopen/tree/master/tle_memory_manuscript_codes.

3. Results

3.1. The structure of relational memory in HC and TLE patients: ANOVA findings

First, we evaluated the Easy versus Difficult manipulation by conducting three paired sample t-tests within each cohort. In both groups, within each module, accuracy scores were significantly higher for the Easy compared to the Difficult condition (ts > 7.0, $p_{FDR} < 0.0001$, Fig. 2a). Next, we compared accuracy on the iREP measurements between HC and TLE groups in a 2 × 6 repeated measures mixed ANOVA (Fig. 2b), where we observed that performance scores on the iREP were modulated by group ($F_{2.6,\ 186.7} = 4.86$, $p < 0.01$, $\eta_p^2 = 0.063$). Decomposing the *group* × *iREP* interaction using simple main effects tests, we confirmed that HC scored significantly higher than TLE patients on nearly all measurements: Epi-E ($F_{1,\ 72} = 7.76$, $p < 0.01$), Epi-D ($F_{1,\ 72} = 15.18$, $p < 0.001$), Sem-D ($F_{1,\ 72} = 6.52$, $p < 0.05$), Spa-E ($F_{1,\ 72} = 6.16$, $p < 0.05$), and Spa-D ($F_{1,\ 72} = 8.02$, $p < 0.01$). In the Sem-E condition, TLE patient scores did not differ from HC ($F_{1,\ 72} = 0.07$, $p = 0.79$). Two additional control analyses in which we accounted for the effects of socio-demographics (*i.e.*, age & sex) and executive/cognitive functions (*i.e.*, MoCA & EpiTrack) confirmed the robustness of group differences in relational memory, especially along episodic and spatial domains (see Supplemental Material for additional covariate analyses). As in the baseline analysis, *group* × *iREP* interactions were significant for both covariate models (socio-demographics: $F_{2.6,\ 186.7} = 4.86$, $p < 0.01$; executive functions: $F_{2.5,\ 165.0} = 3.47$, $p < 0.05$). Of note, MoCA and EpiTrack scores were available for only a subset of the original cohort (nHC = 48/50, nTLE = 19/24). Across both control regimens, between-group differences persisted for Epi-D ($F_{1,\ 72} = 14.10$, $F_{1,\ 65} = 9.30$; ps < 0.01) and Spa-D ($F_{1,\ 72} = 6.54$, $F_{1,\ 65} = 5.62$; ps < 0.05). Findings for Epi-E and Spa-E were significant when controlling for socio-demographics ($F_{1,\ 72} = 7.02$, $F_{1,\ 72} = 5.09$; ps < 0.05), but not when accounting for executive/cognitive functions ($F_{1,\ 65} = 3.30$, $F_{1,\ 65} = 1.74$; ps > 0.07). Neither covariate analysis found significant between-group differences in Sem-E ($F_{1,72} = 0.29$, $F_{1,65} = 3.45$, ps > 0.06).

3.2. The structure of relational memory in individuals with TLE and controls: PLS findings

ANOVA findings were complemented by our PLS results, which revealed that age, group, and hippocampal volume contributed to relational memory performance (see Supplemental Figure for subfield

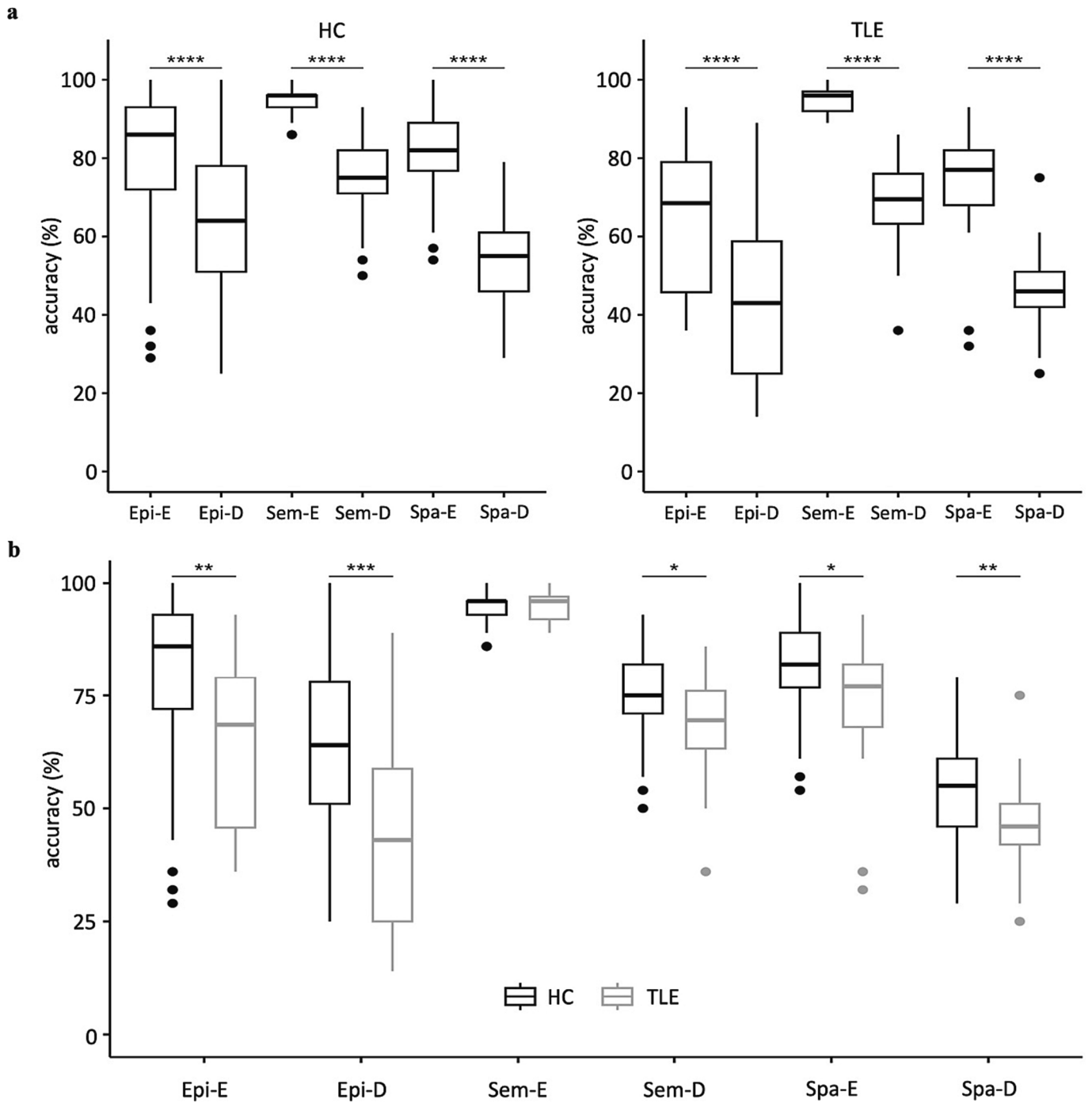

Fig. 2. Irep performance. *(a)* For each group, we ran three paired sample t-tests to validate the Easy *vs*. Difficult manipulation (ts > 7.0, **** $p_{FDR} < 0.0001$). *(b)* Results from the repeated measures mixed ANOVA showed a significant *group* × *iREP* interaction effect ($F_{2.6,\ 186.7} = 4.86$, $p < 0.01$). Simple main effects tests confirmed that HC performed significantly better than TLE on Epi-E ($F_{1,\ 72} = 7.76$, ** $p < 0.01$), Epi-D ($F_{1,\ 72} = 15.18$, *** $p < 0.001$), Sem-D ($F_{1,\ 72} = 6.52$, * $p < 0.05$), Spa-E ($F_{1,\ 72} = 6.16$, * $p < 0.05$), and Spa-D ($F_{1,\ 72} = 8.02$, ** $p < 0.01$). There was no group difference in Sem-E ($F_{1,\ 72} = 0.07$, $p = 0.79$).

analyses). The first latent variable (LV1) obtained via the decomposition of the cross-correlation matrix between clinical phenotypes and iREP accuracies accounted for 86 % of total covariance (Fig. 3a, **left**). The correlation between corresponding clinical and behavioral composite scores along LV1 was also significant, as attested by permutation tests ($r = 0.46$, $p_{perm} < 0.001$, Fig. 3a, **right**). Additional bootstrapping evaluated the robustness of loadings along LV1 (age: −0.52, sex: 0.05, group: 0.90, normalized hippocampal volume: 0.77, Epi-E: 0.79, Epi-D: 0.85, Sem-E: 0.40, Sem-D: 0.58, Spa-E: 0.55, Spa-D: 0.69, Fig. 3b, **left**). Except for sex ($z = 0.29$, $p_{FDR} = 0.89$), all other variables presented with significantly reliable loadings (age: $z = -2.72$, group: $z = 21.17$, normalized hippocampal volume: $z = 7.39$, Epi-E: 11.87, Epi-D: 18.81, Sem-E: 2.56, Sem-D: 5.79, Spa-E: 4.18, Spa-D: 8.04, all $p_{FDR} < 0.05$, Fig. 3b, **right**). Thus, younger age, allocation to the HC cohort, and larger total hippocampal volumes were associated with better performance across all tasks, and while the iREP pattern was shared across modules, episodic accuracies showed highest contributions, followed by spatial, and finally semantic, validating our ANOVA findings. Overall, diagnostic group and episodic scores were the most important features of LV1.

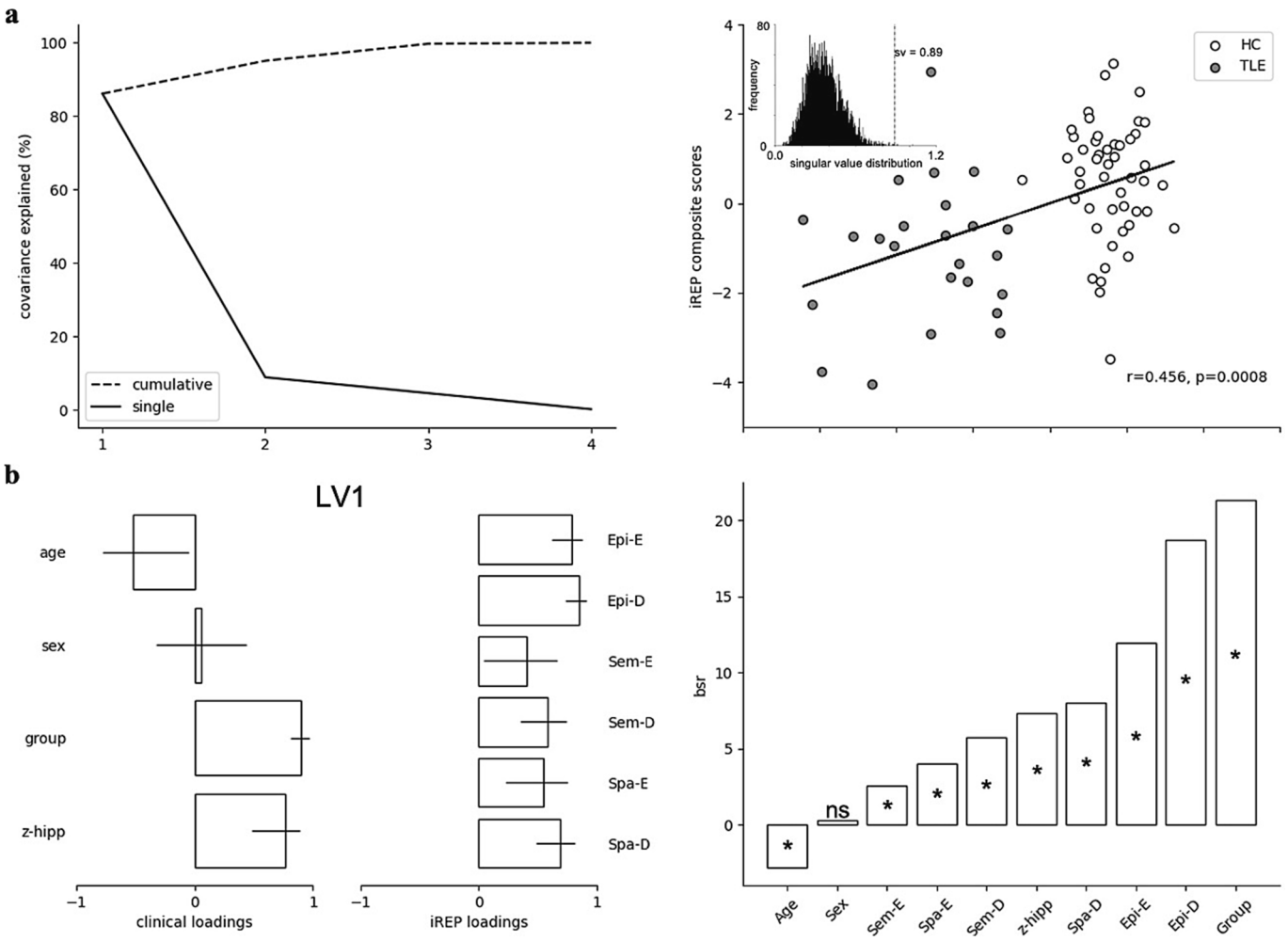

Fig. 3. PLS. *(a) left:* the first latent variable (LV1) accounted for 86 % of the covariance between four clinical features (*i.e.*, age, sex, group, and hippocampal volume) and six iREP measurements (*i.e.*, Epi-E, Epi-D, Sem-E, Sem-D, Spa-E, and Spa-D). *right:* the association between clinical and iREP composite scores along LV1 was significant ($r = 0.46$, $p_{perm} < 0.001$) as attested by 5,000 permutations (inset: dashed line "sv" represents the actual singular value). *(b) left:* clinical and iREP loadings (95 % CIs calculated by bootstrapping). *right:* loading reliabilities were determined by *z* score estimation via bootstrapped ratios (bsr) for each variable by dividing loading coefficients by the estimated standard error derived from 5,000 bootstraps. *Z* scores were adjusted for FDR (* $p_{FDR} < 0.05$).

4. Discussion

Our objective was to analyze the pattern of behavioral impairments across relational memory domains in patients with TLE, the most common pharmaco-resistant epilepsy in adults and a human disease model of memory dysfunction [4,14,39,49,53,66,71,75,78,91,95,96]. We compared the performances of TLE patients to those of age- and sex-matched healthy controls on the different modules of the iREP, a recently developed cognitive assessment tool [84]. The iREP is a comprehensive battery that includes three complementary and homogenous tasks that collectively tap into the episodic, semantic, and spatial memory systems. Modules are further stratified into two conditions that correspond to levels of difficulty, thus offering two degrees of probing resolution into each cognitive domain. In addition to verifying the task difficulty manipulation via paired student t-tests, we applied a repeated measures ANOVA in conjunction with PLS analysis to identify module-specific associations in behavioral scores across groups and iREP measurements, and to discern latent associative patterns between clinical features and performance scores.

Our ANOVA results demonstrated that TLE patients were considerably impaired on the episodic module, a finding that expands on an already well-established scientific corpus [15,41,51,55,82,85,86,90]. Also, PLS analysis revealed that group allocation and performance scores on both conditions of the episodic task were the strongest contributors to the first PLS latent variable, further validating the notion of episodic deficits in TLE. We identified additional contributions from the volume of the hippocampus, supporting a potential link between the integrity of the hippocampi and relational cognition in general, and episodic memory specifically. Age was another important contributor to overall relational memory capacities. The decline in hippocampal contributions to relational memory performance in TLE is likely related to many factors, including regional and whole-brain structural alterations [8,9,17,55,64,69], disruptions in connectivity patterns [8,32,55], and macroscale functional reorganization [49,68,94]. Overall, our PLS findings confirmed a relationship between clinical presentation and general mnemonic ability, where younger age, lower hippocampal volume, and TLE diagnosis were associated with poor behavioral performance, especially on the episodic module. We were also interested in whether socio-demographic factors such as age and sex and more general impairments in cognitive and executive function, attention, and processing speed might have contributed to the observed between-group differences in episodic memory [40,93]. Thus, we ran additional control analyses that accounted for these covariates. In addition to controlling for age and sex, we also administered supplemental behavioral screening tools to ensure that group disparities were not driven solely by neurobehavioral differences in other domains. Specifically, we used the

EpiTrack and MoCA [46,50,60], which are designed to track deficits in executive function and attention as well as mild cognitive impairment and dementia, respectively. Group differences in episodic memory persisted even after controlling for these covariates, suggesting that TLE-associated impairments in this domain are not uniquely mediated by socio-demographic variables or non-relational cognitive processes.

In addition to episodic memory deficiency, we identified impaired spatial cognition in our TLE group. Simulation models of spatial processing in conjunction with findings in healthy controls and individuals with focal hippocampal damage, including TLE patients, point to a fundamental role of the hippocampus in allocentric spatial memory, which involves the three-dimensional relations between objects in an environment independent of the subjective viewpoint [10,16,23,34], with the volume of the hippocampus further associated with proficiency in this allocentric domain [1,35,52]. We had previously shown that in a group of healthy individuals, performance on the Difficult condition of the spatial task (Spa-D) correlated with proficiency on the Four Mountains Task [84], an established protocol for examining allocentric spatial memory in clinical populations that present with localized hippocampal pathology and mild cognitive impairment [19,34]. Therefore, we were expecting to see indications of spatial deficits in our TLE cohort. Indeed, our ANOVA findings showed that, compared to healthy controls, TLE patients clearly underperformed on the spatial module. Specifically, results seemed to have been driven primarily by Spa-D accuracies, given how strongly they contributed to the first PLS latent variable, in addition to the absence of cross-cohort differences in Spa-E when accounting for EpiTrack and MoCA scores. These observations indicate that the Difficult condition of the spatial task is well adapted for identifying behavioral impairments in spatial cognition. Moreover, they build upon findings in kindling models of epilepsy, where interictal epileptiform discharges are mimicked via successive electrically induced seizures, whereby disruptions of physiological sharp-wave ripples in the hippocampus have been shown to compromise spatial memory consolidation [24,28,30]. Our results are also in agreement with previous observations made in pre- and post-surgical TLE patients, where low IQ, age of onset, and epilepsy duration were associated with poor navigational skills on the Hidden Goal Task, a human analogue of the rodent Morris Water Maze [3]. Additional evidence for spatial impairment in individuals with TLE has been reported using virtual reality paradigms, such as the Boxes Room, where patients committed more errors and travelled longer distances to a goal location than did controls [18,31,70]. While TLE-related spatial deficits are not as well documented as episodic memory impairments, the findings we have presented here expand on these prior observations and provide support for the notion that atypical behavioral phenotypes in spatial memory may present an intermediary feature between those associated with episodic and semantic memory.

Group differences were less well defined on the semantic module, as HC scored higher than TLE patients in the Difficult condition only, and even then, group differences vanished when controlling for socio-demographic or other cognitive covariates. Unlike the episodic and spatial tasks, which encompass built-in phases for stimulus encoding and retrieval, the semantic protocol consists of retrieval only. Presumably, the underlying conceptual associations between objects required to complete this module successfully were incidentally and repeatedly encoded throughout the participant's lifetime, implicating long-term memory consolidation, which benefits not only from hippocampal but also non-hippocampal neocortical contributions [45], with further evidence suggesting that the neocortex can rapidly form conceptual associations independent of the hippocampus [77]. Indeed, where TLE patients have been shown to present with semantic deficits, faulty encoding of novel conceptual relations has been suggested as a potential cause [38]. This consideration is in line with the complementary learning systems framework, which posits a division of labour underlying memory and learning, whereby the hippocampus rapidly encodes non-overlapping episodic representations that are gradually consolidated into a latent semantic structure across the neocortex through interleaved reinstatement of episodic engrams [54,62]. Likewise, the multiple trace theory stipulates a resilience of the semantic memory system to lesions of the hippocampus, a structure, which, in contrast to its recurrent involvement in binding disparate neocortical patterns that code for either episodic or spatial information, is surmised to be only transiently active in the context of semantic cognition [59]. In addition, we also note that semantic impairments in people with TLE are typically measured using visual confrontation naming tasks like the Boston Naming Test, which, while suitable for identifying dysnomia, do not necessarily tap into semantic association processes *per se* [5,29]. In fact, TLE patients seem to be relatively intact on semantic assessment protocols similar to our own where conceptual judgment is required [29,47], such as the Intelligenz-Struktur-Test, where an outlier must be selected out of five lexical alternatives (*i.e.*, sitting, lying, *going*, kneeling, standing) [37]. While research is ongoing to elucidate the network dynamics involved in verbal deficiencies associated with TLE [87], behavioral divergence across verbal and non-verbal domains may offer an avenue for mapping out phenotypic differences between TLE and other similar neurological conditions, such as semantic dementia, in which patients appear to be impaired on both domains [13]. Even though the semantic module of the iREP is a valid test of general conceptual knowledge [81,84,92], the absence of a significant between-group difference on Sem-E in the current work does not necessarily entail that TLE patients might be unaffected on more sensitive measures of semantic cognition, as it has been shown that impairments may emerge if tasks are sufficiently difficult [48], which is also supported by our findings on Sem-D. Based on these considerations, we can conclude that TLE-related impairments in memory of general associations between everyday items only become observable when these associations are sufficiently weak, with socio-demographic variables such as age and sex as well as impairments in other more general cognitive areas further compacting semantic deficits.

Collectively, our results demonstrate atypical behavioral patterns of relational memory in TLE patients. They point to impairments in episodic and spatial memory that are associated with variations in age and hippocampal volume, with memory for general semantic associations remaining relatively intact. These findings imply a hierarchical pattern of relational memory dysfunction related to medial temporal lobe pathology, with the episodic domain being more affected than the spatial domain, and the semantic system being the least affected. We acknowledge a range of limitations of the current work, however. First, given stringent diagnostic criteria for inclusion in our TLE cohort, we studied only a relatively modest sample of 24 pharmacoresistant patients. Seizure onset, seizure laterality, duration of epilepsy, hemispheric dominance, and anti-seizure drugs are likely contributors to behavioral outcomes, yet we omitted an in-depth analysis of these variables from our current study because of sample size constraints. With ongoing expansion of our patient cohort, we hope to account for these factors in future works. We further acknowledge that accounting for the effects of the MoCA and EpiTrack may not have controlled for all salient cognitive properties that could have contributed to between-group differences in behavioral phenotypes above and beyond relational memory effects. Given that our testing session was relatively long, compromises had to be made with respect to the number of supplementary assessments. Notwithstanding these limitations, control analyses that also included the MoCA and EpiTrack helped to mitigate concerns that relational memory deficits mainly resulted from alterations in executive function and mild cognitive impairment. Furthermore, our task was administered in a controlled laboratory experiment (in our case in the MRI scanner). This might have, at least in part, contributed to reduced behavioral performance, a finding to be verified using ecologically more valid tasks in future work. Even so, our initial observations already provide novel and detailed insights into differential impairments across relational memory domains accompanying hippocampal damage in TLE patients, warranting complementary investigations into underlying neural substrates. Notably, task paradigm and analysis scripts are openly

available, with the hope of facilitating adoption of our assessment as well as independent replication of our findings. Finally, with ongoing work that addresses pre- and post-op associations in behavior, structure, and function, we aim to expand the clinical relevance of the iREP in TLE patients by devising standardized presurgical evaluation protocols. In an ongoing study, for instance, we are aiming to expand findings in the present work by examining the relationships between whole-brain resting-state functional connectomes derived for each iREP module and homologous behavioral scores. By mapping out between-group differences in dynamic neural properties in tandem with corresponding task performance phenotypes, we can explore both local and network-level functional substrates that underlie the various relational memory domains, potential informing surgical outcome measures.

Author contributions

ST: study and task design, data acquisition, image processing, statistical analysis, manuscript writing; VK: analysis, editing of manuscript; JR/QL/HA: data acquisition, manuscript editing; JDeK: image processing; EJ: task design, manuscript editing; NB/AB: manuscript editing; CH: task design, manuscript editing; JA/RNS: analysis, manuscript editing; LC: study and design; BF: patient identification, manuscript editing; JS: task and study design; BC: study supervision, funding.

CRediT authorship contribution statement

Shahin Tavakol: Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Valeria Kebets:** Investigation, Writing – review & editing. **Jessica Royer:** Data curation, Investigation, Writing – review & editing. **Qiongling Li:** Writing – review & editing. **Hans Auer:** Data curation. **Jordan DeKraker:** Investigation, Writing – review & editing. **Elizabeth Jefferies:** Conceptualization, Writing – review & editing. **Neda Bernasconi:** Writing – review & editing. **Andrea Bernasconi:** Conceptualization, Writing – review & editing. **Christoph Helmstaedter:** Resources, Writing – review & editing. **Thaera Arafat:** Data curation, Writing – review & editing. **Jorge Armony:** Writing – review & editing. **R. Nathan Spreng:** Writing – review & editing. **Lorenzo Caciagli:** Conceptualization, Writing – review & editing. **Birgit Frauscher:** Data curation, Writing – review & editing. **Jonathan Smallwood:** Conceptualization, Writing – review & editing. **Boris Bernhardt:** Conceptualization, Data curation, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2024.109722.

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