COGNITIVE AND PSYCHIATRIC COMORBIDITIES IN EPILEPSY: INSIGHTS FROM NEUROIMAGING RESEARCH

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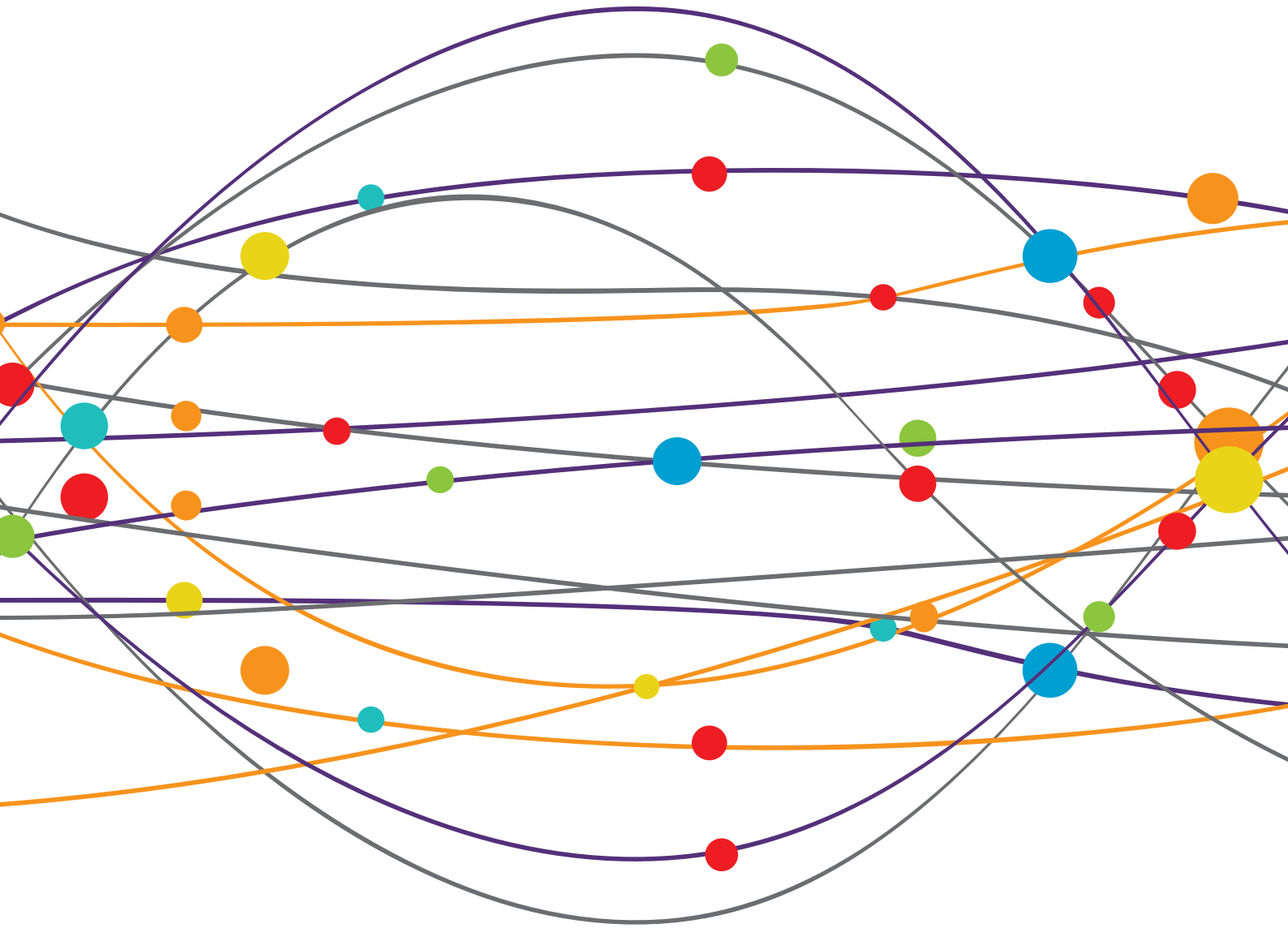

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COGNITIVE AND PSYCHIATRIC COMORBIDITIES IN EPILEPSY: INSIGHTS FROM NEUROIMAGING RESEARCH

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Parcellation of the Hippocampus Using Resting Functional Connectivity in Temporal Lobe Epilepsy

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We have previously shown that the connectivity of the hippocampus to other regions of the default mode network (DMN) is a strong indicator of memory ability in people with temporal lobe epilepsy (TLE). Recent work in the cognitive neuroscience literature has suggested that the anterior and posterior aspects of the hippocampus have distinct connections to the rest of the DMN and may support different memory operations. Further, structural analysis of epileptogenic hippocampi has found greater atrophy, characterized by mesial temporal sclerosis, in the anterior region of the hippocampus. Here, we used resting state FMRI data to parcellate the hippocampus according to its functional connectivity to the rest of the brain in people with left lateralized TLE (LTLE) and right lateralized TLE (RTLE), and in a group of neurologically healthy controls. We found similar anterior and posterior compartments in all groups. However, there was weaker connectivity of the epileptogenic hippocampus to multiple regions of the DMN. Both TLE groups showed reduced connectivity of the posterior hippocampus to key hubs of the DMN, the posterior cingulate cortex (PCC) and the medial pre-frontal cortex (mPFC). In the LTLE group, the anterior hippocampus also showed reduced connectivity to the DMN, and this effect was influenced by the presence of mesial temporal sclerosis. When we explored brain-behavior relationships, we found that reduced connectivity of the left anterior hippocampus to the DMN hubs related to poorer verbal memory ability in people with LTLE, and reduced connectivity of the right posterior hippocampus to the PCC related to poorer visual memory ability in those with RTLE. These findings may inform models regarding functional distinctions of the hippocampal anteroposterior axis.

Keywords: hippocampus, epilepsy, resting state, memory, long axis, default mode network

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INTRODUCTION

Resting state functional connectivity has emerged as a potentially valuable tool for interrogating system integrity and predicting treatment outcome in neurological and psychiatric disease populations (1, 2). Evidence from our group and others has demonstrated that resting connectivity among default mode network (DMN) nodes is altered in temporal lobe epilepsy (TLE) (3–5), is useful for characterizing memory network integrity (4, 5), and is useful for predicting

pre- to post-operative memory change (6) following surgery for TLE. TLE surgery typically involves unilateral resection of the hippocampus, amygdala, and a varying extent of anterior temporal neocortex. Specifically, the epileptogenic hippocampus, considered the site of seizure generation, is consistently reported to have reduced connectivity with major hubs of the DMN, such as the posterior cingulate cortex (PCC) and medial pre-frontal cortex (mPFC) (3, 4, 7)

Recent work in the cognitive neuroscience literature has highlighted a distinction between the anterior and posterior hippocampus in terms of their roles in cognition (8–10) and in terms of network connectivity (11–13). The anterior hippocampus has preferential connectivity to the temporal pole, perirhinal cortex, and mPFC while the posterior hippocampus has biased connections to parahippocampus, fusiform gyrus, and PCC (11–13). The mPFC and PCC are known to be critical hubs for the DMN (14) and, given the biased connectivity along the long axis of the hippocampus, critical network properties may be missed if the hippocampus is treated as a homogenous region of interest. This long-axis distinction is of further importance because structural atrophy in the hippocampus is thought to be biased in people with TLE, with greater atrophy occurring in the head of the hippocampus compared to the body and tail measured on MRI (15), measured post-mortem (16), and on resected tissues (17). Thus, investigating hippocampal connectivity using this anterior and posterior hippocampal distinction has the potential to further elucidate network changes in TLE and how these hippocampal parcels might relate to memory impairments.

This anterior-posterior parcellation has been applied in a prior study of functional connectivity in individuals with TLE. Voets et al. (5) examined the strength of the timeseries correlation between each voxel in the hippocampus to target masks constructed from regions known to be connected to the anterior and posterior hippocampus in the healthy brain. If a voxel showed stronger correlation to the "anterior memory mask" (composed of entorhinal cortex, orbitofrontal cortex, and temporal pole) compared to the "posterior memory mask" (composed of parahippocampal gyrus, lingual/fusiform gyrus, dorsolateral pre-frontal cortex, posterior cingulate cortex, precuneus, and thalamus) then it was assigned to the anterior hippocampus. Conversely, a voxel that showed stronger correlation to the posterior mask was labeled as the posterior hippocampus. Using this technique, they demonstrated that patients and healthy controls showed a similar anterior and posterior division that was split along the long axis of the hippocampus. Further, combining individuals with left lateralized TLE (LTLE) and those with right lateralized TLE (RTLE), revealed that deviations in resting connectivity strength were associated with material-specific memory impairments; i.e., verbal memory impairment in left TLE and visuospatial memory impairment in right TLE. Impaired, relative to intact, memory was associated with both increased connectivity strength between the ipsilateral anterior hippocampus and entorhinal cortex and decreased connectivity strength between the contralateral posterior hippocampus and posterior cingulate cortex.

While these are very important findings linking disrupted connectivity and memory deficits in TLE, there are several assumptions underlying these analyses that may be challenged. First, they used anatomical masks to define their anterior and posterior memory network. Patterns of inter-regional correlation, however, are not strictly circumscribed to the gyral anatomy of most atlases and, in fact, broad networks often cross over and between anatomical boundaries (18). Second, their method for labeling voxels in the hippocampus as either anterior or posterior was somewhat crude. They labeled a voxel as an anterior voxel if it demonstrated greater correlation to the mean time series of the whole anterior memory network mask compared to the posterior memory network mask. This assumes a certain level of homogeneity of correlation of these anterior and posterior memory networks, ignoring connectivity patterns in favor of magnitudes averaged across large networks, which may not be valid especially for networks defined with anatomical boundaries. We submit that identifying abnormalities in connectivity via a data-driven approach with fewer assumptions provides a reliable, complementary solution. An elegant approach drawn from the literature involves parcellation of hippocampus based on a *k*-means clustering of the voxel connectivity patterns to the whole brain as has been done in the thalamus (19), cingulate cortex (20), and hippocampus (11).

Thus, the aim of this study was to use resting state functional connectivity and *k*-means clustering to parcellate the hippocampus of healthy controls and patients with TLE. We further sought to investigate whether the connectivity strength of resulting parcels was related to memory ability. The posterior cingulate cortex (PCC) and the anterior medial pre-frontal cortex (mPFC) are the two core hubs of the DMN (14, 21). Based on our own findings of differential connectivity of anterior and posterior hippocampus to these hubs in the healthy brain (11), together with the patterns indicated in the study by Voets et al. (5), we examined the correlation in resting state BOLD activity between anterior hippocampus and mPFC, and between the posterior hippocampus and PCC. We interrogated whether these correlation patterns would relate to memory ability, highlighting the role of differential anterior and posterior hippocampal connectivity as potential indicators of memory network integrity. Consistent with previous literature on hippocampal functional specialization (9), we hypothesized that the *k*-means clustering would produce anterior and posterior hippocampal clusters. Given that atrophy and gliosis in MTS is biased toward the anterior hippocampus, we also expected that there might be greater alterations in connectivity in anterior hippocampal clusters in people with MTS. Finally, we predicted that individuals exhibiting weaker correlation between the anterior and posterior hippocampal parcels and the respective primary hubs of the DMN (i.e., mPFC and PCC), would have worse material-specific memory deficits.

METHODS

Participants

Forty-six adult patients with pharmacologically intractable unilateral TLE were recruited from the Epilepsy Clinic at Toronto

Western Hospital. Twenty-three patients presented with RTLE and 23 presented with LTLE. Continuous recording of scalp EEG and video monitoring during an inpatient evaluation in our epilepsy monitoring unit were used to determine seizure focus. Nineteen neurologically healthy control subjects were recruited to serve as comparison for our patient sample for to identify alterations in resting-state fMRI networks. All controls gave prospective written informed consent. Prospective written informed consent was obtained from a subset of the patient group, while permission for retrospective analysis of clinical data (both neuropsychological and resting-state fMRI) was obtained from the University Health Network Ethics Board for a group of participants who were scanned prior to the current ethics protocol implementation.

Neuropsychological Testing

A comprehensive neuropsychological battery was administered to patients that included assessment of intelligence, learning/memory, processing speed, and verbal and visuospatial functioning. The battery included the following measures: Wechsler Abbreviated Scale of Intelligence, Warrington recognition memory test for faces, Rey visual design learning test, conditional associative learning test, Warrington recognition memory test for words, and Rey auditory verbal learning test. For each patient, we transformed eight raw scores from these tests into summary factor scores using previously estimated factor loadings from a principle component analysis (PCA) performed by St-Laurent et al. (22). In brief, St-Laurent et al. (22) performed a PCA on neuropsychological scores from a group of individuals with TLE, similar to the current cohort. The PCA revealed three significant components which the authors characterized as reflecting IQ, visuospatial memory, and verbal memory based on the loading of the individual neuropsychological tests to each factor. These factor scores were able to (1) discriminate between patients with right and left TLE and (2) reliably predicted the degree of material-specific memory change following anterior temporal lobe resection (22). Thus, by transforming the raw scores from the neuropsychological assessment of patients in the current study into these summary factor scores we are able to assess a more reliable representation of core abilities than single test scores. The IQ factor reflected loadings from verbal IQ and performance IQ from the Wechsler Abbreviated Scale of Intelligence (23).

The visuospatial memory (VSM) factor was primarily based on loadings from correct responses on the Warrington recognition memory test for faces (RMF), total recall across trials one through five on the Rey visual design learning test (RVDL), and number of trials to criterion for the conditional associative learning test (CAL). The RMF test involves a study period in which 50 faces are viewed, followed by a recognition test in which subjects are asked to make a forced choice recognition decision between previously studied faces and lures (24). The RVDL consists of a study session for 15 abstract visual line designs followed by an immediate recall session in which subjects are asked to draw the previously encountered visual designs (25). This is repeated five times. Finally, the CAL consists of having patients learn a one-to-one association between four cards and four spatial locations through trial-and-error (26).

The verbal memory (VM) factor was based on loadings from correct responses on the Warrington recognition memory test for words (RMW), total recall (RAVLT-tot) over five study-test trials from the Rey auditory verbal learning test (RAVLT) and percent retention (RAVLT-ret) from the RAVLT. The RMW test consists of a study session for 50 words followed by a delayed forced choice recognition test between lures and studied words (24). The RAVLT consists of a study session for 15 words followed by an immediate free recall period. This is repeated five times. Percent retention for the RAVLT is calculated by observing the percentage of words retained from the fifth session on a 20-min delayed recall trial (27).

Statistical Analysis of Behavior and Demographics

To compare clinical, demographic, and behavioral measures, we used SPSS 21 (Chicago, IL). One-way ANOVA's were used to investigate group differences in age and education. Chi-squared tests were used to investigate group differences in sex distribution, and, between the TLE groups, presence of MTS and presence of other lesions. Fisher's exact tests were used to examine group differences in handedness and, between the TLE groups, laterality of language dominance. Student's t-test were used to investigate differences in age of onset, duration of epilepsy, verbal memory, visual memory or IQ between the TLE groups.

MRI Acquisition

A high-resolution 3D anatomical scan was collected on a 3T Signa MR system (GE Medical Systems, Milwaukee, WI, USA) for normalization to standard MNI space for each subject (T1-weighted sequence, FOV 220 mm, 146 slices, flip angle = 12°, 256 × 256 matrix, resulting in voxel size of 0.86 × 0.86 × 1.0). Resting state fMRI (T2*-weighted) scans were acquired with an echo-planar pulse imaging (EPI) sequence (FOV 240 mm, 28–32 slices depending on head size, TR = 2,000 ms, TE = 25 ms, 64 × 64 matrix, 3.75 × 3.75 × 5 mm voxels, for 180 volumes). During resting state scans, subjects were instructed to lie still, and "not to think about anything in particular," with their eyes closed.

Functional MRI Pre-processing

Preprocessing was performed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8), a toolbox running in MATLAB 7.9 (Mathworks). Anatomical and functional images were reoriented so that the origin falls on the anterior commissure. The functional images were then co-registered to the anatomical image before undergoing realignment and unwarping for motion correction. Anatomical images for each subject were segmented into gray matter, white matter and cerebral spinal fluid (CSF) and normalized into standard MNI space. Functional images were then normalized to standard space using the parameters from the anatomical transformation. Smoothing varied for the k-means clustering analysis and the group comparisons analysis. For the k-means clustering analysis, two separate threads of processing then occurred with one thread undergoing spatial smoothing with a 4-mm full-width half-max (FWHM) Gaussian

kernel and the other having no spatial smoothing performed. The reason for these separate smoothing parameter threads will be described below. For group comparisons, we smoothed the data with an 8-mm FWHM Gaussian kernel. Next, using the Artifact detection toolbox (28), fluctuations in global signal >3 standard deviations, translational motion >1 mm, and rotational motion >0.05 radians were identified and regressors were created to exclude these potentially confounding sources of variance. Finally, in the Conn toolbox (28), temporal filtering was performed to exclude low (<0.008 Hz) and high (>0.09 Hz) frequency fluctuations, and a CompCor (29) was used to exclude measures of physiological noise by regressing out the top five components of a principle components analysis from the white matter and CSF masks produced from the SPM8 segmentation. The filtered and corrected images were used for subsequent analyses.

k-Means Clustering

To identify functionally distinct sub-regions of the hippocampus, we performed a functional connectivity-based parcellation using a *k*-means clustering algorithm. First, left and right whole-hippocampus masks were defined using the Harvard-Oxford subcortical structural probabilistic atlas in FSL. For each of the left and right hippocampus region of interest (ROI), we probed the functional organization of the ROI by testing the correlation between the time series of each voxel within an ROI and the time series of every other gray matter voxel in the brain. We therefore used the individual subject segmented normalized gray matter images to isolate the voxels for which the time series correlation to the hippocampal ROIs would be computed. Critically, while the whole-brain gray matter mask was minimally smoothed with a 4-mm FWHM Gaussian kernel (see above), the hippocampal voxel time series were not smoothed, to ensure that spatial adjacency in the clustering results was minimally attributable to spatial correlation between neighboring hippocampal voxels.

For each subject, we computed the Pearson's correlation coefficient between the time series of a given voxel within a hippocampal ROI and every other voxel in our whole-brain gray matter mask. This resulted in a whole-brain gray matter statistical map of correlation coefficients for each hippocampal voxel (i.e., that voxel's "functional connectivity profile"). A second-order correlation matrix of each hippocampal voxel's similarity in functional connectivity profiles was computed for each subject. We then averaged the second-order, within-ROI correlation matrices across participants after sorting the voxel sequences along the matrix dimensions identically and performed *k*-means clustering on the group level second-order correlation matrix with a $k = 2$ parcellation. The squared Euclidean metric was used to define distance between clusters, and cluster centroid values were estimated using the *k*-means ++ algorithm implemented in MATLAB. This procedure places random initial seeds for the analysis, and converges quickly to minimize within-cluster, point-to-centroid distance iteratively. We specified a max of 100 iterations for convergence, and 25 replications with random initial seeds were conducted to reduce the probability of convergence onto local minima. The correlation matrix of functional connectivity profiles within each ROI was sorted according to the cluster labels derived from the *k*-means cluster analysis. These steps are illustrated in **Figure S1**. The results also produced a cluster label for each voxel in the hippocampal ROI which were then projected back to standard brain space at the group level to create anterior and posterior hippocampal masks. The resulting clusters were visually examined (by author AB), and voxels which were located on the periphery of the hippocampus and isolated from other voxels in the cluster assignment were identified and removed, as these voxels were likely misclassified. This resulted in 2/522 voxels being excluded in the Left Hippocampus of Controls, 8/522 voxels being excluded in Left Hippocampus of the RTLE group, and 27/533 voxels being excluded in the Right Hippocampus of the RTLE group.

Region of Interest Analysis

To interrogate the functional connectivity differences between the TLE and healthy control groups, we used the resulting masks from the *k*-means clustering analysis as regions of interest for the subsequent analyses. The mean time course from each ROI was correlated with the smoothed data from every other voxel in the brain. These correlations were then transformed using a Fisher's z transformation. The resulting individual subject maps were entered into a group level between-subject analysis, to examine differences in voxel-wise whole brain connectivity of the anterior and posterior hippocampus from the left and right hemisphere. Analyses were performed separately for the LTLE group and RTLE group. We contrasted the whole brain connectivity maps from each *k*-means cluster between the control group and the TLE groups. Resulting contrast maps were corrected using permutation analysis with 5,000 permutations at $p < 0.005$ cluster defining threshold, and false discovery rate corrected at $p < 0.05$. Given that previous research had shown an increase in left anterior hippocampal connectivity to the entorhinal cortex (5), and posterior hippocampal connectivity to the parahippocampal gyrus, we also explored these connections using a small volume correction with the entorhinal cortex mask from the Juelich histological atlas and the Harvard-Oxford parahippocampal gyrus mask, thresholded at 35% [the same mask used by Voets et al. (5)]. Years of education was entered for each subject and investigated as a covariate of no interest as this differed by group (see below). Following this, we sought to see if the presence of MTS was driving the connectivity differences between TLE and control groups. To that end, we extracted the peak connectivity from the resulting significant voxel clusters that differed between the TLE groups compared to the controls and performed a randomization test between the MTS subgroup and no-MTS subgroups with 5,000 permutations using the mult_comp_perm_t2 function in MATLAB (Groppe, 2015, Toronto).

To examine the relationship between the altered hippocampal connectivity and memory performance, we used the PCC and mPFC seeds reported by Andrews-Hanna et al. (14). The left PCC seed is located at $x = -8$, $y = -56$, $z = 26$, while the right PCC seed is located at $x = 8$, $y = -56$, $z = 26$, with both having an 8-mm sphere drawn around the center points. The left mPFC seed is located at $x = -6$, $y = 52$, $z = -2$, and the

right is located at x = 6, y = 52, z = −2 with 8-mm spheres drawn around the center points. The mean time course of each hippocampal cluster was extracted and correlated with the mean time course of the corresponding PCC or mPFC seed. These correlation coefficients were then Fisher z-transformed and the resulting z-scores were correlated with memory scores using the verbal and visual memory factor scores using SPSS 21 (Chicago, IL). We were specifically interested in how connectivity of the epileptogenic hippocampus related to material-specific memory (verbal memory in LTLE and visual memory in RTLE). Left language dominance is thought to be less consistent in TLE and also appears to play a role in verbal memory (30–32). Therefore, we examined the brain-behavior correlations in individuals with left language dominance. Results for the full analysis are available in **Supplementary Table 1**.

RESULTS

Demographic Data

There were no differences between the three groups in terms of age, $F_{(2, 62)} = 0.51$, $p = 0.6$ or handedness, Fisher's exact test, $p > 0.5$. There was a significant difference between the three groups in terms of education, $F_{(2, 62)} = 9.7, p < 0.01$, with healthy controls having greater education than both the LTLE and RTLE group using a Bonferroni *post-hoc* test. There was a different proportion of male and females between the three groups, $\chi^2(2, N = 65) = 10.2$, $p = 0.006$. Specifically, there was a difference between the LTLE and RTLE group in terms of sex distribution, $\chi^2(1, N = 46) = 8.7, p = 0.003$. There were no differences in age of onset, duration of epilepsy, verbal memory, visual memory or IQ, between the LTLE and RTLE groups, all $t < 1.5$, $p > 0.15$, nor were there any differences between patient groups in presence or absence of MTS, distribution $\chi^2(1, N = 46) = 0.37$, $p = 0.5$, in the presence of other lesions, $\chi^2(1, N = 46) = 1.1$, $p = 0.3$, or in language dominance using Fisher's exact probability test, $p = 0.1$. Demographic information and neuropsychological performance are reported in **Table 1.**

TABLE 1 | Patient demographic data.

	Controls	RTLE	LTLE
N	19	23	23
Age, y (SD)	34 (22–59)	36.9 (18–58)	37.6 (24–53)
Education, y (SD)	18 (13–26)	14.2 (8–22)	14.2 (11–18)
Sex, M/F	11/8	17/6	7/16
Handedness, R/L/BI	17/2/0	22/1/0	20/2/1
Language dominance, R/L/BI	–	0/23/0	1/20/2
Disease duration, y (SD)	–	15.6 (1–48)	18.4 (3–46)
Onset of seizures, y (SD)	–	21.0 (0–51)	19.2 (0.67–50)
Presence of MTS, Yes/No	–	15/8	13/10
Other lesions	–	3	1
Verbal memory factor	–	0.23(1.2)	0.19 (1.1)
Visual memory factor	–	−0.20 (1.1)	0.20 (0.77)
IQ Factor	–	−0.14 (1.2)	0.36 (1.0)

RTLE, right temporal lobe epilepsy; LTLE, left temporal lobe epilepsy; y, years; SD, standard deviation; M, male; F, female; R, right; L, left; BI, bilateral; IQ, intelligence quotient. Characterization of MTS and other lesions was based on radiology (3T MRI protocol). In the RTLE group, one individual had a right amygdala ganglioglioma, one individual had a right amygdala dysembryoplastic neuroepithelial tumor, and one had a right amygdala harmartoma. In the LTLE group, one individual had a left amygdala dysembryoplastic neuroepithelial tumor.

k-Means Clustering

The *k*-means clustering procedure produced visually similar clusters for all three groups in both hemispheres, with anterior and posterior clusters divided along the long axis of the hippocampus. These clusters are displayed in **Figure 1**. A few voxels along the borders of the hippocampus seemed to misclassify. This was likely due to noisy voxels that may represent white matter or cerebral spinal fluid that were encapsulated by the Harvard-Oxford hippocampal mask. Prior to group level connectivity analysis, these voxels were deleted from the clusters.

To examine the preferential functional connectivity of each of these clusters in the groups, we contrasted the voxel-wise correlations of the left and right anterior hippocampi with the left and right posterior hippocampi (**Figure 1**). Consistent with previous work and our predictions, all groups showed stronger positive correlations between the anterior hippocampus and the temporal pole, amygdala, and ventral pre-frontal cortices, including the mPFC while the posterior hippocampal parcels showed stronger positive correlations with the parahippocampal gyrus and thalamus. The LTLE and healthy control groups also showed stronger positive correlations between the posterior hippocampal parcels and the posterior medial regions, such as the PCC, but this was not the case for the RTLE group.

Group Connectivity Differences

When seeding from the left anterior hippocampal cluster, the LTLE group showed reduced connectivity to the parahippocampal cortex bilaterally, reduced connectivity to midline parietal and pre-frontal cortex, bilaterally, and reduced connectivity to the left angular gyrus compared to the healthy control group. There were no areas of increased connectivity with the left anterior hippocampus in LTLE compared to controls when examining the whole brain. Targeted analysis found increased connectivity between the left anterior hippocampus and the left entorhinal cortex, centered around xyz = −24, −14, −32, $t_{(41)} = 3.9, p < 0.001$.

A similar pattern of reduction was seen for the left posterior hippocampal cluster, with reduced connectivity to midline parietal and pre-frontal cortex, bilaterally, and reduced connectivity to the right medial temporal cortex. There were no areas of increased connectivity for the posterior hippocampus even when using a small volume correction with the parahippocampal mask from the Harvard-Oxford atlas, as was used by Voets et al. (5). There were no connectivity differences between the LTLE group and healthy controls for either the anterior or posterior right hippocampal seeds. These results are displayed in **Figure 2** and peak coordinates for these analyses are presented in **Table 2**. We sought to determine whether the presence of MTS influenced connectivity differences, and thus extracted the peak connectivity values from each significant cluster. When we compared the connectivity between

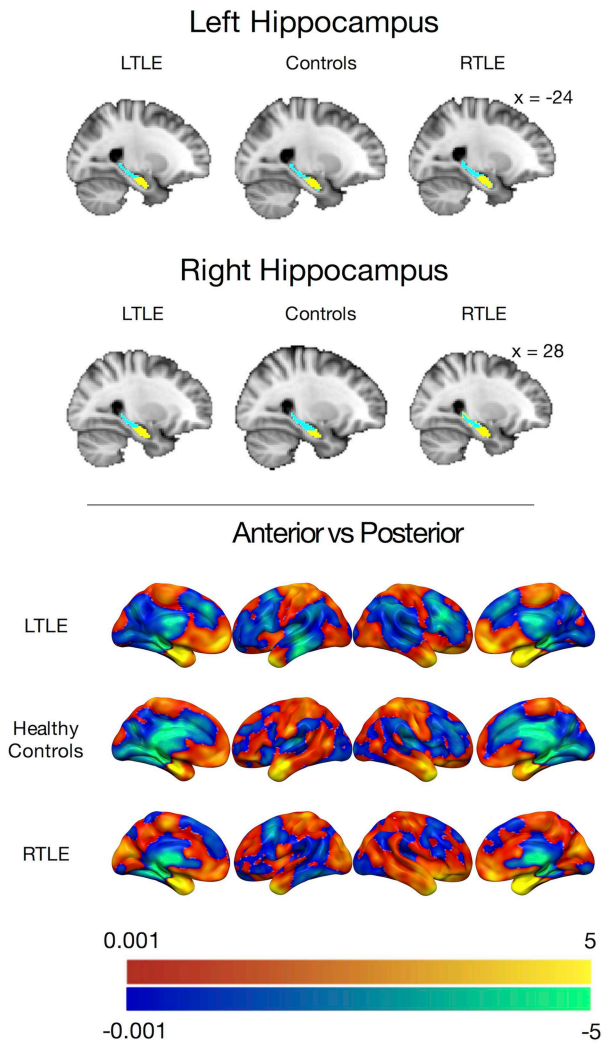

FIGURE 1 | (Top) Group level clusters from k-means clustering procedure, projected onto the standard MNI brain showing an anterior (yellow) and posterior (blue) cluster for both the left and right hippocampus derived from patients with left temporal lobe epilepsy, healthy controls, and patients with right temporal lobe epilepsy. **(Bottom)** Anterior hippocampal connectivity contrasted against posterior hippocampal connectivity in people with left temporal lobe epilepsy (LTLE), healthy controls, and people with right temporal lobe epilepsy (RTLE) presented without statistical thresholding. Warm colors indicate anterior > posterior hippocampal connectivity, while cool colors indicate posterior > anterior hippocampal connectivity. The color bars depict *t*-values.

those with MTS compared to those without MTS we found that the patients with MTS had lower connectivity to DMN regions (Right hippocampus: $p = 0.03$; Frontal pole: $p = 0.003$; Left angular gyrus: $p = 0.02$; Precuneus: $p = 0.009$), and higher connectivity to the left entorhinal cortex ($p = 0.03$), compared to the patients without MTS. In the left posterior seed, however, there were no significant connectivity differences between patients with and without MTS ($p > 0.17$).

There were no significant differences between the RTLE group and the healthy control group when seeding from the right anterior hippocampal region. As this was surprising, we have provided maps for this contrast using a relaxed cluster defining threshold of $p < 0.05$, corrected using FDR at $p < 0.05$ and 5,000 permutations in **Figure S2**, and examined effect sizes in **Supplementary Methods and Results**. When seeding from the right posterior hippocampus, there was reduced connectivity to bilateral medial temporal cortex, right temporal pole, bilateral midline parietal and pre-frontal cortex, right lateral orbitofrontal cortex, and right somatomotor cortex in the RLTE group compared to controls. There were no areas of increased connectivity for the right posterior hippocampus, even when using a small volume correction in the parahippocampal gyrus. There were no connectivity differences between the groups for either the contralateral (left) anterior or posterior hippocampal seeds. These results are displayed in **Figure 3** and peak coordinates for these analyses are presented in **Table 3**. Again, when examining the voxels of peak differences, there were no differences in connectivity for the posterior epileptogenic hippocampus for the patients with MTS compared to those without ($p > 0.05$).

Hippocampal Connectivity and Memory

Given the alterations in connectivity of the epileptogenic hippocampal clusters, we sought to examine how connectivity of these areas to DMN hubs related to verbal and visual memory in people with LTLE and people with RTLE, respectively. In the LTLE group, we observed a medium-sized positive relationship between the verbal memory factor score and functional connectivity of the left anterior hippocampus to PCC, $r_{(18)} = 0.45$, $p = 0.02$, similar to previous reports that examined the whole hippocampus [(6): $r = 0.72$]. A medium-sized positive relationship was also seen between the verbal memory factor score and functional connectivity of the left anterior hippocampus to mPFC, $r_{(18)} = 0.41$, $p = 0.04$. These relationships, however, do not survive corrected statistical thresholds ($p < 0.0125$). The left posterior hippocampus had numerically weaker, and non-significant relationships, as shown in **Figure 4**. While we made no predictions about brain-behavior correlations with visual memory in LTLE, or with regards to the contralateral hippocampal connectivity, we present the full correlation matrix for display purposes.

In the RTLE group, we observed a medium-sized positive relationship between the visual memory factor score and functional connectivity of the right posterior hippocampus to PCC, $r_{(21)} = 0.37$, $p = 0.04$, similar to previous reports that examined the whole hippocampus [(6): $r = 0.73$]. This relationship also does not survive corrected statistical thresholds ($p < 0.0125$). The other connections of interest showed minimal relationships to visual memory, all $r < 0.13$.

We also observed several other relationships, that we were not specifically anticipating, that had comparable strength. We observed a negative relationship between the visual memory factor and functional connectivity of the right anterior hippocampus to mPFC, $r_{(18)} = -0.48$, in the LTLE group. We also observed that connectivity of the PCC to the epileptogenic hippocampus, both anterior and posterior clusters, was related

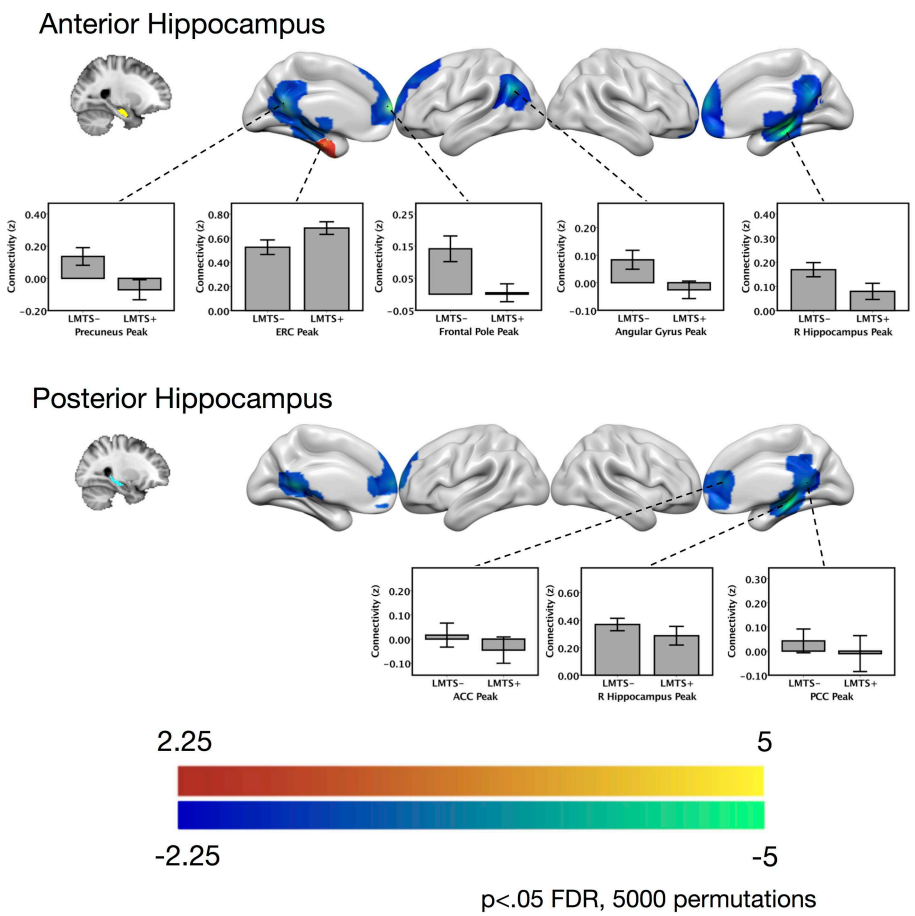

FIGURE 2 | Contrast maps of differences in connectivity between patients with left temporal lobe epilepsy compared to controls, seeding from either the anterior hippocampal seeds (top) or the posterior hippocampal seeds (bottom), thresholded at $p < 0.05$ FDR cluster correction, using 5,000 permutations. Areas of increased connectivity in LTLE, depicted in red, were only significant using a small volume correction in the entorhinal cortex. Areas of reduced connectivity in LTLE compared to controls are shown in cool colors. Bar plots depict mean group connectivity and standard error at voxels of peak difference between the LTLE group and controls, with the LTLE group separated into those with mesial temporal sclerosis (LMTS+), and those without (LMTS−). These peaks are presented below in **Table 2**. The color bars depict *t*-values. ACC, anterior cingulate cortex; ERC, entorhinal cortex; PCC, posterior cingulate cortex; R, right.

to verbal memory in the RTLE group (anterior: $r_{(21)} = 0.43$; posterior, $r_{(21)} = 0.39$).

DISCUSSION

Using a *k*-means clustering procedure, we were able to segment the left and right hippocampus into anterior and posterior divisions in individuals with left and right TLE and healthy controls. This demonstrates that the functional connectivity fingerprints of the hippocampal voxels are sufficiently distinguished along the long axis in the patient population, regardless of the effects of temporal lobe epilepsy. At the group level when these segments are compared directly, the anterior clusters showed greater connectivity to the temporal pole, amygdala and ventral pre-frontal cortices, while the posterior clusters showed increased connectivity to the parahippocampal gyrus and thalamus across all groups. Between group contrasts of functional connectivity showed significant reductions in connectivity between the epileptogenic hippocampus and DMN regions in both LTLE and RTLE groups compared to healthy controls, but in the RTLE group this was limited to the posterior hippocampus at the reported thresholds. In areas of the DMN regions showing reduced connectivity, the LTLE patients with MTS demonstrated notably aberrant connectivity relative to the patients without MTS, restricted to the anterior epileptogenic seed, which suggests that the presence of structural pathology exacerbates network alterations, partially supporting our hypothesis that MTS pathology would preferentially affect anterior hippocampal network changes.

Due to the growing consensus regarding the specialization of function in the long axis of the hippocampus (9), previous work has attempted to characterize functional connectivity differences

TABLE 2 | Cluster regions, peak coordinates, test statistic, and cluster size for connectivity differences between people with LTLE and healthy controls.

Region	Hemisphere	x	y	Z	T	Cluster size (voxels)
LEFT ANTERIOR HIPPOCAMPUS SEED						
Ant Hippocampus	R	24	−16	−16	−7.07	1,418
Angular gyrus	L	−50	−66	28	−4.38	1,462
Precuneus	B	−12	−52	16	−5.17	2,613
Frontal Pole	B	−10	62	14	−5.65	3,140
Entorhinal cortex	L	−24	−14	−32	3.9	207
LEFT POSTERIOR HIPPOCAMPUS SEED						
Post hippocampus	R	26	−28	−14	−5.62	2,680
Posterior cingulate	B	12	−46	12	−4.24	
Anterior cingulate	B	4	44	12	−4.25	1,580

Ant, anterior; B, bilateral; L, left; Post, posterior; R, right. Coordinates are presented in MNI space.

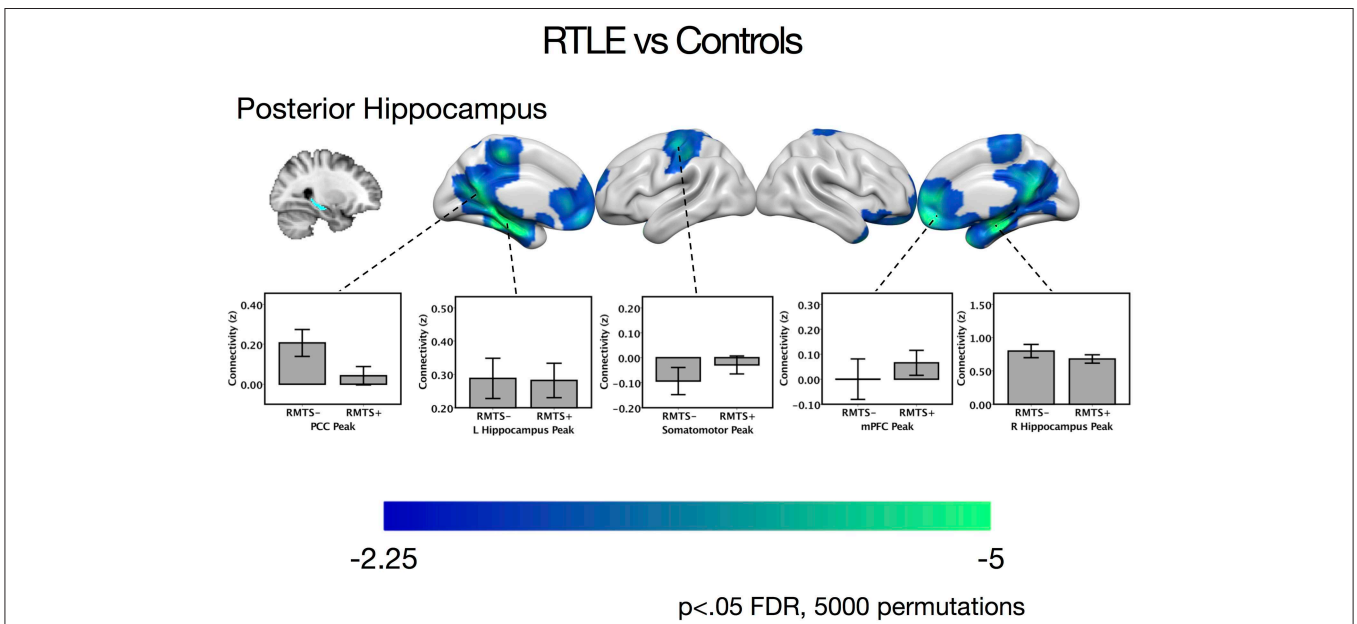

FIGURE 3 | Contrast maps of differences in connectivity between patients with right temporal lobe epilepsy compared to controls, seeding from the right posterior hippocampal seed, thresholded at $p < 0.05$ FDR cluster correction, using 5,000 permutations. Areas of reduced connectivity in RTLE compared to controls are shown in cool colors. Bar plots depict connectivity at areas of peak difference between the RTLE group and controls, with the RTLE group separated into those with mesial temporal sclerosis (RMTS+) and those without (RMTS−). These peaks are presented below in **Table 3**. The color bars depict t values. L, left; mPFC, medial pre-frontal cortex; PCC, posterior cingulate cortex; R, right.

between the anterior and posterior hippocampus (11, 12, 33, 34). Previous characterizations probed the functional connectivity using varying methods such as delineating the hippocampus by anatomical landmarks (33), placing seed spheres along the long axis of the hippocampus (12), examining connectivity slice by slice along the y-axis of the hippocampus (34), and by examining the connectivity of seed masks resulting from hippocampal parcellation using structural connectivity via DTI (11). This previous work has consistently shown that the anterior hippocampus tends to show greater functional connectivity to perirhinal, ventral-temporal, lateral temporal, and temporopolar cortex, while the posterior hippocampus tends to have greater functional connectivity to the parahippocampal gyrus, retrosplenial, and lateral parietal cortex. The resulting parcels from our parcellation results also showed these functional connectivity biases which provided reassurance that our subsequent analyses using these parcels was targeting meaningful networks supported by the literature.

Our parcellation findings are in agreement with previous work by Voets et al. (5) who similarly distinguished anterior and posterior clusters in the hippocampus using functional connectivity. Their methods involved giving a binary label to a voxel based on whether its magnitude of connectivity was arithmetically larger to either an anterior or a posterior memory network mask. This method required specification of regions *a priori*, ignored patterns of connectivity and

TABLE 3 | Cluster regions, peak coordinates, test statistic, and cluster size for connectivity differences between people with RTLE and healthy controls.

Region	Hemisphere	x	y	z	T	Cluster size (voxels)
RIGHT POSTERIOR HIPPOCAMPUS SEED						
Ant hippocampus	R	26	−18	−16	−10.03	18,726
Ant hippocampus	L	−24	−18	−22	−9.44	
Temporal Pole	R	34	12	−40	−6.04	
mPFC	B	2	52	−10	−5.32	
Posterior cingulate	B	−10	−50	4	−5.32	
Precentral	B	−6	−30	54	−5.28	
Precentral	L	−36	−18	56	−5	

Ant, anterior; B, bilateral; L, left; mPFC, medial prefrontal cortex; R, right. Coordinates are presented in MNI space.

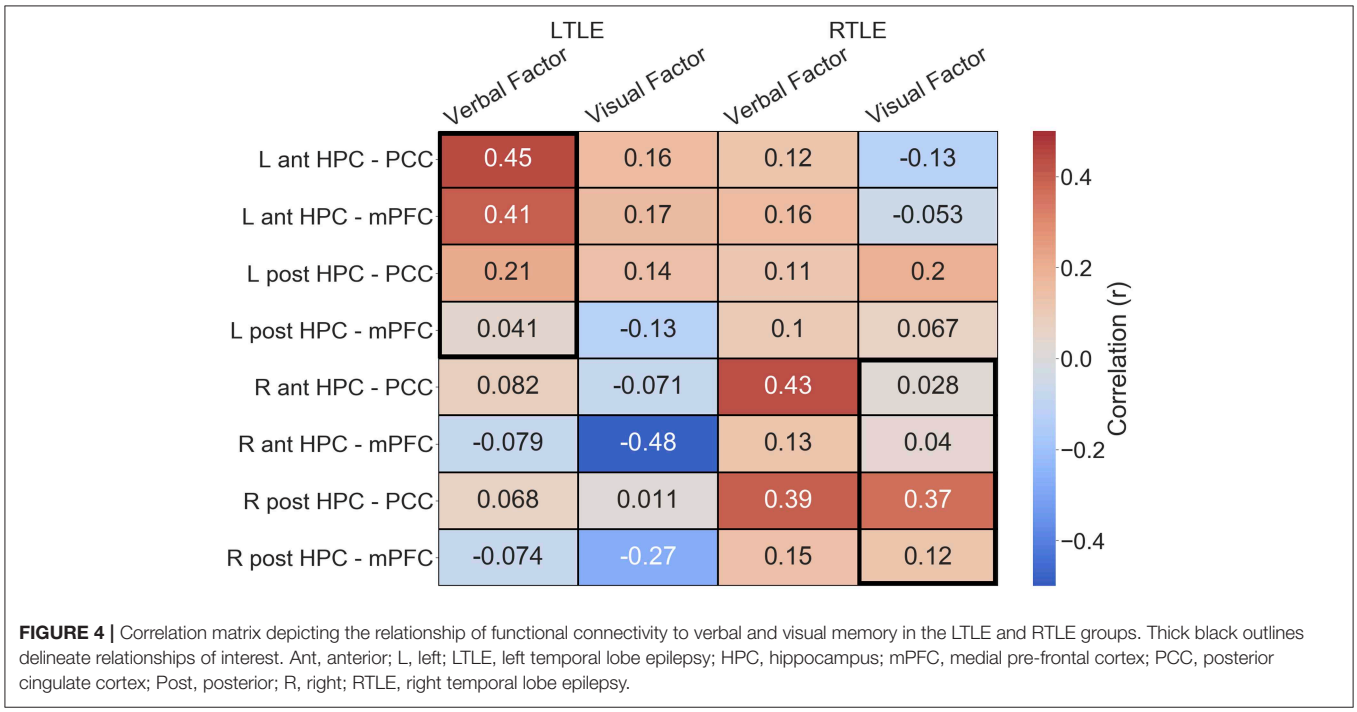

FIGURE 4 | Correlation matrix depicting the relationship of functional connectivity to verbal and visual memory in the LTLE and RTLE groups. Thick black outlines delineate relationships of interest. Ant, anterior; L, left; LTLE, left temporal lobe epilepsy; HPC, hippocampus; mPFC, medial pre-frontal cortex; PCC, posterior cingulate cortex; Post, posterior; R, right; RTLE, right temporal lobe epilepsy.

instead focussed merely on average connectivity magnitude. We refined the analytic approach here, nonetheless providing convergent evidence that the functional connectivity patterns of the hippocampal voxels form an anterior and posterior compartment regardless of the effects of longstanding epileptic seizures arising from the medial temporal lobe.

In our functional connectivity analysis, we found reduced connectivity between the epileptogenic hippocampus and DMN regions in TLE compared to healthy controls, similar to previous studies. More specifically, we observed that the epileptogenic posterior hippocampus had reduced connectivity to the PCC and mPFC, DMN hubs, in both TLE groups compared to healthy controls. Additionally, connectivity between hippocampus and other DMN nodes was also reduced, with significant findings for right posterior hippocampus to temporal pole in the right TLE group. In LTLE, the reductions overlapped considerably between the anterior and posterior left hippocampus, despite observations from previous research that these parcels have different preferred connectivity patterns (5, 11, 12). However, it is important to note that, while these anterior and posterior parcels will have connectivity preferences, both tend to connect with similar DMN regions in the healthy brain (11). The only other study comparable to ours, by Voets et al. (5) demonstrated a somewhat different pattern of connectivity alterations associated with TLE. While they also report a decrease in connectivity between posterior hippocampus and PCC, they further report significant increases in connectivity for both TLE groups (posterior hippocampus to parahippocampal gyrus) and for the left TLE group (anterior hippocampus to entorhinal cortex). While we did replicate their latter finding, using small volume correction, we did not observe the former increase or indeed any other increases in connectivity in TLE groups compared to controls. Some of these differences may be due to methodological factors such as whole-brain analysis vs. a priori regions of interest. There is sparse literature on resting-state connectivity from the hippocampus in TLE, but one other paper

(3) found similar decreases to our work together with increases in primarily subcortical areas none of which are associated with DMN. Clearly more work needs to be done to ascertain the nature of pathological changes in this network.

Altered network connectivity may be the result of interictal epileptic discharges observed in TLE which are known to disrupt the functioning of the DMN (35), leading to the deterioration seen in the cingulum bundle that connects the medial temporal lobe to the PCC and medial pre-frontal cortex (36). In patients who had left MTS, connectivity reductions of the left anterior hippocampus to the DMN were larger than in patients who did not have MTS, which supports research showing greater structural connectivity declines in MTS for regions that connect the DMN such as the cingulum and fornix (37–39). In the RTLE group, we found reductions in connectivity of the right posterior hippocampus to DMN regions, but contrary to expectation, there were no significant connectivity differences in the right anterior hippocampus between the RTLE group and healthy controls. When using a more liberal cluster defining threshold of $p < 0.05$ with FDR correction using 5,000 permutations, we did see reduced connectivity of the right anterior hippocampus restricted to diffuse DMN regions, and, thus, our null finding may relate to our power to detect this effect. When calculating statistical power to detect the estimated effect size for anterior hippocampus, we found that our sample was underpowered to detect an effect in the RTLE group (**Supplementary Results**), which appears to reflect a difference in the impact of MTS on anterior connectivity. This disparity in effect sizes between the LTLE and RTLE groups fits with reports of greater pathology in left sided TLE compared to right, in terms of white matter structure (40), and widespread gray matter structure (41). Further, white matter imaging with DTI has also shown that there is a stronger correlation between the integrity across white matter tracts in LTLE compared to healthy controls and RTLE (42). Higher integrity correlations between tracts such as the fornix and cingulum bundle may suggest a shared underlying process that alters the white matter integrity, such as seizure activity which may propagate farther in LTLE. These previous convergent findings speak to the possibility that seizure-related disruptions propagate more readily in LTLE.

When interrogating the relationship between memory and hippocampal connectivity, we found that poorer material-specific memory was modestly associated with weaker connectivity between the epileptogenic hippocampus and major hubs of the DMN, consistent with previous work (6). While our findings did not survive statistical correction for multiple comparison, we below discuss the pertinent literature and speculate on the role of the hippocampus for memory in TLE. The mPFC and PCC are primary hubs of the DMN (14), a network which shows strong overlap with autobiographical memory regions (43), and have been implicated in episodic memory in TLE (4). The mPFC and PCC both have many proposed roles in memory, but both are implicated in contextual representation (44, 45) and episodic retrieval (46). At a global level, weaker connectivity to these hubs may indicate a reduced ability to bind information to the encoding context or an inability to reinstate the original context at retrieval. The anterior hippocampus is thought to communicate with regions such as the anterior temporal pole, and perirhinal cortex (11, 12) which represent concepts and item level features, respectively (47, 48). Thus, reductions in connectivity between the anterior hippocampus and these DMN hubs may indicate a reduced ability to bind conceptual verbal information with contextual information, as was seen in the LTLE group. On the other hand, the posterior hippocampus has stronger resting connections to ventral visual regions such as the fusiform, lingual gyrus and parahippocampus (5, 12), which represent visual and configural information, and also actively communicates with these regions during vivid elaboration of autobiographical memories (49). In RTLE, the right posterior hippocampus had significantly reduced connectivity to posterior medial regions and mPFC and, as such, greater reductions in connectivity between the right posterior hippocampus and the PCC may indicate a reduced ability to bind visual information and contextual information. This conceptualization will require further experiments to interrogate and may eventually inform theoretical frameworks of hippocampal functioning.

One limitation of the current study is that all patients were taking anti-epileptic drugs during the scanning period and it is difficult to exclude the effect that this may have had on functional connectivity of the brain. It is also possible that undetected interictal epileptiform discharges occurring during either scanning or neuropsychological test sessions could have led to alterations in connectivity. However, individuals with epilepsy rely on these medications in their everyday life, and may also experience interictal discharges, and thus, the state of their brain connectivity as depicted here is a reflection of their day to day experience. Another limitation was that each person's brain was transformed into standard space prior to *k*-means clustering which inherently leads to some signal blurring which could affect the parcellation at cluster boundaries. This step was performed to ensure each *k*-means clustering procedure was sampling from the same number of voxels in order to generate group level masks. While some small amount of smoothing may have occurred during transformation to standard space, we did not smooth with a Gaussian kernel inside the hippocampus, and performed minimal smoothing in the rest of the brain. Our results also produced clusters that replicate previous findings in the literature (5), including our previous work which performed clustering in native space (11). Finally, this study also did not examine whether these measures of connectivity were related to post-surgical memory change. Only a small number of this patient group has had surgery and returned for follow-up neuropsychological evaluation, precluding the possibility for statistical analysis. Future studies will assess whether the connectivity in the anterior or posterior hippocampus to the PCC is related to post-operative memory change as this would help inform clinicians and patients of the risk for cognitive morbidity from the surgery.

In conclusion, we demonstrated for the first time that the hippocampus can be parcellated into an anterior and posterior component based on its functional connectivity fingerprint to the brain and this can be done in both healthy adults and in patients with TLE, suggesting that the hippocampus in TLE retains some preferential connectivity along its long axis. We also show that the epileptic hippocampus has reduced connectivity

to the mPFC and PCC, the two key hubs of the DMN, and that this connectivity is modestly related to material specific memory ability, with anterior hippocampal connectivity in left TLE relating to verbal memory and posterior hippocampal connectivity in right TLE relating to visual memory. This aligns with our previous findings that hippocampal to DMN connectivity is a useful marker for memory network integrity in individuals with temporal-lobe epilepsy. Furthermore, future studies would be helpful in identifying whether anterior and posterior biases in connectivity can be related to more specific memory operations impaired in individuals with TLE.

ETHICS STATEMENT

Informed consent was obtained from all subjects in this study, which was approved by the UHN Research Ethics Board.

AUTHOR CONTRIBUTIONS

AB: study design, data collection, and analysis and manuscript drafting. VM: *k*-means clustering analysis and manuscript editing. MM: study design, supervision of data collection, and manuscript drafting.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.00920/full#supplementary-material

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Impaired Social Cognition in Epilepsy: A Review of What We Have Learnt From Neuroimaging Studies

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Background: Social cognition refers to specific mental processes that subserve social interaction. Impaired social cognition has been increasingly reported in patients with epilepsy and negatively affects overall quality of life (QOL). In this article, we will review neuroimaging studies of social cognition in people with epilepsy.

Methods: An electronic search of the literature was conducted and 14 studies qualified for inclusion in the review.

Results: Although the studies reviewed revealed a varied pattern of neural activations in response to emotion recognition and theory of mind tasks, consensual findings included altered pattern of signal activation in the social cognition network in patients with mesial temporal lobe epilepsy (MTLE) compared to healthy controls and significantly reduced signal activations and functional connectivity within this network in patients with right mesial temporal lobe pathology.

Conclusion: This review contextualizes our current understanding of the pathophysiology of impaired social cognition in epilepsy and makes recommendations for further research.

Keywords: neuroimaging, epilepsy, functional magnetic resonance imaging, social cognition, review

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INTRODUCTION

Healthy social functioning serves to enhance quality of life (QOL) by affording meaningful interactions between people and facilitating cooperative relationships. At a more fundamental level, related skills acquired through social learning ensure our very survival (1).

Social cognition encompasses an array of discrete but interacting mental processes. It is conceptualized as a form of information processing that supports the accurate perception and interpretation of the behaviors, thoughts, and feelings of others and guides appropriate responses. A range of sub-processes are involved in social cognition including theory of mind (ToM), emotion recognition (ER), empathy, prosody perception, and body language interpretation (2).

Deficits in social cognition are apparent across a variety of neurological, neurodegenerative, and psychiatric disorders. Although empirical studies on social cognition in epilepsy are limited, this is a growing and important area of research. Impairments in ER and ToM are frequently reported in people with TLE as well as those with extratemporal lobe epilepsy (extra-TLE), and these deficits compromise QOL (3, 4). Impaired ER is a common feature of mesial temporal lobe epilepsy (MTLE) with an average drop-off of 20% in patient scores on related tasks, compared to healthy peers (5). Meta-analyses have shown that early seizure onset and right temporal lobe

seizures are associated with the more significant deficits. Tasks of ER and ToM are the most commonly administered in research studies, and there is a need to explore social skills more comprehensively through investigating other domains including empathy, prosody, and body language interpretation in people with epilepsy, as well as the impact of functional deficits on QOL. Further research is also required to better understand the mechanisms of impaired social cognition in this patient population.

People with epilepsy are pre-disposed to social cognitive deficits for a variety of reasons, including psychosocial, neuropsychological, psychiatric, and pathophysiological. Epilepsy-related stigma, role restrictions, over-protectiveness, and fear of seizures all reduce social engagement and compromise the ability to learn and practice social skills. Cognitive impairments in domains of attention, memory, and language, as well as comorbid affective disorders also negatively affect the functional integrity of social cognition (4). In addition to these contributing factors, the network of brain regions subserving social cognition are the same neural circuits affected in temporal and frontal lobe seizure disorders.

Much has been learned about the neural substrates of social cognition in healthy people and those with neurodegenerative diseases. Since social cognition encompasses a variety of skills to be effective, the neural correlates are generally explored at the level of brain networks. Neuroimaging studies have identified neural networks involved in ER and ToM, which involve frontal, temporal, parietal, and occipital cortex, as well as subcortical mesial temporal regions and periaqueductal gray (6, 7). The ER neural network includes brain regions involved in the perception of the human face and regions recruited more selectively in response to emotion. According to a meta-analysis of 105 functional magnetic resonance imaging (fMRI) studies in healthy volunteers, the former includes fusiform gyrus, the fusiform face area, the occipital face area, and posterior superior temporal gyrus, while the latter additionally engages medial frontal gyrus and inferior frontal gyrus, anterior insula, amygdala, cuneus, and lingual gyrus (6). The fusiform face area is understood to mediate low-level processing, attention, and emotional detection of faces (8, 9), while the cuneus and lingual gyrus are activated when emotions are attributed to self and others and attention is directed to face recognition (10). Medial and inferior frontal gyri have shown to be recruited during the processing of emotive facial expression and social and moral behavior, and the anterior insula subserves emotional awareness and empathy of both self and other-orientated body and feeling states (11–13). The right amygdala is most frequently implicated in fear processing (14, 15).

Comparatively little neuroimaging research has investigated impaired social cognition in people with epilepsy, despite the prevalence of related deficits. Further work in this area will help elucidate the mechanisms of disturbed social cognition in this patient population. The aim of this review to summarize what we have learnt from neuroimaging studies conducted to date and make recommendations for further research.

METHODS

Literature searches were conducted in PubMed, Medline, and PsychInfo electronic databases by both authors independently. No date restrictions were stipulated, and search terms included the following: (social AND cognition) in the title and (epilepsy) AND (fMRI OR neuroimaging OR MRI) in the abstract. Empirical studies were included in the review if they were published in English and involved neuroimaging of epilepsy patients using ER or ToM tasks. Reference lists of the studies meeting inclusion criteria were searched for additional relevant publications. The search was completed on January 15, 2019, and 14 studies were extracted, all of which are included in the review (**Table 1**). A flowchart of the search strategy is detailed in **Figure 1**.

RESULTS

Functional MRI (fMRI) was conducted in all of the 14 studies included in this review. Two studies used event-related task designs and the remaining 12 used block designs. Two studies included functional connectivity analyses of activated clusters during tasks. Of the 14 studies reviewed, 12 focused on ER/emotional processing (EP), and two explored ToM. Seven studies employed fMRI tasks using static faces expressing emotion and six studies administered a task depicting the dynamic expression of fear. In the two studies investigating the neural mechanisms of impaired ToM, one relied on the dynamic fearful face task and the other used an animated shapes task that has previously been shown to probe explicit and implicit components of the function.

Neuroimaging Studies Exploring ER Using Static Faces Expressing Emotion

Lesion and neuroimaging studies have demonstrated the critical role of the mesial temporal lobe in recognizing emotion. MTLE affects the hippocampus, the entorhinal cortex, and the amygdala, with discrete amygdala damage observed in 10% of patients (29). Impaired ER is thus common in MTLE, particularly if seizures commence before the age of 5 years. In 2004, Benuzzi et al. explored the effects of unilateral hippocampal sclerosis (HS) on the processing and recognition of the emotion in an fMRI study employing a series of static faces expressing fear (17). BOLD signal activation maps of 8 patients with right MTLE, 5 with left MTLE, and 14 healthy controls (HC) were compared, in response to discriminating gender in fearful and neutral faces. Although no amygdala activations were generated in the comparison of fearful vs. neutral faces, significant unilateral BOLD signal increases were observed in the left inferior frontal gyrus and bilaterally in occipito-temporal regions in HC and in patients with left MTLE. By comparison, there were no significant clusters of activation in patients with right MTLE.

These authors used the same task to investigate possible reorganization of ER network following anterior temporal lobectomy (ALT) in six of these patients (four with right MTLE and two with left MTLE) (18). Improved ER was observed in behavioral testing 6 months after surgery and, in patients with

TABLE 1 | Neuroimaging studies of social cognition in epilepsy included in the review.

First author	Sample	Domain	Modality	Task	BOLD signal increases
Batut et al. (16)	6 L MTLE 6 R MTLE 15 HC	ER	fMRI	Static faces	Fear vs. neutral HC = **L** IFG, MFG, OL; **R** AMG; **BL** PC LTLE = **L** AMG, CU, UN; **R** IFG, MTL; **BL** PC RTLE = **L** PC, MFG, PHP Sad vs. neutral HC = **L** MTL, PC, SPL, IFG, OL; **R** CU, FFG, ITL, SFL LTLE = **L** MTL, SFL, MFG; **R** FFG, MTL PC, SPL, STG RTLE = **L** MTL; **R** SPL, MTL, SFL Happy vs. neutral HC = **L** CU; **R** PH, MTL, STL LTLE = **L** CU, FFG, IN; **R** MOL RTLE = **L** SFL; **R** MTL, STL
Benuzzi et al. (17)	5 L MTLE 8 R MTLE 14 HC	ER	fMRI	Static faces Gender discriminate	Fearful vs. neutral HC = **L** IFL; **BL** OL, LG, TL, FFG LTLE = **R** PH; **BL** IFL, IOL, MOL, TL, FFG RTLE = 0
Benuzzi et al. (18)	2 L MTLE 4 R MTLE	ER	fMRI	Static faces Gender discriminate	Fearful faces before vs. after ATL LTLE = **L** OFC; **BL** IPFC, EXST RTLE = **BL** OFC, EXST
Bonelli (19)	26 L MTLE 28 R MTLE 21 HC	ER	fMRI	Static faces	Fearful vs. happy HC = **L** AMG LTLE = 0 RTLE = **BL** AMG
Broicher et al. (20)	12 R HS 16 L HS 18 HC	ToM	fcMRI (ICA)	Dynamic fearful faces	Fearful faces vs. landscapes HC = **L** THL; **R** MTG; **BL** AMG, HP, PG, IFG, IN LTLE = **R** AMG, HP, PG, IFG, MTG, FFG, MTL,PL RTLE = **L** AMG, HP, STG; **R** IFG Group differences in connectivity LTLE = - **L** AMG, HP, STG; **R** IFG RTLE = - **R** AMG, HP, TP, ACC
Ciumas et al. (21)	13 BCECTS 11 HC	ER	fMRI	Static faces	Happy vs. rest BCECTS = **R** LG, CU HC = **R** LG, CU, MOL Fearful vs. rest BCECTS = **R** LG, CU HC = **R** LG, CU, MFG, IFG, STG
Hennion et al. (22)	13 R TLE 13 L TLE 25 HC	ToM	fMRI	Animated shapes	ToM vs. non-ToM group comparisons HC > RTLE = R PC, FFG HC < RTLE = R SFG, DMPFC; LG, CB HC > LTLE = R SFG HC < LTLE = R PHP
Ives-Deliperi et al. (23)	19 R TLE 35 L TLE 6 B TLE 12 exTLE 13 HC	ER	fMRI	Dynamic fearful faces	Fearful faces vs. landscapes HC = **BL** MTL LTLE = **R** MTL RTLE = **L** MTL
Labudda (24)	19 R TLE 18 L TLE 20 HC	ER	fMRI	Dynamic fearful faces	Fearful faces vs. landscapes HC = **BL** MTL, LTL, OL, FL LTLE = **R** MTL, LTL, SFG; **BL** OL RTLE = **BL** PTL, OL Region of interest analysis Lateralized MTL structures in MTLE groups
Schacher (25)	6 R MTLE 6 L MTLE 17 HC	ER	fMRI	Dynamic fearful faces	Fearful faces vs. landscapes HC = **BL** AMG LMTLE = **R** AMG RMTLE = **L** AMG

(Continued)

TABLE 1 | Continued

First author	Sample	Domain	Modality	Task	BOLD signal increases
Steiger et al. (26)	16 R MTLE 17 L MTLE 15 ex TLE 15 HC	ER	fcMRI Seed-based	Dynamic fearful faces	Connectivity analysis within groups HC + EXTLE = **BL** AMG, PAG, IFG, PG, ATL, PTL LMTLE: **R** AMG-PG, aSTG-pSTG RMTLE: 0
Szaflarski et al. (27)	12 L TLE 12 PNES 12 HC	ER	fMRI	Static faces Gender discriminate	Group comparisons between HC and TLE Fearful vs. control = PNES + OL, ITL, PL Sad vs. control = PNES – PT Connectivity analysis = LTLE – FL, TL, OL
Toller et al. (28)	18 R MTLE 16 L MTLE 30 HC	ER	fMRI	Dynamic fearful faces	Fearful faces vs. landscapes HC = **BL** AMG, HP; **R** PG, STG, IFG, PT LTLE = **BL** HP; **R** AMG, PT, IFG, PG, MTG, AIN, STG RTLE = **BL** THL; **R** AIN
Vuilleumier et al. (8)	13 HS+AS 13 HS 14 HC	ER	fMRI	Static faces	Fearful vs. neutral HC and HS = **L** ITL, MTL; **R** STG; **BL** IN, AMG, FFG HS+AS = **L** ITL, IFG; **R** AMG, IN

R, right; L, left; HC, healthy controls; MTLE, mesial temporal lobe epilepsy; PNES, psychogenic non-epileptic seizures; HS, hippocampal sclerosis; AS, amygdala sclerosis; ER, emotion recognition; ToM, theory of mind; fMRI, functional MRI; fcMRI, functional connectivity MRI; AMG, amygdala; HP, hippocampus; IFG, inferior frontal gyrus; MFG, medial frontal gyrus; MTL, mesial temporal lobe; FL, frontal lobe; TL, temporal lobe; OL, occipital lobe; PL, parietal lobe; PG, precentral gyrus; PHP, parahippocampal gyrus; PC, precuneus; CU, cuneus; UN, uncus; FFG, fusiform gyrus; SFL, superior frontal lobe; IPL, inferior parietal lobe; SPL, superior frontal lobe; ITL, inferior temporal lobe; MOL, mesial occipital lobe; STG, superior temporal gyrus; IN, insula; DMPFC, dorsal medial prefrontal cortex; BCECTS, benign childhood epilepsy with central temporal spikes; LG, lingual gyrus; EXST, extra-striatal cortex; THL, thalamus; ACC, anterior cingulate cortex; CB, cerebellum; PAG, periacqueductal gray; EXTLE, extra temporal lobe epilepsy; ATL, anterior temporal lobe; PTL, posterior temporal lobe; PT, putamen; aSTG, anterior superior temporal gyrus; pSTG, posterior superior temporal gyrus; AIN, anterior insula.

right MTLE, both the occipital and the frontal regions of the right hemisphere were newly recruited in response to fearful faces (18).

In 2006, Batut et al. compared EP of fearful, happy, and sad faces in patients with left and right MTLE compared to HC (16). Results showed differing recruitment of the ER network in patients compared to HC across all emotions. In the *fearful vs. neutral* condition, activations were generated in the left inferior frontal gyrus, mesial frontal gyrus, bilateral occipital lobe, and in the right amygdala and precuneus, in HC. In patients with left MTLE, activations were generated in the same regions but with differing lateralization. Signal increases were noted in the left amygdala, cuneus, and uncus, and in the right inferior frontal and medial gyri and in the precuneus bilaterally. In patients with right MTLE, activations were only noted in the left precuneus, parahippocampal gyrus, and medial frontal gyrus. In the *sad vs. neutral* condition, HC showed activation of the left medial temporal lobe, precuneus, superior parietal lobe, inferior frontal gyrus, and occipital lobe, with right activation of the cuneus, fusiform gyrus, inferior temporal lobe, and superior frontal lobe. Patients with left MTLE showed similar activations with differing lateralization once again, with signal increases in left medial temporal regions, superior and medial frontal lobe, and the right fusiform gyrus, medial temporal lobe, inferior parietal lobe, precuneus, superior parietal lobe, and superior temporal gyrus. Patients with right MTLE showed activations in the left medial temporal lobe and right superior parietal lobe, medial temporal lobe, and superior frontal lobe. Lastly, in the *happy vs. neutral* condition, BOLD signal activations were noted in HC in the left cuneus and right parahippocampal gyrus, medial temporal lobe, and superior temporal gyrus, while left MTLE patients demonstrated activations of the left cuneus, fusiform gyrus and insula, and right medial occipital lobe. Signal increases were noted in patients with right MTLE in the left superior frontal lobe and right medial temporal lobe and superior temporal gyrus.

Static faces expressing fear and happiness were also used as stimuli in a study exploring the utility of fMRI, and amygdala activations in particular, to predict post-operative emotional disturbance in patients undergoing temporal lobectomy (19). BOLD signal changes in response to *fearful vs. happy* faces were compared across three groups; 28 patients with right HS, 26 with left HS, and 21 HC. A block design task was used, displaying a series of pictures, words, and faces (23 fearful faces, 23 happy, and 24 neutral faces) to explore amygdala activation. Significant unilateral BOLD signal increases were observed in the left amygdala in HC, while bilateral amygdala activations were noted in patients with right HS and no significant activations were reported in patients with left HS. Bilateral signal increases in the amygdala of patients with right HS were significantly correlated to post-operative anxiety and depression scores, with right amygdala activation related to increased anxiety and depression after surgery.

Benign childhood epilepsy with centrotemporal spikes (BCECTS) is associated with pathology in the frontotemporal regions and, as such, offers a unique opportunity to study functional pathology in the social cognition network. An event-related potential fMRI study of 13 children with BCETCS was conducted, employing a static face paradigm, to assess the differences in neural activation in response to EP compared to HC (21). The study included two analyses, *happy faces vs. rest* and *fearful faces vs. rest*. Limited activation was generated in

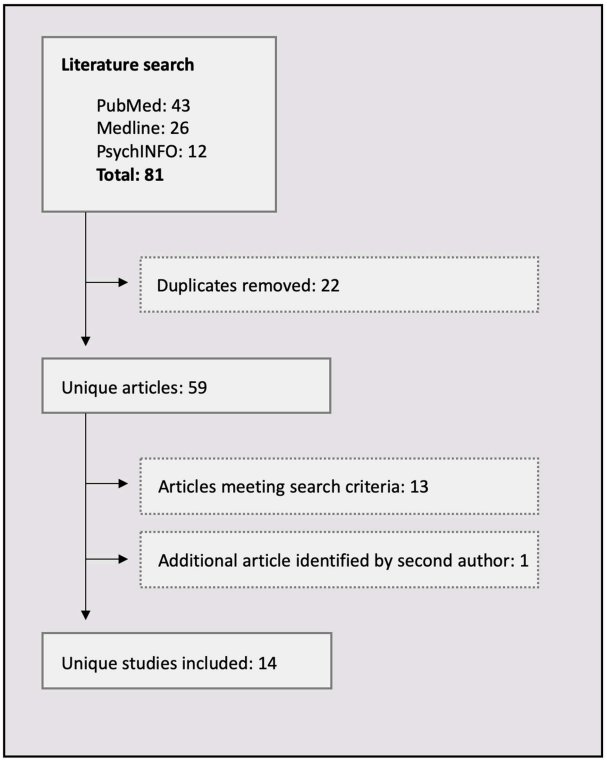

FIGURE 1 | Flowchart of the literature search process.

the patient cohort in either condition, with significant signal increases limited to the right lingual gyrus and cuneus in response to both. In contrast, widespread signal increases were noted in HC, with additional activations in right medial occipital lobe, medial and inferior frontal lobe, and superior temporal gyrus. Group contrasts revealed reduced bilateral activations in the insula, caudate, and lentiform nuclei in the BCECTS cohort in response to fear processing. The BCECTS cohort also demonstrated increased response time during the task, confirming dysfunction in the social cognitive network. These findings are consistent with reports of altered ER in children with TLE (30).

An earlier study investigated the modulatory influences of the amygdala on distant but connected brain regions during emotion processing of fearful faces, combining imaging, and lesion approaches (8). Activation patterns in various ER conditions were compared between 13 patients with hippocampal and amygdala sclerosis (HS+AS), 13 patients with isolated HS, and 14 HC. HC and HS patients showed a similar pattern of activation in response to *fearful vs. neutral* faces, with BOLD signal increases in the fusiform gyrus, bilaterally in HC and in the left hemisphere in patients with HS, bilateral increase in amygdala and insula, right superior temporal gyrus, and left inferior and medial temporal regions. By contrast, there were no significant signal increases in the HS+AS group, with evidence of only a weak signal change in left inferior posterior temporal gyrus. In a multiple regression analysis across the groups, a significant relationship emerged between the extent of AS and hypoactivation of the visual cortex, left hypothalamus, left hippocampus, bilateral anterior cingulate cortex, and right parietal lobe and superior temporal gyrus, during fear processing.

Szaflarski et al. conducted an fMRI and resting state (RS) connectivity analysis, comparing EP in 12 patients with TLE, 12 patients with psychogenic non-epileptic seizure (PNES), and 24 HC (27). In the fMRI analysis, greater BOLD signal increases were noted in response to happy, neutral, and fearful static faces in the PNES group compared to the TLE cohort. Increased signal was reported in visual, temporal, and parietal regions with decreased activity in response to sad faces in the putamen bilaterally. Seed-based functional connectivity analysis of RS data showed increased functional connectivity in patients with PNES between cerebellar, visual, motor, and frontotemporal regions, as well as between right and left amygdala compared to TLE patients and HC. TLE patients had delayed response times to stimuli in behavioral testing and exhibited hypoactivation of frontal, temporal, visual, and midline brain regions in response to all facial expressions. In addition, no significant correlations were found between the ROIs for the TLE group in RS connectivity analysis.

Neuroimaging Studies Exploring ER Using Dynamic Fearful Expression

The dynamic presentation of fearful faces has been used in fMRI studies of EP in TLE patients since the development of a related paradigm in 2006 (25). In this blocked design paradigm, patients are presented with fearful expressions of emotion in a series of thriller and horror movie clips, interleaved by control blocks of dynamic landscape video recordings. The perception of motion has been shown to activate amygdala, and together with emotionally laden content, the aim of developing the task was to maximize amygdala reactivity. In the initial study applying the paradigm, significant bilateral BOLD signal increases were generated in the amygdala in 12 HC while 11 of 12 patients with MTLE showed unilateral signal activations in the amygdala, contralateral to the side of seizure onset. Comparable signal asymmetry was noted in hippocampal activations in response to a visual memory task. This study provided not only preliminary evidence of the efficiency of the paradigm to lateralize MTLE but also insights into disturbed functional integrity of the medial temporal lobe during EP in these patients.

These findings have since been replicated (20, 23, 24, 28). In an fMRI study of 37 patients with MTLE (18 left MTLE and 19 right MTLE) and 20 HC, activations were evident in a widespread bilateral network in HC in response to the task. Activated regions included the mesial and lateral temporal lobe, occipital lobe, and frontal lobe (24). Consistent with Schacher's findings, left MTLE patients showed unilateral activations of the right mesial and lateral temporal lobe and superior frontal gyrus, and bilateral activations were noted in posterior regions of the lateral temporal and occipital lobes in patients with right MTLE. A further ROI analysis showed lateralized medial temporal activations in the right hemisphere in patients with left MTLE and in the left hemisphere in patients with right MTLE. Self-reported fear ratings were reduced in the right MTLE cohort.

Lateralized activations of the amygdala were replicated in a more recent study recruiting a larger sample of 60 TLE patients, only 15 of whom had confirmed mesial temporal lobe pathology

on MRI. Single-subject analyses were conducted in 35 left TLE patients, 19 with right TLE, 12 with extra-TLE, and 13 HC (23). Right amygdala activations were generated in 23 of the 35 patients with left TLE, and left amygdala activations were reported in 10 of the 19 patients with right TLE. Bilateral amygdala activations were generated in all but one non-epileptic subjects and no clear pattern of signal asymmetry was evident in the extra-TLE group.

The dynamic fearful face task was also applied to investigate whether MTLE is associated with altered empathy-related brain activations in the amygdala, periaqueductal gray, and anterior insula (28). Activation patterns in response to the dynamic task were compared across 16 patients with left MTLE, 12 with right MTLE, 16 with extra-TLE, and 30 HC. Comparable lateralization of amygdala activations was noted in the MTLE group as in previous studies and decreased activations were also noted in periaqueductal gray bilaterally, in the right MLTE group, with preserved right insula activations.

To further interrogate these findings, a seed-based functional connectivity analysis was conducted to assess connectivity between the brain regions activated during the viewing of the fearful face paradigm (26). Widespread bilateral functional connectivity was observed between the amygdala, limbic, cortical, subcortical, and brainstem regions in HC. Specifically, connectivity was evident between the amygdala and periaqueductal gray bilaterally and between right hemisphere inferior frontal gyrus, precentral gyrus, and anterior and posterior temporal lobe. A smaller network of connectivity was noted in patients with left MTLE, involving only the right amygdala and right precentral gyrus, anterior and posterior superior temporal gyrus, and putamen. No significant functional connectivity was present in patients with right MTLE.

Findings From fMRI Studies Investigating Tom

The dynamic fearful face task was also applied in an fMRI and functional connectivity study investigating which structures within the amygdala network relate to ToM performance (20). The analyses included 16 patients with left HS, 12 with right HS, and 12 HC, and functional connectivity between temporal, frontal, and parietal structures was explored using independent component analysis (ICA). The findings build on evidence of reduced functional and structural connectivity between the hippocampal structures and adjacent brain region in patients with MTLE (31, 32). Once again, bilateral amygdala activation was generated in response to fearful faces in HC, along with bilateral signal increases in hippocampus, precentral gyrus, inferior frontal gyrus and insula, as well as right medial temporal gyrus and left thalamus. Unilateral amygdala activations were observed in patients with left MTLE, contralateral to the lesioned hippocampus, together with right hippocampus, precentral gyrus, inferior frontal gyrus, medial temporal gyrus, fusiform gyrus, medial temporal pole, and palladium. In patients with right MTLE, activations were generated in the left amygdala, hippocampus, superior temporal gyrus, and ipsilateral inferior frontal gyrus. Group differences in connectivity, taking into account duration of epilepsy and IQ, revealed significantly reduced co-activation of the left amygdala, hippocampus, superior temporal gyrus, and right inferior frontal gyrus in patients with left HS compared to HC, and reduced co-activation of the right amygdala, hippocampus, temporal pole, and anterior cingulate cortex in the right HS group compared to HC. Reduced amygdala connectivity with medial temporal pole, right medial temporal gyrus, and left inferior frontal gyrus was also noted in patients with right MTLE compared to those with left MTLE, and this correlated with reduced performance on the Faux Pas test.

The second neuroimaging study to explore the neural underpinnings of impaired ToM in people with epilepsy used an animated shapes fMRI paradigm in 13 patients with right TLE, 13 with left TLE, and 25 HC (22). The task employed both explicit reasoning about mental states and implicit processing of information. Earlier research has shown that patients with MTLE have impaired performances in this task relative to HC, having difficulty in interpreting ToM interactions (20). The task has also been used in neuroimaging studies of ToM in healthy subjects in which the implicit component of the task activated fusiform gyrus, superior temporal gyrus, inferior frontal gyrus, and premotor areas while the explicit component recruited the medial prefrontal cortex (MPFC) and temporal parietal junction (33–35). Different neural activation patterns were generated within the neural networks of the two ToM components in patients with MTLE compared with HC, and these patterns were influenced by the laterality and age at seizure onset. A similar pattern of activation was noted in HC as in earlier studies; however, activations were limited to inferior and medial occipital lobe in patients with right MTLE and no significant activations were noted in patients with left MTLE.

DISCUSSION

Difficulties in social cognition are common in people with epilepsy, and the earlier the onset of seizures, the more pronounced these deficits (5). The clear overlap between neural networks involved in temporal and frontal lobe epilepsies and the social cognitive network offers a plausible physiological basis for such deficits (6, 7).

The aim of this study was to review what we have learnt from neuroimaging studies of social cognition in people with epilepsy. Since BOLD signal changes generated in fMRI studies are highly specific to the stimuli presented during the in-scanner tasks, meaningful comparisons can only be drawn between studies using the same tasks and comparable protocols. The findings of studies included in this review will therefore be grouped according to (a) those measuring ER/EP to static faces expressing emotion, (b) those measuring ER/EP using dynamic facial expression, (c) those investigating ToM, and (d) those studying connectivity patterns between regions activated in response to fMRI tasks.

The primary findings of the review are as follows: (1) A diverse pattern of BOLD signal increase is reported across studies investigating ER/EP in people with epilepsy and HC using static faces; however, patients with right MTLE generally show

hypoactivation of regions in the ER network and performed more poorly on behavioral tasks. (2) More consistent findings are reported across studies investigating ER using a dynamic fearful face task, showing bilateral amygdala activation in HC and lateralized activation in patients with MTLE, contralateral to the side of seizure onset. (3) Studies investigating ToM show reduced signal changes in MTLE patients in the ToM network and reduced connectivity between activated regions, as well as greater recruitment of executive regions in right hemisphere MTLE patients during implicit ToM. (4) Functional connectivity between activated regions during ER is typically reduced in patients with MTLE and particularly so in patients with right MTLE.

EP Responses to Static Faces Expressing Emotion

The findings of studies reviewed in this paper using static faces expressing emotion report BOLD signal activations in a number of the same regions activated in ER studies of healthy adults (6). The pattern of activations within and across studies, however, varies in terms of lateralization and precise localization. A consistency across all studies was abnormal signal activation within the ER network of patients with right MTLE, and significant correlations between such aberrations and impaired ER on behavioral testing, particularly recognition of fear (16, 17). It has been shown that the greatest impairments in MTLE lie in the recognition of fear and that this impairment is significantly more pronounced for those with right MTLE (3). These findings lend support to the theory that the right MTL is preferentially involved in processing fear and that related lesions disrupt the overall ER network. Right-sided pathology was also shown to relate to greater impairments in young BCECTS patients, who performed more poorly on tasks of emotion recognition and showed reduced activation in the ER network (21). Further to this, isolated amygdala damage was shown to alter activations across the ER network, suggesting that activation of regions involved in EP, in temporal, frontal, and visual cortices, is dependent on the functional and structural integrity of the amygdala (8).

EP Responses to Dynamic Faces Expressing Emotion

The most outstanding findings across studies using static faces vs. dynamic faces expressing emotion were bilateral signal increases in the amygdala in healthy subjects and unilateral amygdala activation in MTLE patients, in response to the expression of fear. Unlike the studies employing static faces, the dynamic fearful face paradigm generated comparable lateralized amygdala activations across groups in all of the studies reviewed.

Additional activations in response to dynamic fearful vs. scenic video clips in HC included bilateral activation of the hippocampus and right medial temporal gyrus. Activations are also evident in inferior frontal gyrus, superior temporal gyrus, precentral gyrus, and insula in more than one study; however, lateralization of activations in these regions differs. Overall signal activations are reduced in patients with right MTLE.

Right-hemisphere amygdala activations tended to be dominant in functional maps showing bilateral amygdala signal increases in HC and extra-TLE patients, providing evidence for the important role of the right amygdala in vicarious experiences of fear. Stronger activations of the right amygdala in HC and patients with left MTLE correlated significantly with self-reported ratings of fear, and right MTLE patients reported significantly reduced fear ratings (24). An association between right amygdala activation and empathy scores in HC and MTLE patients was also evident, with reduced signal intensity in right amygdala and periaqueductal gray, correlating with reduced empathy scores (28). This has been proposed as a potential mechanism through which right MTLE patients demonstrate reduced responses to fear (28). Together with the overall hypoactivation of other EP regions in patients with right MTLE, the results suggest that the medial temporal lobe may provide fundamental interoceptive input for empathic feelings of fear. Collectively, these findings also suggest that left amygdala is unable to compensate in terms of fear responses in the face of right amygdala damage.

ToM

Only one study directly investigated the neural underpinning of impairments in ToM in people with epilepsy (22). The same authors previously reported impairments in detecting and understanding faux pas, sarcastic remarks, and mentalistic actions in over 80% of patients with TLE (36). Related impairments have been implicated in abnormal psychosocial functioning and poor QOL in epilepsy (36–38).

Lesion and neuroimaging studies have identified regions of the brain that contribute to cognitive ToM abilities as well as affective ToM abilities. The dorsal MPFC has been shown to be recruited in inferring cognitive mental states and the ventral MPFC in inferring emotional states (39–44). Research findings suggest that both cognitive and affective subcomponents of ToM are impaired in patients with TLE (36). The findings reported by Hennion et al. neuroimaging study confirmed an association between such impairments and task performance and a similar pattern of activation in HC as reported in earlier studies. MTLE patients performed more poorly in the task and showed reduced activation of regions involved in the implicit component of ToM. More intense activations were also evident in regions involved in explicit component of the task in patients with right MTLE (MPFC and temporoparietal junction) (22). The results of this study suggest that the integrity of contralateral mesiotemporal lobe structures plays a more important role in MTLE patients in ToM than remaining spatially connected ipsilateral activity.

Functional Connectivity Analyses

Resting state connectivity analysis showed reduced connectivity within the ER network in patients with left MTLE compared to patients with PNES and HC (27). This study demonstrated significant connectivity in cerebellar, visual, motor, and frontotemporal regions, as well as between right and left amygdala in PNES patients compared to those with TLE and HC. This finding is consistent with an early investigation measuring functional connectivity between brain regions activated during

a social cognition task in HC, which reported significant correlations between signal activations in medial temporal gyrus, temporoparietal junction, anterior insula, lingual gyrus, and cerebellum bilaterally (45).

Results of functional connectivity analysis within the network of activated regions in response to the dynamic task were replicated in two separate studies. Widespread bilateral connectivity was observed between the amygdala, limbic, cortical, subcortical, and brainstem regions in HC in both seed-based analysis (26) and ICA (20). A smaller network of connectivity was noted in patients with left MTLE and no significant functional connectivity was evident in patients with right MTLE. Comparable connectivity patterns in the extra-TLE group to those in HC further suggest that altered patterns of connectivity could not be attributed to seizure activity or AED treatment (26). Similarly, amygdala co-activation with temporal and frontal regions was significantly reduced in patients with right MTLE in ICA (20). Amygdala connections in patients with left MTLE were comparable in strength to those in HC while significantly reduced in right MTLE patients, and these connectivity patterns were strongly associated with scores on a ToM test. These findings emphasize the important role played by medial temporal lobe in ER and ToM in MTLE patients.

SUMMARY AND CONCLUSION

This review of neuroimaging studies of impaired social cognition in people with epilepsy included studies employing a variety of tasks and imaging paradigms to investigate EP and ToM, reporting variable findings. The majority of studies reviewed reported BOLD signal activation in, and connectivity between, regions implicated in the social cognition network with differing lateralization and localization of activations in patients with MTLE compared to HC. There was apparently greater consistency in activation patterns between HC and patients with left MTLE and hypoactivation, and reduced functional connectivity was generally more pronounced in patients with right MTLE, which further correlated with poorer behavioral performance on social cognition tasks. Specifically, right medial temporal lobe damage was associated with impaired recognition of fear as well as hypoactivation of the social cognition network, and localized amygdala lesions altered the functional pattern of activation in distal regions of the entire social cognition network.

These findings are in agreement with the suggestion that the right medial temporal lobe is preferentially involved in the processing of fear and that related lesions disrupt the overall neural network involved in social cognition. In addition, the left amygdala appears to have a limited capacity to compensate in case of right amygdala damage. Widespread functional disruptions in MTLE are also in line with the new understanding of epilepsy as a network disease.

Limitations and Recommendations for Future Studies

Assimilating findings from functional neuroimaging studies to identify commonalities is a challenging exercise regardless of the functional domain under study. The reasons for this are multifactorial. fMRI results are highly specific to the paradigms and protocols employed and sensitive to scanner resolution, and the scanning environment and ultimate data analysis platforms and techniques are applied. Results are also dependent on a patient's cognitive functioning of level of participation in the fMRI task during scanning, which is troublesome to control. Nevertheless, reviewing neuroimaging findings makes an important contribution to detecting trends and outstanding neural correlates of affected functional domains in neurological diseases and guiding further research. As such, insights into the mechanisms of social cognitive deficits in people with epilepsy will assist in the management and treatment of these patients in an effort to improve overall QOL.

It will be important for future studies to elaborate on the salient findings presented in this review, particularly interrogating the mechanisms of disturbed social cognition in patients with right MTLE, as well as exploring potential deficits in patients with right frontal and occipital lobe epilepsy, which involve other important structures in social cognition. Future studies could also explore the relationship between poor social cognition in epilepsy and other aspects of cognitive impairments, comorbidities, and access to social support. Resting state functional connectivity is a useful technique to employ in exploring disruptions in the social cognition network across a variety of patient populations, to control for some of the aforementioned confounds related to fMRI. Resting state functional connectivity has been recommended in the study of mechanisms of social cognition in healthy and diseased populations as it shifts the focus from context-dependent aberration to independent aberrations in the functional network architecture. Analyses of RS data would also afford a fairer comparison between studies and findings may be considered in concert with structural connectivity and molecular imaging results (46). Once the neuroimaging literature of social cognition in epilepsy reaches such maturity, meta-analyses using techniques like activation likelihood estimations [ALE; (47)] would lead to valuable insights.

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All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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MINI REVIEW
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The Role of EEG-fMRI in Studying Cognitive Network Alterations in Epilepsy

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Brain functions do not arise from isolated brain regions, but from interactions in widespread networks necessary for both normal and pathological conditions. These Intrinsic Connectivity Networks (ICNs) support cognitive processes such as language, memory, or executive functions, but can be disrupted by epileptic activity. Simultaneous EEG-fMRI can help explore the hemodynamic changes associated with focal or generalized epileptic discharges, thus providing information about both transient and non-transient impairment of cognitive networks related to spatio-temporal overlap with epileptic activity. In the following review, we discuss the importance of interictal discharges and their impact on cognition in different epilepsy syndromes. We explore the cognitive impact of interictal activity in both animal models and human connectivity networks in order to confirm that this effect could have a possible clinical impact for prescribing medication and characterizing post-surgical outcome. Future work is needed to further investigate electrophysiological changes, such as amplitude/latency of single evoked responses or spontaneous epileptic activity in either scalp or intracranial EEG and determine its relative change in hemodynamic response with subsequent network modifications.

Keywords: EEG-fMRI, epilepsy, review, neuroimaging, interictal epileptiform discharge

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INTRODUCTION

Epilepsy cannot be reduced solely to the dysfunction of the seizure onset zone (SOZ), as more widespread abnormalities can be seen, resulting in heterogeneous deficits across cognitive domains (1–6). This supports the view that epilepsy is a network disease associated with complex cognitive deficits (7–11). While these cognitive deficiencies are increasingly recognized as important co-morbidities of epileptic disorders, they are still insufficiently understood and investigated. These deficits can also affect cortical regions that are remote from the epileptogenic zone. For instance, patients with temporal lobe epilepsy can suffer from frontal lobe dysfunction (executive functions) (12, 13). Conversely, patients with frontal lobe epilepsy can suffer from medial temporal lobe dysfunction (memory encoding) (14).

Epileptic Activity Can Dynamically Affect Cognition

Different hypotheses have tried to explain these deficits. A disruptive role of interictal epileptic discharges (IEDs) during ongoing physiological activity has been shown even if these discharges do not result in clinical signs of a seizure; the occurrence of IEDs can therefore be related to transient cognitive impairment (15–18). Previous studies based on intracranial EEG have investigated how

epileptic activity can alter normal cognitive processing through large-scale network disruption (16–18); however, due to the low spatial sampling of electrophysiological recordings, it is often challenging to map these networks without prior assumptions on the relevant brain regions to be recorded. Although intracranial EEG has high temporal and spatial resolutions, it has a low spatial sampling, thus preventing this tool to be used alone to investigate large-scale networks.

Interactions Between Epileptic Activity and Cognitive Networks

Cognition engages large-scale brain networks (19–21). Resting-state fMRI (rsfMRI) investigates synchronous activity between regions in the absence of an explicit task and can be subdivided into Intrinsic Connectivity Networks (ICNs) (22). The spatial organization of ICNs has been consistent with relevant cognitive tasks, however with subtle variations (23). As such, previous studies have implied that cognitive networks remain dynamically active even during periods of rest (24, 25). The effect of interictal activity could explain part of the nature of cognitive dysfunction in patients with epilepsy. So far, studies have mostly focused on the cognitive disturbances associated with the occurrence of IEDs (15–18). However, the interactions between detailed spatio-temporal aspects of epileptic activity and changes in ICNs and task-related cognitive networks have not been greatly explored. Therefore, the current review will discuss the current applications of EEG-fMRI in relation to cognition in both human and animal studies.

EEG-fMRI

The simultaneous recording of EEG and fMRI allows for data acquisition with high spatio-temporal resolution, thereby making it possible to map hemodynamic changes related to interictal epileptic activity (26, 27). EEG-fMRI is classically used to estimate the localization of the epileptogenic zone in the context of pre-surgical investigation of epilepsies (28–31), and only a few studies have used EEG-fMRI to investigate the direct effect of epileptic activity on cognition (22, 32).

METHODS

For this review, we performed a comprehensive literature search on the Medline PubMed database of all original research articles to date (July 2019) within the last 5 years (see **Figure 1**) with the keywords: (1) "epilepsy" AND "cognitive OR cognition" AND "EEG-fMRI", (2) "epilepsy" AND "cognitive OR cognition" AND "EEG AND fMRI AND simultaneous." However, due to the restrictive parameters, we only received one paper as a result in animal studies; therefore the parameters were extended to become more permissive by excluding the "cognitive OR cognition" criteria and expanding the timeline. Articles were excluded from the review if they were case studies or not in English. Some of the resulting papers (see **Table 1**) were methods-based, and were therefore summarized in the review, but not explained in detail as the purpose was to explore the role of EEG-fMRI in cognition. In the following sections, we discuss the role of EEG-fMRI in investigating the interaction between epileptic discharges and cognitive networks.

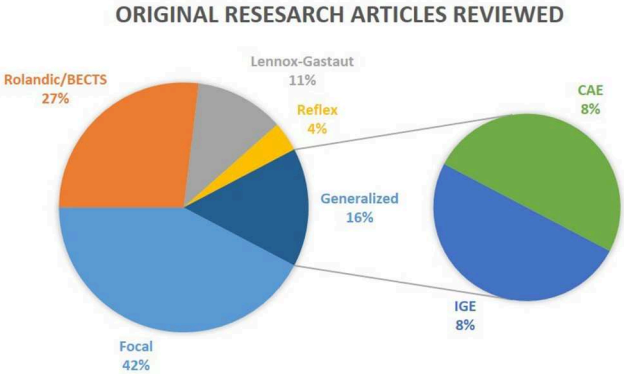

FIGURE 1 | Epilepsy types reviewed. The results of the review on clinical studies are separated into five distinct categories: Rolandic/BECTS, Lennox-Gastaut, Reflex, Focal, and Generalized. CAE and IGE patients are considered subgroups of Generalized epilepsy. Reviews were not taken into consideration in this illustration.

EEG-fMRI in Animal Models of Epilepsy

The use of combined EEG-fMRI in animal models, and in particular animal models of epilepsy, comes with two major benefits: first, it allows us to control for more parameters than in human research, thus providing more insights into the biological substrates of the BOLD signal, as illustrated by studies using optogenetic tools (65). Second, it gives access to the epileptic network (10, 11, 75), as it offers the opportunity to sample multiple brain regions related to the activity of the epileptic focus, with much higher spatial and temporal resolution in comparison to studies in humans (76).

BOLD signal analysis can highlight the network recruited during epileptic seizures. Different studies on animal models of generalized seizures (70, 72–74) have shown that the increase in BOLD activity is heterogeneous, and involves specifically thalamo-cortical circuits. These results are in line with the hypothesis that generalized seizures actually represent rapidly-propagating seizures with bilateral onset (77). Thus, fMRI signal can be used to map the network related to one particular "pre-identified" neural activity.

The inverse approach, i.e., to use BOLD signal to identify regions of interest and then guide electrophysiological recordings, is also a powerful tool, as shown in an elegant study in a rat model of temporal lobe epilepsy (69). In this study, the authors investigated the mechanisms of loss of consciousness using EEG-fMRI together with choline amperometry recordings. In short, they found that during focal limbic seizures, BOLD signal increases in the hippocampus [as expected (66)] and also decreases in cortical areas. This result was associated with a decreased firing of cholinergic neurons, but not non-cholinergic neurons, in the subcortical arousal system of the brainstem (69). This could explain, at least in part, the alteration of arousal during focal seizure. Very brief or partial arousal impairment could play

TABLE 1 | Epilepsy types reviewed.

	Type of epilepsy	Primary question	General result/ observation	References	Statistical analysis	# of SUBJECTS	Age range
(A) CLINICAL STUDIES							
1	Focal epilepsy (mTLE only)	What are the changes in the DMN, SN, and DAN networks in relation to the onset of interictal spikes?	Decreased synchronization of FC prior to the onset of interictal spikes	(33)	Functional connectivity	Patients = 15, controls = 15	Adults
2	Focal epilepsy	What is the value of IED-related BOLD maps in terms of pre-surgical planning?	Overlapping of IED-related BOLD maps with surgical resection is a marker of good prognosis	(34)	IED-related map and comparison with surgical resection	Patients = 30	Mixed: children and adults
3	Focal/Generalized	Can we account for the behavior of epileptic generators when no spikes are visible? And will this improve localization?	Yes, and it improves upon traditional spike-based analysis	(35)	GLM	Patients = 20, controls = 20	Mixed: children and adults
4	Focal epilepsy (mTLE only)	What are the changes in FC prior to spike onset in mTLE?	Significant loss of synchronization between bilateral hippocampi during the pre-spike periods	(36)	Functional connectivity	Patients = 15, controls = 15	Adults
5	Focal epilepsy	Can solely fMRI-driven results be used to localize the focus?	Yes, and it could be useful for EEG-negative patients	(37)	ICA and a cascade of classifiers	Patients training set = 12, patients test set = 18, controls = 13	Adults
6	Focal epilepsy	Is there an identifiable epileptic network outside the occurrence of IEDs?	The connectivity of the epileptic network remains high after removal of the IED contribution	(38)	Comparison of the IED-related network as identified by fMRI (ICA with best overlap with EEG-driven network) and the one identified by EEG	Patients = 10	Mixed: children and adults
7	Focal epilepsy	Does a new fast fMRI sequence (MREG) increase sensitivity to detect IED BOLD-related changes?	MREG increases sensitivity in detecting negative BOLD responses of IEDs in the DMN	(39)	GLM	Patients = 15	Mixed: children and adults
8	Focal epilepsy	Comparison of functional networks between patients with focal epilepsy and controls	Patients show higher local connectivity and decreased long-range connections; Epochs with and without IEDs do not change significantly	(40)	Functional connectivity maps	Patients = 23, controls = 63	Mixed: children and adults
9	Focal/ Generalized	Review	Simultaneous EEG-fMRI can help delineate epileptic foci and propagation pathways using rsfMRI	(41)	N/A	N/A	N/A
10	Focal/ Generalized	Review	Simultaneous EEG-fMRI improves our understanding of the electrophysiological correlates of epileptic/BOLD activity	(42)	N/A	N/A	N/A
11	Focal epilepsy	Are early BOLD responses in epilepsy patients a result of "temporal bleeding"	The HRF is affected by "temporal bleeding"? ±3 sec; authors recommend using a HRF at−6 sec to avoid "temporal bleeding"	(43)	GLM	Patients = 7, controls = 6	Adults
12	Focal epilepsy	Can task-induced HFAs be seen in simultaneous iEEG-fMRI?	HFAs can be reliably seen in iEEG-fMRI	(44)	Multi/single-trial analysis	Patients = 3	Adults

(Continued)

TABLE 1 | Continued

	Type of epilepsy	Primary question	General result/ observation	References	Statistical analysis	# of SUBJECTS	Age range
(A) CLINICAL STUDIES							
13	Focal epilepsy	What is the impact of interictal IEDs on ICNs (ECN and VN) in pediatric patients?	When IEDs are controlled for, ICNs are not different in patients vs. controls	(22)	Functional connectivity	Patients = 27, controls = 17	Children
14	Focal epilepsy (TLE only)	What are the real-time effects of IEDs on hippocampus and amygdala FC?	IEDs in the left hemisphere disconnected the left hippocampus and the DMN	(45)	Dynamic FC	Patients = 21	Mixed: children and adults
15	Focal epilepsy	Is EEG-fMRI accurate in detecting the ictal onset zone at varying statistical thresholds?	Increased sensitivity and specificity was achieved using a specific threshold	(46)	GLM and ROC curves	Patients = 21, controls = 21	Adults
16	Focal/Generalized	Review	EEG-fMRI can be used to localizing epileptic networks	(47)	N/A	N/A	N/A
17	Focal epilepsy (mTLE only)	Can amplitude of low frequency fluctuations (ALFF) and FCD be used for localization?	Increased ALFF is in mTLE structures and decreased FC attributed to desychronization between mTLE structures and the whole brain	(48)	ALFF and FCD	L mTLE patients = 26, R mTLE patients = 21	Adults
18	BECTS	How do IEDs affect ICNs (AN, BGN, DAN, DMN, SMN)?	Patients with IEDs show decreased FC in the DMN	(49)	Functional connectivity	Patients = 43, controls = 28	Children
19	BECTS	What are the dynamic changes seen in FC of BECTS patients?	Patients showed decreased dynamic FC in the orbital frontal cortex, ACC, and striatum; furthermore, both active and chronic effects of epilepsy contribute to altered dynamics of FC	(50)	Dynamic FC	Patients = 45, controls = 28	Children
20	BECTS	How does epileptic activity interfere with whole-brain networks?	Functional defects in brain networks contribute to patient symptomatology (i.e.: decreased nodal centralities in areas related to linguistics and attention control)	(51)	Functional connectivity and graph theory metrics	Patients = 73, controls = 73	Children
21	BECTS	Do BECTS patients with ADHD show specific network changes in comparison to patients without ADHD/healthy controls?	BECTS patients with ADHD show decreases in FC in the DAN in comparison to BECTS patients without ADHD/controls	(52)	Functional connectivity	Patients with ADHD = 15, patients without ADHD = 15, controls = 15	Children
22	BECTS	What are the real-time effects of spikes on cognitive function (i.e.,: language and behavior)	Interictal CTS disrupts networks involved in cognition (positive correlation between bilateral BECTS areas and left IFG/Broca's area)	(53)	Dynamic FC	Patients (medication-naïve) = 22	Children
23	BECTS	What is the effect of Levetiracetam on activations/deactivations and CTS?	Overall decreased activation (in higher cognition networks) in the medicated group compared to the drug-naïve patients	(54)	GLM	Medicated patients = 20, drug-naïve patients = 20	Children
24	BECTS	Can network abnormalities be used to differentiate between patients without IEDs and controls?	Patients without IEDs can be distinguished from controls	(55)	Amplitude of low frequency fluctuations and multivariate pattern classification	Patients with IEDs = 20, patients without IEDs = 23, controls = 28	Children

(Continued)

TABLE 1 | Continued

	Type of epilepsy	Primary question	General result/ observation	References	Statistical analysis	# of SUBJECTS	Age range
(A) CLINICAL STUDIES							
25	Lennox-Gastaut	Review	Epileptic activity in LGS can be seen in large scale networks such as attention default mode networks and can be categorized as a "secondary network epilepsy"	(56)	N/A	N/A	N/A
26	Lennox-Gastaut	Are the affects of LGS on cognitive networks persistently abnormal?	Abnormal connectivity was present during periods with/without IEDs	(57)	Functional connectivity	Patients = 15, controls = 17	Mixed: children and adults
27	Lennox-Gastaut	How does the FC change in a LGS patient with good post-surgical outcome?	Increased small-worldness, stronger connectivity subcortically, and greater within-network integration (between-network segregation)	(58)	Functional connectivity and graph theory metrics	Patient with good post-surgical outcome = 1, patients with no surgery = 9	Children
28	Lennox-Gastaut	What are the brain regions underlying interictal generalized proxysmal fast activity (GPFA)?	GPFA propagates from the prefrontal cortex to the brainstem via corticoreticular pathways; this network is present in both children and adults	(59)	Event-related analysis and DCM	Patients under anesthesia = 10, patients without anesthesia = 15	Mixed: children and adults
29	Reflex epilepsy	What are the regions associated with the initiation of seizures in reflex epilepsy?	Different networks show changes related to a specific type of reflex epilepsy (startle myoclonus, eating, and hot water)	(60)	GLM	Patients = 3	Mixed: children and adults
30	IGE	What regions terminate absence seizures?	Lateral prefrontal cortex involved at GSWD termination	(61)	Event-related analysis	Patients = 18	Mixed: children and adults
31	EMA, IGE	What are the structural/functional changes in EMA and IGE patients with epileptic activity triggered by eye closure?	Functional changes show increased activity in visual cortex, posterior thalamus, and motor control; structural changes include gray matter increases in visual cortex and decreases in frontal eye fields	(62)	Random-effects analysis and VBM	EMA patients = 15, IGE patients = 14, controls = 16	Mixed: children and adults
32	CAE	How do network properties change during seizure onset and offset in the DMN and thalamus networks?	There is an anti-correlation between the thalamus and DMN, which gradually decreases after seizure onset	(63)	Dynamic FC and graph theory metrics	Patients = 11	Children
33	CAE	How do GSWDs impact different ICNs and cognitive processes?	ICNs associated with higher-order cognitive processes (DMN, CEN, DAN, SN) had decreased connectivity while perceptive/motor processes were spared; ICNs showed different temporal responses to GSWDs illustrating a hierarchy	(48)	GLM and ICA	Patients = 16	Children

(Continued)

TABLE 1 | Continued

	Type of epilepsy	Primary question	General result/ observation	References	Statistical analysis	# of SUBJECTS	Age range
34	Genetic epilepsy (ring chromosome 20)	Review	Patients have both interictal and ictal disruptions in basal ganglia-prefrontal networks	(64)	N/A	N/A	N/A
(B) ANIMAL STUDIES							
1	No epileptic disorder	Proof of principle study for studying combined optogenetic stimulation, electrophysiology, and fMRI acquisition	Optogenetic stimulation elicits large-scale BOLD activity network, not restricted to the stimulated site	(65)	fMRI, LFP measurement, frequency analysis	13 rats (see paper for # of animals per experiment)	N/A
2	Pilocarpine- and electrically-induced limbic seizures	What is the nature of ictal neocortical slow-waves during limbic seizures?	Neocortical slow-wave represent decreased activity in the neocortex, not seizure propagation	(66)	LFP identification of seizure and BOLD-activity based map related to seizures	62 rats	N/A
3	No epileptic disorder	What is the neuronal activity underlying resting state functional connectivity?	Differential contribution of LFP frequency bands in BOLD signal	(67)	LFP-BOLD power-power correlation and phase-amplitude coupling	29 rats	N/A
4	No epileptic disorder	Is combined optogenetic-fMRI reliable to study large-scale network?	Methodological paper making optogenetic-fMRI a suitable method to study large-scale networks	(68)	Large-scale BOLD activity (see paper for details)	3–8 rats per experiment	N(A
5	Electrically-induced focal seizures	What is the biological substrate of decreased consciousness in focal seizures?	Decreased activity of subcortical arousal systems leads to decreased cortical function	(69)	BOLD activity, electrophysiology, and amperometry-based neurotransmitter measures	Total of 138 rats (see paper for specific experiments)	N/A
6	Animal model of absence epilepsy and bicuculline-induced GTCS	What is the BOLD network associated with SWD and GTCS of generalized epilepsy?	Increase BOLD activity in somatosensory cortex and thalamus, decrease in occipital cortex	(70)	Large-scale BOLD activity related to epileptic activity	16 rats	N/A
7	No epileptic disorder	What is the neuronal activity underlying the BOLD activity?	BOLD fluctuation correlate with power of γ-range LFP activity, more than with AP frequency	(71)	Analyses of BOLD-LFP correlation under visual stimulation	5 cats	N/A
8	GHB animal model of absence epilepsy	What is the regional BOLD activity during absence seizures?	(i) BOLD increase in thalamus (ii) BOLD decrease in motor and temporal cortex (iii) Heterogeneous BOLD response in parietal cortex	(72)	Comparing alternating periods of rest and induced absence seizures via GLM	8 rats	N/A
9	WAG/Rij rat model of spontaneous absence seizures	What is the regional BOLD activity during absence seizures?	(i) BOLD increase in thalamus (ii) Widespread cortical increase (temporal, parietal) (iii) No negative BOLD identified	(73)	Comparing alternating periods of rest and induced absence seizures via GLM	10 rats	N/A

(Continued)

TABLE 1 | Continued

	Type of epilepsy	Primary question	General result/ observation	References	Statistical analysis	# of SUBJECTS	Age range
(B) ANIMAL STUDIES							
10	GBL non-human primate model of absence epilepsy	Development of a non-human primate model of absence epilepsy to study the regional BOLD activation during absence seizure	(i) BOLD increase in widespread cortical regions (pre-/post-central, frontal, and temporal cortices, thalamus) (ii) No negative BOLD identified	(74)	Comparing alternating periods of rest and induced absence seizures via GLM	6 marmoset monkeys	N/A

Section A refers to the clinical studies that resulted from the search criteria. The last 5 years produced 34 papers from 2014 to 2019 (five of which were reviews and are written in red). Section B displays the search for animal studies, which went beyond the 5 years criterion due to otherwise limited results and produced 10 papers. Methodological papers that did not recruit patients/animals with epilepsy are written in blue. The table is organized by alphabetical order (of the first author). ACC, Anterior Cingulate Cortex; ALFF, Amplitude of Low Frequency Fluctuations; AN, Auditory Network; AP, Action Potential; BECTS, Benign Epilepsy with Centro-Temporal Spikes; BGN, Basal Ganglia Network; CAE, Childhood Absence Epilepsy; CEN, Central Executive Network; CTS, Centrotemporal Spikes; DAN, Dorsal Attention Network; DMN, Default Mode Network; ECN, Executive Control Network; EMA, Eyelid Myoclonus with Absences; FCD, Functional Connectivity Density; GBL, γ-ButyroLactone; GHB, γ-HydroxyButyric acid; GLM, General Linear Model; GPFA, Generalized Paroxysmal Fast Activity; GSWD, Generalized Spike-Wave Discharges; GTCS, Generalized Tonic-Clonic Seizure; HFA, High Frequency Activity; HRF, Hemodynamic Response Function; ICA, Independent Component Analysis; icEEG, intracranial EEG; IED, Interictal Epileptiform Discharge; IFG, Inferior Frontal Gyrus; IGE, Idiopathic Generalized Epilepsy; LFP, Local Field Potential; MREG, Magnetic Resonance Encephalography; mTLE, mesial Temporal Lobe Epilepsy; rsfMRI, resting state functional Magnetic Resonance Imaging; SN, Salience Network; SWD, Slow-Wave Discharge; VBM, Voxel-Based Morphometry; VN, Visual Network; WM, Working Memory.

an important role in transient cognitive impairments. Therefore, BOLD-guided electrophysiology provides a complementary tool to investigate the perturbation of brain networks during seizures. Aside from consciousness, EEG-fMRI studies of cognition in animals have remained scarce thus far (67, 71).

EEG-fMRI in the Study of Cognition in Humans

Previous studies have commented on the relationship between cognition and ICNs extracted from traditional resting state fMRI, especially in relation to patients with epilepsy (78–80). ICNs can be ascribed to specific functions, such as self-awareness, attention, cognitive control, or perceptions such as visual, auditory, or motor (81–83). There is some spatial overlap between these networks in both patients and healthy controls; however the abnormal modulation of activity between these networks can be indicative of a patient's clinical syndrome.

Over the last 5 years there has been a substantial increase in the use of EEG-fMRI, especially for pre-surgical evaluations for patients with epilepsy (7, 35, 37, 41, 46, 47). However, the effects of IEDs on cognitive networks were not often explored until recently. Following pioneering work relating IED-correlated decreases in Default Mode Network activity in temporal lobe epilepsy (84) and generalized epilepsy (85), recent works have shown the possible impact of interictal activity on several ICNs in focal epilepsy in adults (33, 36, 45), focal epilepsy in children (22), children with idiopathic focal epilepsy [Benign Epilepsy with Centro-temporal Spikes (BECTS)] (53, 55, 86), epileptic encephalopathy (56–59), as well as generalized epilepsies (61, 64), including Childhood Absence Epilepsy (CAE) (87), and even reflex epilepsies (60). The majority of recent EEG-fMRI studies who evaluate the interaction between interictal discharges, ICNs, and their relationship to neuropsychological outcome have been in BECTS patients; these studies found a negative correlation between cognitive functioning and Functional Connectivity (FC). Nevertheless, though patients with epilepsy are a heterogeneous population, all groups show a widespread influence of interictal activity on ICNs; as ICNs have previously been related to cognitive function, this strengthens the notion that IEDs have a definitive impact on cognitive functioning.

IEDs and Cognitive Performance

There are two ways to study the impact of IEDs on cognitive processing. One is to compare cognitive processing between patients with different IED occurrences (or other IED parameters such as: duration, or periods before vs. after onset of IEDs). Some evidence suggests that IEDs can be a marker of poor cognitive prognosis (88, 89) and their treatment could improve behavior in children (90). IED burden also plays a role, as shown by the fact that a diurnal occurrence of IEDs >10% of EEG duration is correlated with poorer information processing speed, verbal memory and visuo-motor integration in children (91).

Another way to probe the mechanisms through which IEDs perturb cognitive functions is to ask whether or not the occurrence of a single IED can directly affect brain processing. Indeed, IEDs could affect normal cognitive processing through *transient* disruption of brain networks, a paradigm known as *transitory cognitive impairment* (TCI) (92). Aarts et al. (93) showed that the occurrence of IEDs in patients with different kinds of epilepsy affected performance during a cognitive task, and further showed that left-sided IEDs tended to elicit errors in the verbal task and right-sided IEDs in the non-verbal task. Kleen et al. and Ung et al. added a level of complexity by showing that the laterality of the IEDs relative to the epileptic focus determined the existence of abnormal processing. It is interesting to observe that cognitive processing in turn can also modulate IED frequency (17, 94). An increase of temporal IEDs was indeed observed during cognitive tasks involving temporal structures (94), suggesting that increases in physiological activity might also favor the recruitment of local pathological networks.

This further entangles the relationship between epileptic and physiological activity.

IEDs and Cognitive Networks

These studies highlight the fact that consideration of IEDs has to be integrated with network imaging to understand how IEDs affect brain processing. This was investigated in a patient with idiopathic generalized epilepsy using EEG-fMRI during a memory task, which showed that IEDs perturb the brain network recruited by the task (95). Furthermore, recent studies have found that IEDs interfere with whole brain networks (49, 51), and indeed a recent review found a consensus between studies in both BECTS and CAE patients confirming the significant impact of IEDs on FC measurements (96).

If IEDs and sub-clinical features affect ICNs and therefore the underlying cognitive attributes, the next step is to understand when and how these changes occur. To answer the first question, both Burianová et al. (33) and Faizo et al. (36) explored connectivity prior to IED onset in TLE patients to determine the temporal extent at which connectivity is altered. Regardless of the presence of IEDs, both studies showed patients with abnormal connectivity networks. Burianová et al. (33) demonstrated decreases in functional connectivity (FC) in prefrontal cortices and increases in subcortical areas such as the thalamus (33). However, FC changes were also found prior to IED onset in hippocampal areas (36), thus corroborating the evidence suggesting decreases in FC between the hippocampus and PFC in TLE patients (28). They also found reduced connectivity of the DMN, which occurred prior to IED periods, while reduced connectivity of the salience network occurred during IED periods, relating to behavioral changes in consciousness and attention. Changes in connectivity seen prior to IEDs are particularly interesting as pre-IED hemodynamic changes have also been seen when studying the hemodynamic response function using deconvolution (43, 97, 98). Though the origin of this phenomenon is still unknown, it certainly reflects the existence of pre-IED specific neuronal activity. It would be interesting for future studies to explore the variability of HRF change in this context.

Transient Effects of IEDs On Epileptic and Cognitive Networks

Differences in connectivity measures remain in the absence of IED activity and this implies a separation between "transient" and "non-transient" effects. This can be seen in both adults and children. The connectivity pattern obtained from IED-correlated fMRI analysis is largely preserved in the absence of IEDs (38, 40).

Regarding cognition, Shamshiri et al. (22) found connectivity differences in cognitive networks (related to attention) in a group of children with focal epilepsy compared to controls. However, no evidence remained for non-transient differences in network connectivity between patients and controls, after accounting for IED effects (see **Figure 2**). These results were also consistent with a MEG study in children with focal epilepsy patients by Ibrahim et al. (99), but are inconsistent with those studies mentioned above (33, 36), possibly due to differences between adult and pediatric populations and their respective variability in plasticity and disease duration (99). Instead, for BECTS patients, several studies reported decreases in functional connectivity regardless of the presence of IEDs (50, 51, 86, 100). These patients showed decreased FC in the inferior frontal gyrus, anterior cingulate cortex, and the striatum, which have previously been related to cognitive control (86). This is particularly interesting as patients with BECTS often display behavioral difficulties and language delays (53). However, the effect of medication should also be taken under consideration when determining differences in functional connectivity. Indeed studies in BECTS patients have shown decreased connectivity in higher order functioning cognitive networks of drug naïve patients in comparison to medicated patients (54). The investigation of the difference between transient vs. non-transient changes in connectivity could benefit from simultaneous EEG-fMRI recordings and accounting for the age-related influence on long-term connectivity changes.

Spatial Considerations of IEDs

It is not only the temporal dynamics of interictal activity that are interesting, but also where these events occur. Indeed the spatial pattern can have an influence on which cognitive domain is predominantly affected. For example, in TLE patients the laterality of IED activity can preferentially damage certain cognitive abilities, such that left temporal IEDs were associated with disconnections to the hippocampus and the Default Mode Network (DMN) while right temporal IEDs were co-activated with the reward-emotion network, which could be involved in forced normalization (a condition in which patients show psychiatric degradation when the IEDs disappear under treatment) (45).

In contrast to local IEDs, such as those seen in TLE patients, generalized (bilateral synchronous) epileptic activity can have a more global effect on ICNs. CAE patients also have widespread GSWD-related decreases found in DMN, DAN, central executive, and salience networks (87). Also, in ring chromosome 20 syndrome, which is a rare and severe form of generalized epilepsy, increases in slow wave rhythm were related to decreases in activity of the DMN and Dorsal Attention Network (DAN) (64). However, the clinical meaning of this slow-wave activity, and whether it supplies transient or long-term effects on cognition, is still under debate. Patients with Lennox-Gastaut syndrome suffer from diffuse cognitive impairment and present widespread, often "generalized" epileptiform activity. In this group, there is no difference in network behavior between fMRI periods affected or unaffected by discharges (101). This pattern is in favor of a more chronic and enduring impairment in this condition, as reflected by the associated encephalopathy. Therefore, generalized epilepsies also show widespread decreases in ICNs especially corresponding to higher order cognitive processes (64, 87).

Perspectives

The study of IED-related effects on cognitive networks may be difficult in many patients, given the lack of frequent IEDs to model. Other approaches to model pathologic activity using EEG topographies (31, 34) or other EEG features such as

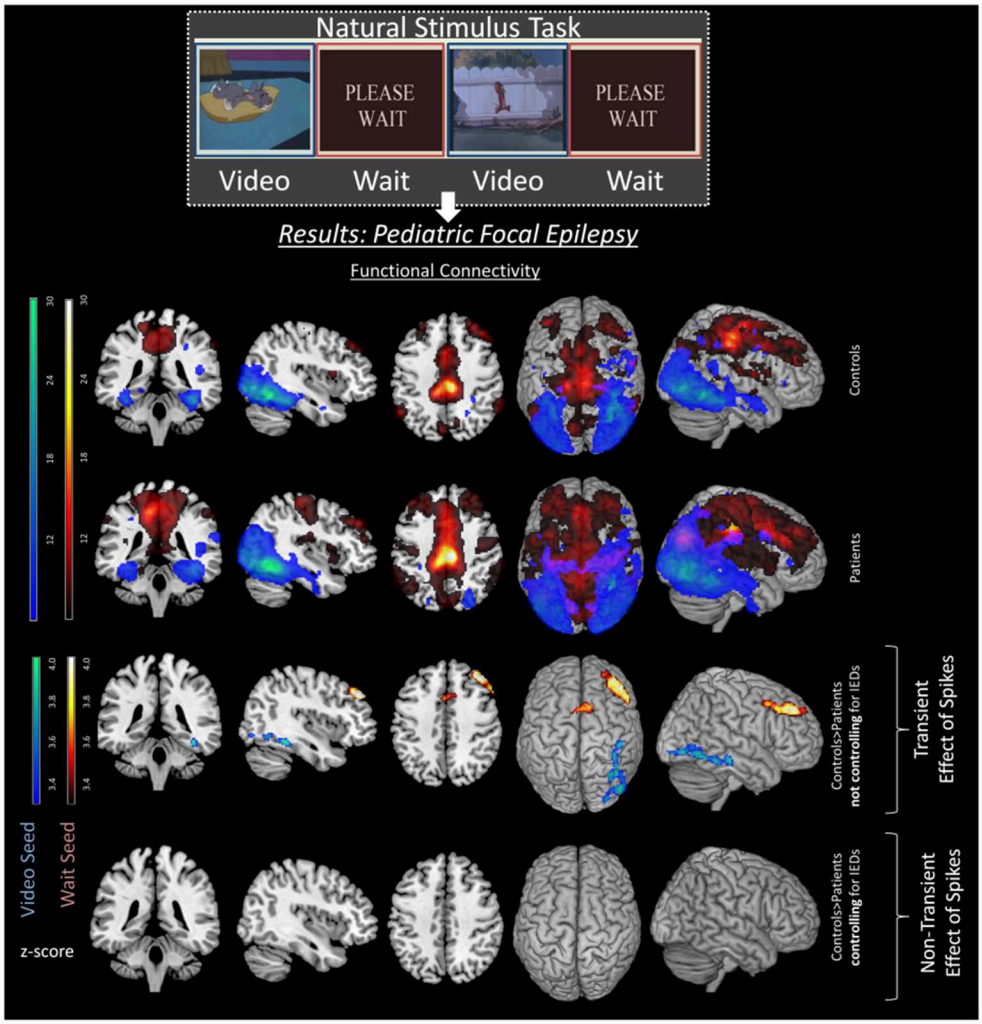

FIGURE 2 | Transient effects of IEDs in pediatric focal epilepsy patients. Image with permission Shamshiri et al. (22) illustrating the effects of spikes on FC networks of a resting state task. Differences between controls (top row) and patients (second row) can be seen in the third row. These differences are including both transient and long-term effects of spikes as spikes are not controlled for in the analysis. However, once the transient effects of spikes are accounted for, the group differences disappear (fourth row), emphasizing the effect of IEDs on ICNs.

decomposition using Independent Component Analysis (102) may offer alternative markers of epileptic activity to correlate with cognitive network alterations.

Simultaneous intracranial EEG and fMRI would allow to better map fMRI network alterations correlated to intracranial pathological EEG activity. Such recordings (103, 104) focused on the mapping of epileptic network (32) and the coupling between neuronal activity and hemodynamic changes, which is related to the fundamental assumptions underlying fMRI studies. These fMRI studies take advantage of the relationship between neuronal activity (mainly post-synaptic potentials) and deoxyhemoglobin concentration (42) to show the focal changes related to the epileptogenic zone, and reveal distant BOLD modulations related to the interictal epileptic network (104). Simultaneous recordings of intracranial EEG and scalp EEG could also uncover new non-invasive markers of epileptic activity that are currently undetectable on scalp EEG but could nevertheless affect cognitive processing. Such markers could be used to refine EEG-fMRI analysis (105, 106).

The possibility to inform fMRI analysis using EEG-derived brain activity offers several perspectives to study the spatio-temporal aspects of cognitive networks, at rest or engaged in specific tasks, in a more selective way than using fMRI, EEG or MEG alone. The characteristics of task-related EEG evoked responses (amplitude, latency) can be included in the fMRI analysis to model and map the network involved in such responses, such as attention and error monitoring (107, 108) and therefore also study interactions with epileptic activity. EEG measures of arousal (e.g., drowsiness or sleep) could also be valuable to study alterations of cognitive networks. Changes in arousal have a significant effect on fMRI connectivity

patterns than can even be used to monitor drowsiness during scanning (109). This could be particularly relevant when studying patients with epilepsy vs. controls when drowsiness could show group differences, notably related to drug-induced sedation, sleep deprivation or scanner related anxiety. Antiepileptic drugs affect fMRI brain networks in healthy controls (110) and the effect other drugs, such as donepezil and memantine in the field of dementia, have also been documented (111). This contribution of medication is hard to disentangle from the effect of disease, notably due to the high variability of drug regimes in patient groups and the difficulty to recruit drug naïve patients. EEG markers of medication, such as beta activity or increased drowsiness could be used to try to model this effect in the analysis.

Conversely, fMRI offers the possibility of high spatial resolution to localize cortical and subcortical brain regions at a whole brain scale that are involved in EEG patterns and therefore make it superior in this regard to source localization and connectivity measures based on EEG or MEG alone. Also, taking advantage of the combined high temporal and spatial resolution of EEG and fMRI, EEG connectivity analysis describing directed connections and dynamic aspects (high temporal resolution) could be based on spatial networks revealed by fMRI (whole brain, high spatial resolution) to enhance network characterization.

Future studies could also address the relationship between IEDs and brain rhythms (11, 17), and how this disrupts normal cognitive processing, which are known to rely on specific brain oscillatory activity (19, 20, 112–114).

CONCLUSION

Overall, the temporal and spatial effects of epileptic activity and medication can all influence changes in ICNs and cognitive functioning. Although there has been an increase in interest regarding EEG-fMRI and the effects of epileptic activity on ICNs, as reflected by the number of results from our search (see **Figure 1**, and **Table 1**), there is still much to learn about how to use this information to understand the long-term impact of interictal activity and cognition and improve the decision making regarding the therapy of patients with epilepsy. Globally, there are differences between focal/non-focal epilepsies, especially in regards to which ICNs or task-related networks are more sensitive to IEDs and how the epileptogenic network influenced the findings. Nevertheless all groups show a widespread influence of interictal activity but also some IED-independent alterations.

AUTHOR CONTRIBUTIONS

ES researched, wrote, and reviewed all work pertaining to human subjects. LS researched, wrote, and reviewed all work pertaining to animal models. SV edited all work that was reviewed in this article.

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REVIEW
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Pharmaco-fMRI: A Tool to Predict the Response to Antiepileptic Drugs in Epilepsy

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Pharmacological treatment with antiepileptic medications (AEDs) in epilepsy is associated with a variety of neurocognitive side effects. However, the mechanisms underlying these side effects, and why certain brain anatomies are more affected still remain poorly understood. Advanced functional magnetic resonance imaging (fMRI) methods, such as pharmaco-fMRI, can investigate medication-related effects on brain activities using task and resting state fMRI and showing reproducible activation and deactivation patterns. This methodological approach has been used successfully to complement neuropsychological studies of AEDs. Here we review pharmaco-fMRI studies in people with epilepsy targeting the most-widely prescribed AEDs. Pharmco-fMRI has advanced our understanding of the impact of AEDs on specific brain networks and thus may provide potential biomarkers to move beyond the current "trial and error" approach when commencing anti-epileptic medication.

Keywords: functional MRI, epilepsy, antiepileptic drugs, pharmaco-fMRI, side-effects, drug response

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INTRODUCTION

Epilepsy is one of the most common neurological disorders, characterized by neurobiological, cognitive and psychosocial impairments. Over 20 anti-epileptic medications (AEDs) with various mechanisms of actions are available to suppress seizures, but refractoriness to pharmacological treatment still occurs in approximately 30% of patients with epilepsy (1). After failing two AEDs, the chance of achieving long-term seizure freedom with the addition of any further drugs is <15% no matter what AEDs are used (2). People with pharmaco-resistant epilepsy show remarkably higher trend of neurocognitive comorbidity, morbidity and premature mortality than people with better seizure control. Cognitive impairment in epilepsy, a frequent comorbidity, is due to multiple factors: AEDs, genetic factors, and seizures. Cognitive dysfunction contributes to psychological disturbance, reduced employability and social disadvantage in people with epilepsy (3). Cognitive side effects are often the main complaint of a person with epilepsy, which lead to non-concordance with AED treatment, increasing risk of injury and death. The neural basis of cognitive effects remains unclear and the individual susceptibilities for adverse events are ill-defined. At present, we have no means other than "trial-and-error" to predict the most effective and best-tolerated treatment with AEDs. In particular, there are no reliable predictors for cognitive side-effects.

Advances in neuroimaging techniques contribute to the clinical diagnosis and management of epilepsy (4, 5). Functional magnetic resonance imaging (fMRI) identifies highly reproducible functional brain maps of activation or deactivation patterns triggered by performing specific

cognitive tasks such as language, motor and memory (1, 6). This method explores disease-related effects on both localized and network-level fMRI brain maps, and may improve the understanding of specific epileptic syndromes. Disease processes underlying epilepsy implicate complex large-scale brain network interactions beyond the epileptic focus. Recent advances in fMRI methodology allow us to study the impacts of medications and their effects on specific cognitive networks in those who receive neurocognitive pharmacological treatments. This so-called pharmaco-fMRI is a methodology based on the presumption that patterns of activation or deactivation can be affected and quantified in a differential manner by various AEDs (7, 8). Pharmaco-fMRI studies may provide surrogates biomarkers to investigate drug effects at the network-level and to predict the response and cognitive side effects of AEDs. Considering the more than 20 AEDs used in the treatment, and the various functional brain networks involved in the heterogeneity of specific epilepsy syndromes, early determination of AED efficacy and likelihood of neurocognitive adverse effects through fMRI methods are in urgent need.

ROLE OF PHARMAO-fMRI STUDIES IN EPILEPSY

Functional MRI has long been used to detect the underlying neurophysiological and anatomic mechanisms of specific behavior and stimuli on various conditions. It measures neuronal activity in an indirect manner via a signal called the Blood-Oxygen-Level-Dependent (BOLD) contrast. This signal derives from changes in the ratio between oxygenated and deoxygenated hemoglobin because of metabolism elicited by neuronal activity. Functional MRI can be scanned when subjects execute specifically designed cognitive tasks, testing for expressive language, episodic and working memory, executive functions and sensory-motor processing (3, 9–12), so-called task-based fMRI. On the other hand, resting-state fMRI techniques detect spontaneous fluctuations of BOLD contrast during "rest," which means subjects are scanned during task free conditions (4, 13). Resting-state fMRI identifies "functional connectivity" between brain regions, which are a stable reproducible group of cortical and subcortical regions with strongly correlated signal time-courses. These sets of brain regions are also detected in cognitive fMRI with high correspondence with task-implicated systems. In the presurgical evaluation of people with pharmaco-resistant epilepsy, fMRI is clinically utilized to identify brain regions of interest that are crucial for memory, sensori-motor functions and speech. In combination with white matter tractography, MRI methods can reveal white matter tracts which play a vital role in the functions with high correspondence, thus lowering the risk of morbidities inflicted by epilepsy surgery (5). In addition, simultaneous electroencephalography (EEG) and fMRI methodology can be used to help detect and localize the epileptogenic focus and help in planning the implantation of intracranial EEG electrodes (5).

Imaging studies examining the effects of AEDs in epilepsy have been performed mainly with functional MRI methods using non-standardized task or rest-state paradigms, and have been so far cross-sectional (14).

Pharmaco-fMRI studies in epilepsy are challenging for various reasons: (i) patients often need to start treatment immediately with AEDs; (ii) the influences of co-medicatons and other confounders, such as seizure duration or comorbidities have to be considered; (iii) the changes in resting-state fMRI in relation to one specific add-on medication may be too weak to be detected (15, 16). Pharmaco-fMRI studies thus far have been mainly retrospective and cross-sectional (17–20), and mostly used task-based fMRI (18–20). Medications effects are studied as an interactive influence during cognitive tasks fMRI scan (6, 21). The brain maps of activation and deactivation patterns in one specific cognitive fMRI task can be compared for a medication and a placebo condition but the interpretation of the results must be considered within the context of how the illness influences neurovascular coupling (22). Pharmaco-fMRI can explore effects of medications at a highly connected network of brain regions of highest densities of medication targeting effects (23). Thus, pharmaco-fMRI enables to assess large-scale cortical and subcortical systems, providing functional brain maps across different cognitive tasks, irrespective of the different pharmacodynamic properties (24). Pharmaco- fMRI provides mechanism-related activation and deactivation maps which can serve as targets for testing drug effects. A growing number of recent pharmaco-fMRI studies have shed a light on mapping possible mechanisms behind cognitive side effects of AEDs (18–20, 25), corroborating and extending the findings reported in previous neuropsychological studies. AEDs appear to ameliorate either task-related activation or task-relevant deactivation in brain maps including cortical and subcortical areas, which are important for the specific epilepsy syndrome as well as the brain networks responsible for neurocognitive function.

In this review, we performed a pubmed search using the search terms "pharmaco-fMRI," "epilepsy," "fMRI," and "AED." We only selected manuscripts, which were original articles and includes AED-related functional MRI studies (task and rest-state) in patients with epilepsy. We summarize pharmaco-fMRI studies of the most commonly used AEDs, and contrast these findings in pharmaco-resistant epilepsies to studies of so-called "benign" non-lesional focal epilepsies, which often go untreated.

Valproate

Valproate (VPA) is a widely used AED used for treating both focal and generalized epilepsy syndromes (26). VPA acts on both, neurotransmitter-dependent and non-dependent cellular conditions. Amongst its many putative mode of actions, it increases GABA turnover rates, thus empowering GABAergic function in the specific set of brain areas. Furthermore, VPA mediates neuronal excitation through a NMDA subtype of glutamate receptors (27). Given the various molecular and cellular patho-mechanisms underlying different seizure syndromes, the diversity of VPA's neurophysiologic and cellular properties of VPA might explain its broad-spectrum antiepileptic efficacy.

VPA is considered as the first-choice AED in juvenile myoclonic epilepsy (JME) (26). Previous imaging analysis

revealed that structural as well as functional connectivity are increased among motor and prefrontal brain cognitive networks in JME, likely explaining myoclonic jerks triggered by demanding cognitive activities, a reflex trait known to occur frequently in this syndrome (17, 28). JME patients showed increased activation of the primary motor cortex and supplementary motor area (SMA) during fMRI working memory task with an increasing load of cognitive task, which was modulated by disease factors, including seizure duration and seizure frequency. In addition to co-activation of motor areas, default mode network (DMN) areas failed to de-activate during cognitive tasks (17). Both abnormal co-activation in SMA and impaired deactivation in DMN were attenuated with increasing VPA dose (**Figure 1**). This is in keeping with the clinical experience that VPA is particularly effective in treating myoclonic jerks in JME without any cognitive side effects (17, 29).

Using interleaved fMRI/transcranial magnetic stimulation (TMS) methodology, TMS was applied to the motor regions in a placebo-controlled, combined fMRI/TMS study. VPA and lamotrigine (LTG) demonstrated different network specific effects: both medications reduced effective connectivity in relation to TMS between the primary motor and prefrontal areas and also between the primary motor and SMA. While TMS was applied over the prefrontal cortex, only LTG was found to be associated with higher effective connectivity between anterior cingulate cortex and the left dorsolateral prefrontal region (30).

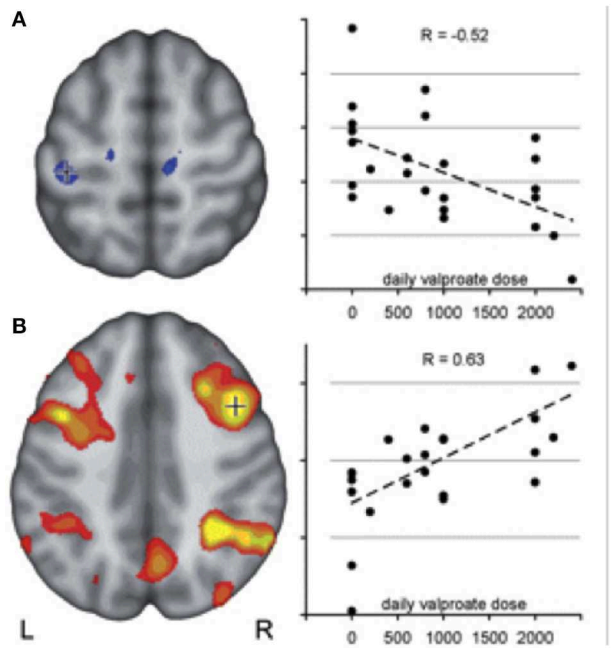

FIGURE 1 | Motor cortex coactivation correlates with valproic acid dosage in JME duting working memory task fMRI. Co-activation of motor and cognitive areas during a visuo-spatial working memory task was detected in JME compared with controls. The figure illustrates: **(A)** a negative correlation between left central activation (voxels underneath crosshair) and daily valproate dose indicating a normalizing effect of VPA on motor cortex hyperactivity. **(B)** Activity within the typical bilateral frontal and parietal working memory network, on the other hand, correlated positively with valproate dose, indicating a normalizing effect of valproate on the cortical activation pattern in JME. Reproduced with permission from Vollmar et al. (17).

In a recent resting state fMRI study of a so-called "benign" type of idiopathic focal epilepsy, rolandic epilepsy (31), measures of regional homogeneity of fMRI time courses were used to investigate the effects of AEDs. Regional homogeneity (ReHo) is a type of measurement of local synchronization of resting-state fMRI time-series across a group of neighboring brain voxels (32). Cortical areas including frontal and centrotemporal regions and subcortical structures like the thalamus, showed attenuation of regional homogeneity in children with VPA treatment compared with untreated children. These regions were believed to be implicated in rolandic/epileptic spike generation in this syndrome. Attenuation of ReHo in centrotemporal regions was found to be dose-related. Compared with levetiracetam (LEV), the VPA effect was more evident in the thalamus but weaker in the cortex. Furthermore, children treated with VPA demonstrated a preserved covariance of functional metrics between thalamus and centrotemporal areas, likely suggesting a balanced effect of VPA on both cortex and subcortical regions (31). These findings support the clinical impression that VPA is the drug of choice for generalized epilepsies with broad efficacy.

In focal epilepsies, structural imaging studies found the use of VPA to be associated with reduced parietal cortical thickness and reduced total gray and white matter volume (33). This effect could possibly be explained by its influence on brain development. Hence, VPA's variable effects require further imaging studies with multi-modality investigations in well-characterized cohorts of patients and healthy controls, which would allow for better understanding of its effects on anatomo-functional trajectories.

Topiramate

Topiramate (TPM) is widely used in monotherapy as well as an add-on treatment of epilepsy, and is also clinically used as a migraine prophylaxis (34). Cognitive dysfunctions along with TPM use have long been reported in people with epilepsy or migraine and healthy controls, which include impaired short-term memory, reduced sustained attention and decreased psychomotor speed. Impaired working memory and dysfunctional expressive language are frequently reported (35–39). These dysfunctions are even noted after single-dose administration and on steady-state doses in mono- or add-on treatment despite good seizure control (38).

TPM is the most studied AED using pharmaco-fMRI: a total of five studies employed either expressive language tasks after a single dose in healthy subjects or, in people with either epilepsy or migraine, on a steady dose of TPM. Given the importance that effective deactivation of the DMN has played an equally important role in executing task successfully in cognitive fMRI scans (40), these studies suggest an underlying mechanism by which TPM impairs cognitive processing during speech function. They shared the following functional abnormalities: (i) Activation was reduced in brain areas relevant for language, including inferior frontal and middle frontal gyri (IFG and MFG), superior temporal gyrus in the language-dominant

hemisphere (41–43). (ii) DMN regions failed to deactivate in subjects who executed language task (25, 43, 44). In addition, activation during verbal fluency task correlated with TPM dosages in the precuneus (25), which is an essential part of the DMN (21) and also plays a part in language networks when expressive language functions are engaged (45). More importantly, similar cognitive side effects and disturbance of language task relevant DMN deactivations were also described in healthy controls with the use of TPM (25). Overall, the above fMRI findings highlight the sensitivity of pharmaco-fMRI to detect the neurocognitive side effects of AEDs on functional brain networks.

Zonisamide

Zonisamide (ZNS) is used to treat both focal and generalized epilepsies, and leads to neurocognitive side effects similar to TPM albeit more moderate (39). Mechanisms of drug action of ZNS include modulation of dopaminergic and serotoninergic transmission, blockade of voltage-sensitive sodium channels and T-type calcium channels, as well as a neuroprotective effect from free-radical damage (46). One recent retrospective study of verbal fluency fMRI compared people with focal epilepsy syndromes taking TPM, ZNS, and LEV. Wandschneider et al. described a similar drug effect of ZNS and TPM on frontoparietal cognitive networks (19) (**Figure 2**). However, altered deactivations in the DMN including lateral temporal regions and inferior parietal lobes were found in people treated with TPM but not in the ZNS group. Activations of parietal structures, which support general task performance in the cognitive tasks including working memory and sustained attention system, in addition to activation of frontal networks relevant for language becomes apparent with the increase of cognitive demand in this study (47). Considering the execution of the verbal fluency task requires relatively low cognitive demand, decreased activation in expressive language-specific regions (IFG and MFG), sustained attention (parietal cortex) and working memory (frontoparietal lobes) implies that TPM and ZNS might suppress higher-level neurocognitive processing.

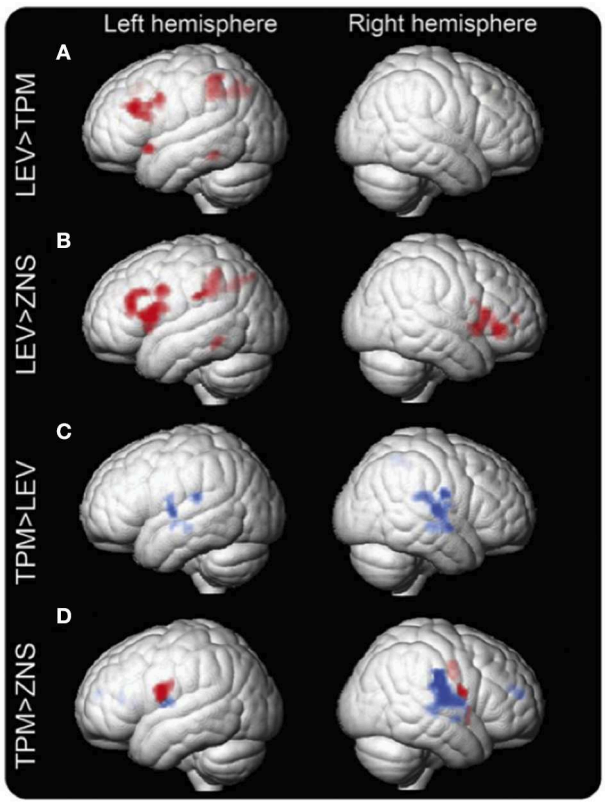

FIGURE 2 | Group differences in the verbal fluency task fMRI activation maps between LEV, TPM, and ZNS. Group differences in fMRI activation maps during the verbal fluency task Significant group differences between patients on levetiracetam (LEV), topiramate (TPM), and zonisamide (ZNS) are demonstrated. Patients on TPM and ZNS have less activation in frontal and parietal cognitive networks than patients on LEV. In patients on TPM, activation is reduced in the left middle frontal gyrus (MFG) and left dorsal parietal region **(A)**. In patients on ZNS, activation is reduced in the left MFG and bilateral inferior frontal gyrus (IFG), as well as the left dorsal parietal region **(B)**. In terms of task-relevant deactivation networks, bilateral lateral temporal regions and rolandic opercula and the right inferior parietal lobule and supramarginal gyrus are less deactivated (blue) in patients on TPM compared to those on LEV **(C)**. Compared to ZNS, TPM shows increased activation in the IFG, insular cortex, and rolandic operculum on the left and the insular cortex, inferior parietal lobule, supramarginal gyrus, superior temporal gyrus, and rolandic operculum on the right. Differences in the left are due mainly to increased activation of task-relevant regions as shown in red (inclusively masked with LEV activation maps); on the right, activated regions lie mainly within task-negative areas, i.e., are due to impaired deactivation as shown in blue (inclusively masked with LEV and ZNS deactivation maps) **(D)**. $p < 0.005$, 20-voxel threshold extent. Reproduced from Wandschneider et al. (19).

Carbamazepine

Carbamazepine (CBZ) was the first AED to be investigated in a pharmaco-fMRI design in patients with epilepsy (48). Twenty-one people with pharmaco-resistant temporal lobe epilepsy (TLE) performed a visuo-spatial memory retrieval task, which elicited activations of mesiotemporal regions by the means of cognitive navigation through a familiar route in the scanner. They observed reduced brain activations within mesiotemporal areas with the increased CBZ serum levels, independent of the lateralization of the epileptic foci (48).

Oxcarbazepine

One recent pharmaco-fMRI study in people with TLE using resting-state fMRI compared a subgroup of participants treated with CBZ or oxcarbazepine (OXC) with people with other AEDs. Using a graph-theoretical approach to characterize the organizational properties of functional networks, abnormal "hubness" was reported in people treated with CBZ/OXC (49): while less highly connected "hubness" was detected in the CBZ/OXC group, "betweenness centrality" was decreased in the thalamus and limbic circuit, but increased in the DMN regions including cingulate and posterior cingulate/precuneus. These results suggest redistribution of "hubness" with more remarkable shifts from limbic to lateral cortices in people with TLE on CBZ/OXC. Previous fMRI findings in TLE with graph theoretical analysis showed a "re-distribution" of hubness areas with high betweenness centrality to mainly temporal association cortical

areas and paralimbic and (50). Hence, the findings in this study suggest a region-specific drug effect of CBZ/OXC on epilepsy-related brain network changes. Another interesting finding in this study is that attenuation of activation of mesiotemporal lobes was dose-dependent.

Levetiracetam

Levetiracetam (LEV) is one of the most widely used AEDs for focal and generalized epilepsies with good efficacy and tolerance (51). LEV binds to the synaptic vesicle protein SV2A. Its mechanism is believed to be via the modulation of synaptic neurotransmitter release (52). In most neuropsychological studies LEV has been shown to have a favorable cognitive profile (53), exerting a positive impact on cognition, and as a result even ameliorate neurocognitive performance (54, 55).

In keeping with these observations, pharmaco-fMRI studies showed a beneficial impacts of LEV on neurocognitive networks (18–20). One recent pharmaco-fMRI study compared people on LEV with those not treated with LEV via a verbal and visual-spatial working memory task in people with unilateral TLE. People on LEV showed more extended DMN deactivated regions relevant for the task in the affected temporal lobe than people not treated with LEV. Specifically, this effect was observed (i) in the left mid-temporal gyrus in people with left TLE during the verbal task; (ii) in the right hippocampus in those with right TLE performing the visual- spatial task. These drug effects became more obvious with increasing LEV dosages, suggesting a significant dose-dependence. This study revealed the task-specific difference of effects on syndrome-specific fMRI regions between left and right TLE. Since people taking LEV showed similar task-related brain maps of activation and deactivation patterns with healthy controls, LEV is believed to be associated with normalizing effects on task fMRI brain activation and deactivation patterns in people with epilepsy (18).

Previous fMRI studies investigating the functional networks of working memory illustrated that amelioration of activation of mesiotemporal lobes contributed to effective task performance (56, 57). This may occur as part of a brain activity resource redistribution from task-irrelevant to task-relevant cortices in order to reduce interference (58). Recent cognitive fMRI studies examining working memory in people with TLE described failure to deactivate the ipsilateral hippocampus to the presumed epileptic focus in comparison with healthy controls. This kind of derangement points to a disruption in the segregation between task-negative and task-positive regions, specifically mesiotemporal and parietal lobes (59, 60).

In children with rolandic epilepsy, this effect of LEV was also observed in resting-state fMRI: in comparison with drug-naïve children, lower ReHo was found in children on LEV in frontal and centrotemporal cortices and subcortical areas including thalamus and basal ganglia. These regions are believed to be involved in the generation of rolandic spikes. Comparing ReHo patterns in children treated LEV with subjects on VPA revealed different spatial specificity of the effects of these two AEDs. Specifically, LEV had a pronounced effect on frontal and temporal regions and caudate while exerting a less evident impact on thalamus. Additionally, LEV had dissociating effects on the fMRI local covariance metrics of thalamus and centrotemporal regions (31). However, the absence of healthy controls in this study does not allow us to establish whether ReHo patterns in children on LEV may reflect a "normalizing effect" to normal baseline status.

People with amnestic mild cognitive impairment who have a risk of progressing into Alzheimer's disease were studied with pharmaco-fMRI and LEV. Abnormally higher activation in hippocampus in the dentate gyrus/CA3 regions was attenuated with the administration of low-dose LEV which was corroborated by improvement of out-of-scanner memory measures (61, 62).

Overall, pharmaco-fMRI revealed specific effects of LEV with predominant focus on the networks in relation to pathomechanisms underlying diseases. Its effects of restoring abnormal activation and deactivation patterns may explain its positive cognitive profile.

Lamotrigine

Lamotrigine (LTG) is effective for both focal and generalized epilepsy syndromes, which are recorded to be associated with fewer cognitive and behavioral changes compared with other AEDs (63, 64). In a retrospective study using verbal fluency fMRI, we investigated the cognitive side effects of sodium channel–blocking AEDs in people who had been taking CBZ or LTG, while we also included healthy controls (20). Forty-two people on levetiracetam (LEV) were used as patient controls because of LEV's "normalizing effects" on cognitive activation patterns (18). In people treated with LTG, abnormal fMRI findings were limited to failed deactivation of the DMN regions, while those on CBZ showed decreased activations in the dominant IFG. Clinical measures of category and word fluency tests found that the performance of people treated with CBZ was worse than those treated with LEV or LTG.

Combination Studies

The combination of these two pharmaco-fMRI studies provided preliminary evidence for altered activation of task-related regions and failed deactivation in the DMN (**Figures 2**, **3**), which is highly correlated with progressively worse neurocognitive side effects (**Table 1**):

- LTG usage is associated only with abnormal deactivation in the DMN, which has a limited impact on clinical language performance;
- ZNS and CBZ show similar dysfunctions in the activation patterns relevant for language, and both medications are associated with poorer performance in verbal fluency;
- TPM is associated with worse cognitive functions compared with other AEDs, and results in both, decreased language-specific frontal fMRI activations and altered task-relevant deactivation of the DMN regions (19, 65).

NEUROIMAGING IN DRUG-SENSITIVE EPILEPSIES

Functional imaging studies may help to phenotype individuals who show positive responses to certain AEDs or distinguishing

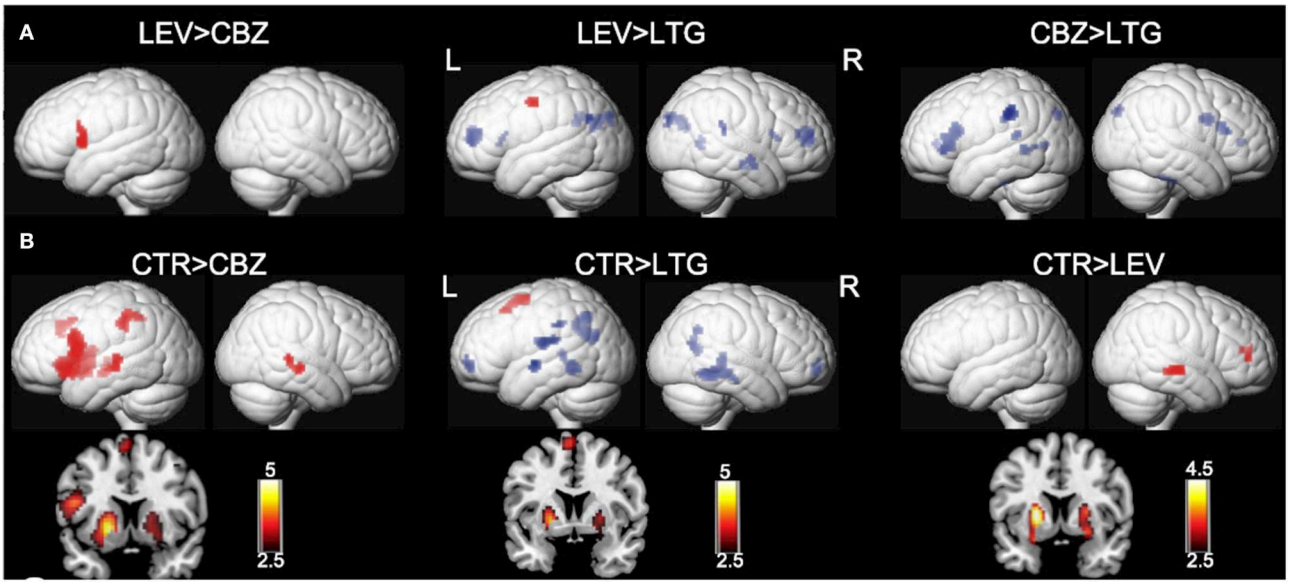

FIGURE 3 | Effects of carbamazepine and lamotrigine on functional magnetic resonance imaging cognitive networks. Significant group differences between patients on carbamazepine (CBZ), levetiracetam (LEV), and lamotrigine (LTG) and healthy controls (CTR) are demonstrated on a surface-rendered brain template, and the subcortical changes are demonstrated on a coronal brain template with a bar chart indicating z score. **(A)** Patients on CBZ activated less in the left inferior frontal gyrus than patients on LEV. In patients on LTG, deactivation was reduced in the task-negative areas, including the middle frontal gyri and left dorsal parietal region of the precuneus, compared with patients on LEV and CBZ. $P < 0.005$, 10-voxel threshold. **(B)** All three groups of patients activated the putamen less bilaterally (left > right) than CTR. Patients on CBZ activated the left inferior frontal gyrus less than CTR. There was less deactivation in the bilateral medial frontal gyri and bilateral lateral temporal regions, left rolandic operculum, and left inferior parietal lobule in patients on LTG. $P < 0.005$, 10-voxel threshold. L, left; R, right. Reproduced with permission from Xiao et al. (20).

TABLE 1 | The summary of impaired activation and deactivation in verbal fluency task pharmaco-fMRI studies in epilepsy.

AEDs	Activation	Deactivation	Effects on cognition
Topiramate	↓	↓	↓↓
Zonisamide	↓	N/A	↓
Carbamazepine	↓	N/A	↓
Lamotrigine	N/A	↓	N/A

↓, *impaired;* ↓↓, *severely impaired.*

responders from non-responders. In one resting state fMRI study with genetic generalized epilepsy, Szaflarski et al. compared people who are responsive to VPA and those who are not. Their findings suggest that people with VPA-responsive and VPA-resistant genetic generalized epilepsy might have different generalized spike waves discharges (GSWD) generators, and that these differences in GSWD generators are likely to account for the different responses to VPA. Furthermore, reduced functional connectivity was more prominent in treatment-resistant epilepsy and functional connectivity was significantly reduced with greater duration of epilepsy (66).

One recent study in rolandic epilepsy explored the difference in dysfunctional white matter networks between treated and untreated children (67). Based on previous findings of white matter abnormalities in the rolandic networks (68, 69), Jiang et al. obtained several white-matter functional networks and analyzed conventional functional connectivity in four frequency sub-bands. They further employed functional covariance connectivity (FCC), which is an indicator for the estimation of the covariance between two white matter networks based on their correlations with multiple gray matter regions (70, 71). In comparison with healthy children, the untreated group showed increased functional connectivity and FCC in rolandic regions and sensorimotor network (precentral and postcentral regions), and decreased functional connectivity and FCC in dorsal frontal network while these abnormalities were not evident in the those children with AED treatment. These results are in consistence with our previous fMRI findings showing underlying functional network abnormalities in this "benign" type of epilepsy, which appear to be responsive to AED treatment (72). Methodological approaches of combined functional and structural MRI metrics analysis offer the promising outcome predictors for the future selection of suitable AED treatment choices with efficacy as well as good tolerance.

CONCLUSION

The neuroanatomical mechanisms underlying the drug effects of AEDs are more complex than just a general decrease in

cortical neuronal excitability (73, 74). Seizure control measures often rely on subjective ratings, and as such seizure frequency according to the patients' or care-givers' accounts are often unreliable. Neuroimaging techniques, particularly fMRI, have largely contributed to clinical presurgical evaluation in epilepsy treatment, but also have the potential to provide further insights into the mechanisms underlying effects of AEDs. Pharmaco-fMRI studies investigate AEDs' effects on functional brain networks, and could help to determine early treatment response and unravel mechanisms of drug efficacy and adverse effects, and through this advance new AED research and development. One limitation of current pharmaco-fMRI studies in epilepsy is the variability of techniques used and a lack of standard for methodology (22). The challenges faced in methodology of pharmaco-fMRI could be mitigated by choosing suitable experimental drug and matching drug effects to regional BOLD signal (22). In addition, study design with multimodal complementary approaches including ASL, electrophysiological measurements and pharmacogenetics could also be utilized to provide additional information of the complex patterns of the brain's functional anatomy.

For now, most pharmaco-fMRI studies in epilepsy either cross-sectional or retrospective. Longitudinal studies will be required, in which causality can be addressed, controlling for the influences of clinical, psychosocial, and medication-related factors. Ideally, pharmaco-fMRI studies should recruit people who are going to have AED treatment at different time intervals from new-onset to chronic disease throughout their disease course, with a complete battery of neuropsychological testing. Specifically, prospective studies of people with new-onset epilepsy enables to better prevent medication-related effects from the contamination of epilepsy-related cofounders.

Current pharmaco-fMRI studies in epilepsy provide spatially detailed information at the group level. If AED-related fMRI effects can be utilized for individually precision medicine remains to be shown. Jirsa et al. proposed a "Vitual Epileptic Patient" to develop individualized whole brain networks for epilepsy, which could be used for future personalized pharmaco-fMRI studies (75).

AUTHOR CONTRIBUTIONS

FX: articles search and drafting/revising the manuscript. DZ: drafting/revising the manuscript, study concept, and study supervision. MK: drafting/revising the manuscript, study concept or design, and study supervision.

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BECTS Substate Classification by Granger Causality Density Based Support Vector Machine Model

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Objectives: To investigate the performance of substate classification of children with benign epilepsy with centrotemporal spikes (BECTS) by granger causality density (GCD) based support vector machine (SVM) model.

Methods: Forty-two children with BECTS (21 females, 21 males; mean age, 8.6 ± 1.96 years) were classified into interictal epileptic discharges (IEDs; 11 females, 10 males) and non-IEDs (10 females, 11 males) substates depending on presence of central-temporal spikes or not. GCD was calculated on four metrics, including inflow, outflow, total-flow (inflow + outflow) and int-flow (inflow – outflow) connectivity. SVM classifier was applied to discriminate the two substates.

Results: The Rolandic area, caudate, dorsal attention network, visual cortex, language networks, and cerebellum had discriminative effect on distinguishing the two substates. Relative to each of the four GCD metrics, using combined metrics could reach up the classification performance (best value; AUC, 0.928; accuracy rate, 90.83%; sensitivity, 90%; specificity, 95%), especially for the combinations with more than three GCD metrics. Specially, combined the inflow, outflow and int-flow metric received the best classification performance with the highest AUC value, classification accuracy and specificity. Furthermore, the GCD-SVM model received good and stable classification performance across 14 dimension reduced data sets.

Conclusions: The GCD-SVM model could be used for BECTS substate classification, which might have the potential to provide a promising model for IEDs detection. This may help assist clinicians for administer drugs and prognosis evaluation.

Keywords: benign epilepsy with centrotemporal spikes, granger causality density, seizure disorder, support vector machine, classification, prediction

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INTRODUCTION

Recently, functional neuroimaging methods have been widely used to describe functional network changes and the relationships among different brain networks in diseases. The most widely used method is functional connectivity, which involves calculation of the correlation of time courses between one brain region and each of the rest of brain regions. Another method, functional connectivity density, which unbiasedly measures the functional connectivity strength

over the whole brain, could reflect the communication amounts among brain regions (1). However, both methods cannot reflect the directed information flow among different brain regions. Although granger causality analysis fulfills this requirement (2–4), it is based on priori hypotheses of definition of regions of interest. Reliable and accepted methods are needed. A new method, called granger causality density (GCD), aggregates conditional information sets according to community organization using weighted connectivity density map, reflecting the average effect connectivity strength between each voxel and the rest of voxels of whole brain. The proposed GCD analysis could avoid redundancy and overfitting, which makes it suitable for neuroimaging data analysis, and even for high-dimensional and short dataset. Furthermore, this method could provide an opportunity for unbiased searches abnormalities within the entire connectivity matrix without any priori hypotheses, and reflect the directed information flow among different brain networks from voxel levels. However, it has not been applied into any diseases.

Group-based methods are not helpful in inferring specific clinical outcomes for individual patients. Current functional MRI researchers mainly focus on describing group differences between subject classes (knowing the label of each subject), which cannot be classified across different types of subjects. Therefore, for the purpose of individual classification, a desirable method would be one that can compare a single subject's scan to a group. The interictal epileptiform discharges (IEDs) detection remains a challenging problem for simultaneous EEG-fMRI examination because of the absence of long-term data recordings, which are not like the single EEG data recordings, and the insufficient data recordings cannot be used for training and testing (5, 6). Support vector machine (SVM) classifier recognition algorithm is a sensitive neuroimaging bioindicator and efficient feature-selection method. The SVM can train a classifier to classify the label of an unseen subject by taking multiple features into account jointly. There is a growing findings in data-analytic modeling for detection and seizure prediction from intracranial EEG recording (5–8). Seizure prediction has the potential to transform the management of patients with epilepsy by administering preemptive clinical therapies (such as neuromodulation, drugs) and patient warnings (9). The SVM-based model can help us to explore the voxel features or target brain regions with a high contribution to classification or prediction, and has been successfully applied to EEG data (6), but whether the functional MRI data could be used for IEDs prediction or classification left largely unknown. Epilepsy is a disease with brain network disorders (10, 11). Observation of the directed information flow propagation of the IEDs is one of the most important clinical purposes of epilepsy. Benign childhood epilepsy with central-temporal spikes (BECTS), also known as Rolandic epilepsy, is the most common type of idiopathic epilepsy in childhood. BECTS is a highly prevalent idiopathic epilepsy, affecting about 15.7% of epilepsy with 75% starting between 7 and 10 years (12, 13). Children's brains are developmentally immature and the nerve excitabilities are high, and therefore the children are more susceptible to epilepsy due to internal and external factors (13), which makes the BECTS considered to be an ideal model to describe the directed information flow differences in brain networks between IEDs and non-IEDs substates.

Seizure refers to the transformation of normal neurons into abnormally high excitatory and super synchronous electrical activities, resulting in recurrent episodes of transient seizures and brain dysfunction (14, 15), which is thought to be caused by an imbalance between excitation and inhibition (14). It has been suggested that brain excitation/inhibition imbalance is an important mechanism for leading to an overexcited epilepsy-related networks (16–18). The onset of the IEDs may break the excitatory/inhibition balance of neurons, leading to high excitatory and super synchronous electrical activities of epilepsy-related neural networks, and resulting in an imbalance of directed information flow among these networks. Therefore, we hypothesized that the IEDs substate may differ from the non-IEDs substate. Since the spread of epileptic activity is characterized by input and output information flow (19–24), combining the input and output information flow features may reach up the classification performances. To address these hypotheses, the present study is the first to apply the GCD-SVM model to explore a highly sensitive neuroimaging biomarker for BECTS substates classification. Previous studies have found that the GCA method may help patients with epilepsy for substate classification to discriminate between interictal and ictal status (25), which has important guiding significance for the decision-making of intraoperative surgical procedures. The present study may provide a potential biomarker to discriminate the BECTS having or not having the IEDs, and evaluate the possible mechanism of brain damage caused by the differences, which may be helpful to build an imaging model to predict remission and prognosis of BECTS, and have the potential to assist clinicians for clinical administration and monitoring the efficacy of disease-modifying therapies.

MATERIALS AND METHODS

Subjects

Forty-two children with BECTS (21 females, 21 males; mean age, 8.6 ± 1.96 years) underwent simultaneous EEG-fMRI examination. The BECTS were classified into IEDs (11 females, 10 males; 5∼12 years) and non-IEDs (10 females, 11 males; 6∼12 years) substates depending on the presence of central-temporal spikes or not from the EEG-fMRI examination.

Inclusion criteria were as follows: (a) clinical and EEG findings indicative of BECTS, (b) aged between 5 and 17 years, (c) attending school regularly for education, (d) no developmental disabilities, (e) full-scale intelligence quotient of more than 70, and (f) no history of addictions or neurological diseases other than epilepsy. Patients received diagnoses on the basis of all available clinical and EEG data according to the following criteria: (a) International League Against Epilepsy classification (26) and current literature (13); (b) presence of simple partial, often facial, and motor or tonic-clonic seizures during sleep; and (c) spike waves in centrotemporal regions.

Exclusion criteria were (a) pathological focal brain lesions on T1-weighted and T2-weighted fluid-attenuated inversion-recovery MR images, (b) falling asleep during the MRI session

(assessed by means of self-report and occurrence of sleep waves in simultaneously recorded EEG data), (c) head motion with more than 1.5 mm in translation or 1.5° in rotation, (d) age <5 years, (e) any history of significant head trauma or loss of consciousness >30 min, (f) any foreign implants, and (g) any history of neurological disorders or psychiatric illnesses.

This study was approved by Medical Research Ethical Committee of our Hospital in accordance with the Declaration of Helsinki and written informed consent was obtained from all subjects and their guardians.

Simultaneous EEG and Functional MR Imaging Acquisition

During the fMRI data acquisition, the EEG data were continuously recorded with an MR-compatible recording system (Brain Products, Gilching, Germany). A total of 32 channels MR compatible Ag/AgCl electrodes (Brain Product, Munich, Germany) with reference at the electrode FCz and electrocardiography were attached to the scalp and connected to a Brain map amplifier. EEG data sets were processed offline to remove MR and ballistocardiographic artifacts (Brain Vision Analyzer 2.0; Brain Products, Munich, Germany). The EEG data were transmitted via an optic fiber cable from the amplifier placed inside the scanner room to a computer outside. The IEDs were marked on artifact-removed EEG by an experienced electroencephalographer and a neurologist.

Functional and structural imaging data were acquired with a clinical 3-Tesla MRI scanner (SIEMENS Trio Tim, Erlangen, Germany) with a standard eight-channel head coil. A total of 176 high-resolution T1-weighted anatomical slices were acquired with a three-dimensional magnetization prepared rapid-gradient-echo sequence in a sagittal orientation (repetition time = 2,300 ms, echo time = 2.98 ms, thickness = 1.0 mm, matrix = 256 × 256, field of view = 256 mm × 256 mm, flip angle = 9^0). A total of 250 functional images were acquired using a single-shot Gradient-Recalled Echo-Planar Imaging pulse sequence (repetition time = 2,000 ms, echo time = 30 ms, thickness = 4.0 mm, inter-slice gap = 1.2 mm, field of view = 220 mm × 220 mm, matrix = 64 × 64, flip angle 90°, 30 transverse slices). The scan time of the functional data was 8 min and 10 s.

GCD Data Processing

Data Preprocessing

The first 10 time points of the functional images were discarded due to the possible instability of initial MRI signal and inadaptation to the scanning environment. The remaining data were entered into pre-processing by Data Processing & Analysis for Brain Imaging (DPABI 2.1, http://rfmri.org/DPABI) toolbox, including the steps of data format transformation, slice timing, head motion correction, spatial normalization, and spatial smoothed using a Gaussian kernel of 8 × 8 × 8 mm^3 full-width at half-maximum. Participants with more than 1.5 mm maximum translation in x, y, or z directions and/or 1.5° degree of motion rotation were removed.

To limit the impact of micro-movements artifacts, we implemented a "head motion scrubbing regressors" procedure as part of data preprocessing. An estimate of head motion at each time point was calculated as frame-wise displacement (FD) using Friston 24 head motion parameters procedure. The Friston 24 head motion parameter model was used to regress out the head motion effects. Images with FD >0.5 mm were removed and replaced by a linear interpolation. Linear regression was applied to remove other sources of possible spurious covariates, including the global mean signal, white matter, and cerebrospinal fluid signal. After the head-motion correction, the remaining images were spatially normalized to Montreal Neurological Institute (MNI) space and re-sampled at a resolution of 3 × 3 × 3 mm^3. The time series for each voxel were further linearly detrended and temporally band-pass filtered (0.01–0.1 Hz).

Voxel-Based GCD Analysis

It is based on the idea that, given two time series of two voxels of x and y, if knowing the past of y is useful for predicting the future of x, then y must have a causal influence on x. The auto-regression model of the granger causality influence between the two time series of x and y variables were defined as follows:

$$y_t = a_0 + a_1 y_{t-1} + a_2 y_{t-2} + \ldots + a_m y_{t-m} + e_1;$$
$$y_t = a_0 + a_1 y_{t-1} + a_2 y_{t-2} + \ldots + a_m y_{t-m} + b_d x_{t-d} + \ldots + b_f x_{t-f} + e_2;$$

The lagged value of d represents the earliest one in the significant time point of the *x(n)* variable, and *f* represents the closest one. Accordingly, the lagged value of m represents the earliest one of the *y(n)* variable.

The e_1 represents the estimate residual of the autoregressive models of the time series of $x(n)$, and the e_2 represents the estimate residual of $y(n)$ after adding the time series of $x(n)$. Similarly, the definition of the variable of h_1 and h_2.

$$\text{Generally, residual } e_{(t)}: |e_1| >= |e_2|;$$

If x has a causal influence on y, the influence is defined as: $F_{x->y} = \ln(|e_1|/|e_2|)$;

Similarly, the $F_{y->x}$ means y has a causal influence on x, and is defined as: $F_{y\to x} = \ln(|h_1|/|h_2|)$.

The GCD algorithm has been improved based on the granger causality analysis algorithm. The GCD algorithm takes any one voxel of the brain voxels to define its time series as x, and the time series of the rest voxels are defined as y. Then, the linear direct influence of x on y ($F_{x->y}$) and the linear direct influence of y on x ($F_{y->x}$) were calculated voxel by voxel across the whole brain.

The $F_{x->y}$ value means output information flow from the targeted voxel (x) to whole brain voxels (y), and the $F_{y->x}$ means input information flow to the targeted voxel (x) from rest whole brain voxels (y). For the whole brain voxels, a series of $F_{x->y}$ and $F_{y->x}$ values are achieved, which reflects the output and input causal effective connectivity, respectively.

The density map of output causal influence of x variable on y variable is defined by the summation of the $F_{x->y}$ values (the threshold was defined as $p < 0.05$), namely outflow connectivity. Similar definition of the density map of input influence of y variable on x variable ($F_{y->x}$), namely inflow connectivity.

Considering that the graph GCD is directed, all topological properties are calculated on four metrics, including inflow, outflow, total-flow (inflow + outflow) and int-flow (inflow − outflow) connectivity.

The total-flow connectivity is defined as the combined effects of inflow and outflow connectivity. The int-flow connectivity is defined as the differences between the inflow connectivity and the outflow connectivity ($F_{y->x} - F_{x->y}$), which identify nodes that have distinctive causal effects on network dynamics. Specifically, a node with a relatively high negative int-flow connectivity is regarded as more causal sources (driven effect), whereas a node with a relatively high positive int-flow connectivity is more causal targets (target effect).

Voxel-Based Analysis for Each GCD Metric

The LIBSVM toolbox (http://www.csie.ntu.edu.tw/~cjlin/libsvm/) was used to perform the classifications. Principal component analysis was used for dimension reduction. Finally, a linear SVM was used for images training and testing (**Figure 1**). Each image is treated as a point in a high dimensional space (space dimension = number of voxels in the image). In the present study, we classified the images into two classes (here, IEDs and non-IEDs substates) to find a potential separating hyperplane or decision boundary. The GCD images were entered into the classification procedure which consists of training phase and testing phase. A leave-one-out cross-validation test was used to evaluate the classification accuracy of the SVM classifier. The clusters with higher than 70% classification accuracy and contiguous voxels of more than 5 voxels were considered as accuracies. The resulting spatial map at each voxel with higher than 70% classification accuracy was used to find brain regions that exhibited differences between-groups.

Classifier Performance of Combinations With Multiple GCD Metrics

The classification accuracy of the combinations with more than two GCD metrics were calculated using the linear SVM classifier. Multivariate pattern analysis (MVPA) technique was used to extract features, as the input of pattern analysis. The classifier is trained by providing examples of the form <x, c>, where x represents a spatial pattern (number of voxels in the image; here is pre-selected features of GCD images) and c represents the class label (here, IEDs and non-IEDs substates). To identify the set of voxels with highest discriminative power, SVM recursive feature elimination (SVM-RFE) was applied (27). The SVM-RFE classifier is repeatedly trained, and at each iteration, a feature-ranking criterion is used to remove a subset of the least informative features. Once the decision function is learned from the training data, it can be used to classify the class of a new test sample. The parameter (C) controls the trade-off between zero training errors and misclassifications, which was fixed at C = 1 for all cases (default value).

The performance of the classifier was validated by the commonly used 5-fold cross validation approach, which tested the robustness of the classification results. Subsequently, the class assignment of the test subjects was calculated during the test phase. Permutation test can be used to evaluate the probability of obtaining specificity and sensitivity values higher than the ones obtained during the cross-validation procedure by chance. We permuted the labels 100 times, each time randomly assigning the two labels to each image. The whole nested cross-validation process was repeated 5 times, and the final result was the average accuracy of 5 repetitions of the 5-fold cross-validation procedure. Classifier performance was evaluated using basic receiver operating characteristic (ROC) curve. The area under curve (AUC), sensitivity and specificity of the classifier were quantified.

STATISTICAL ANALYSES

Comparisons of demographic factors between the two BECTS substates were performed using two-sample *t*-tests. Chi-square (χ^2) test was used for categorical data. Statistical analysis was performed using IBM SPSS 21.0 version. Data are presented as mean ± standard deviation. All the quoted results are two-tailed values, and $p < 0.05$ was considered as statistically significant.

RESULTS

Sample Characteristics

There were no significant differences between the two BECTS substates in mean age ($t = -1.743$, $p = 0.089$), sex ($\chi^2 = 0.095$, $p = 0.758$) and epilepsy duration ($t = -1.388$, $p = 0.174$). The number of IEDs was (29.71 ± 25.31; range, 4∼92) times in the IEDs substate (**Table 1**).

Voxel-Based Analysis for Each GCD Metric

The Rolandic area, caudate, dorsal attention network, visual cortex, language networks, and cerebellum showed discriminative effect on distinguishing the IEDs substate from the non-IEDs substate (**Figures 2A–D**, **Table 2**). Specifically, the discriminative effect of the Rolandic area was only found in the GCD metric of outflow connectivity (**Figure 2B**).

Classification Performance

Across the reduced data sets of the evaluated GCD metrics, the combinations with more than three GCD metrics received good classification performances (**Figures 3A–D**, **Table 3**). The combination with total-flow, inflow and int-flow connectivity, and the combination with total-flow, outflow and int-flow connectivity did not receive good classification performances (**Figures 3A,B**). However, the combination with inflow, outflow and int-flow connectivity significantly reached up the classification accuracy and received the best classification performance with the highest accuracy rate (90.83%) and specificity (95%), as well as extremely high AUC value (0.928) and sensitivity (86%) (**Figure 3C**). Subsequently, the GCD metric of total-flow connectivity entered into the classification and the sensitivity could reach up to 90% (**Figure 3D**), but the AUC value, accuracy rate and specificity decreased (**Table 3**). Furthermore, when the functional connectivity density as the input of SVM, poor classification performance was found (sensitivity, 86%; specificity, 48%; **Supplementary Figure 1**).

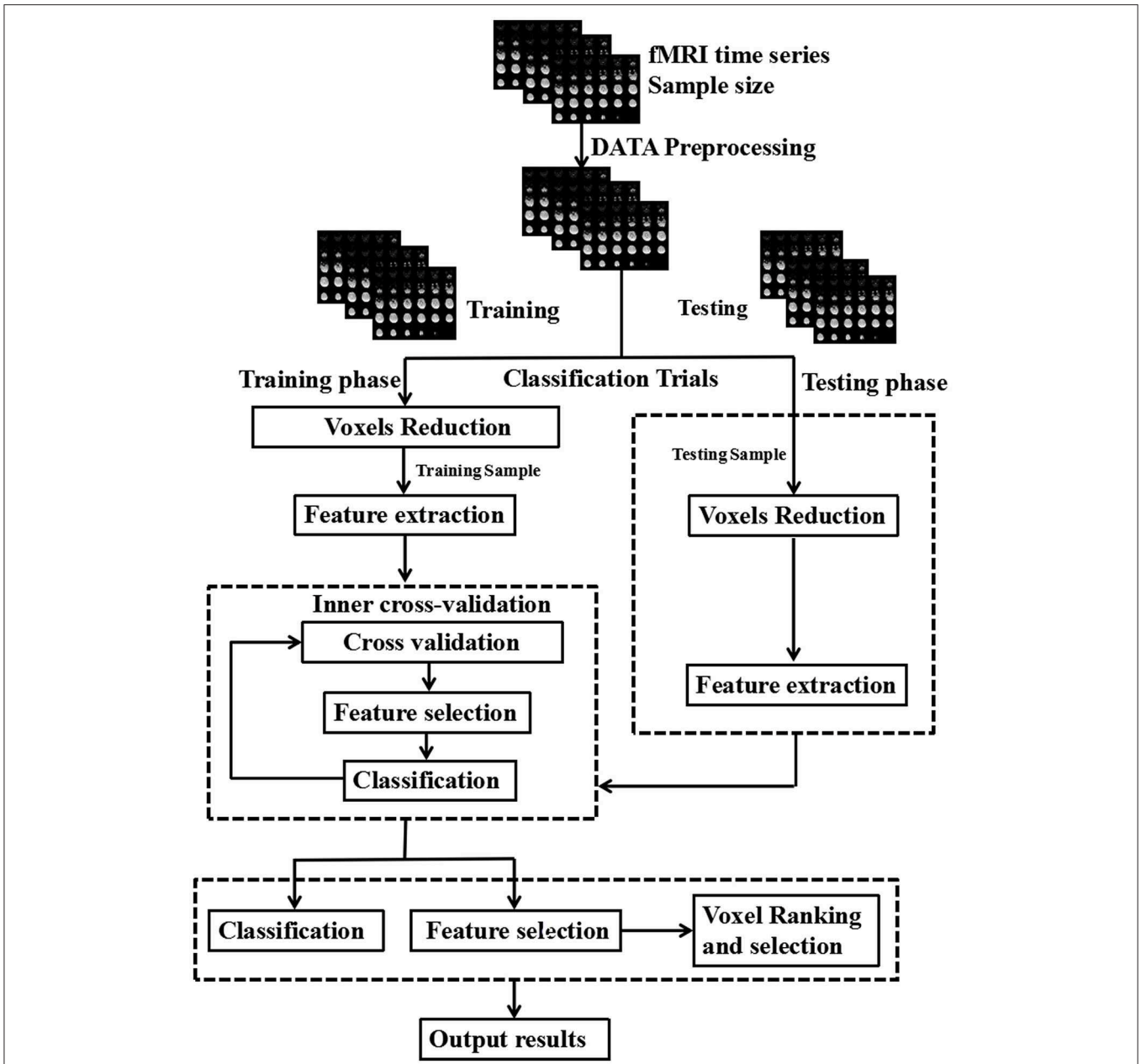

FIGURE 1 | Schematic diagram overview of machine learning classification framework. The inner cross-validation was used to determine the optimal number of features and the outer cross-validation was employed to estimate the classification performance.

TABLE 1 | Characteristics of BECTS.

	IEDs	Non-IEDs	*t*-value	*p*-value
Mean age, year	8.14 ± 1.88	9.19 ± 2.02	−1.743	0.089
Sex (male, female)	21 (10, 11)	21 (11, 10)	0.095#	0.758
Epilepsy duration, month	16.12 ± 16.16	24.66 ± 23.1	−1.388	0.174
Number of IEDs, time	29.71 ± 25.31	N/A	N/A	N/A

Data are mean ± standard deviation values; #chi-square value; N/A, Not applicable. BECTS, benign childhood epilepsy with central-temporal spikes; IEDs, interictal epileptiform discharges; N/A, not applicable.

Classification Capacity

Since the combination with inflow, outflow and int-flow connectivity received the best classification performance, we therefore calculated the classification performance of this combination at each reduced data set to evaluate its stability. Here, we reported fourteen reduced data sets-50, 250, 500, 750, 1,000, 1,500, 2,000, 2,500, 3,000, 3,500, 4,000, 4,500, 4,750, and 5,000 voxels. This combination received good and stable classification performance when the dimension reduced data sets were more than 750 voxels (**Figure 4**).

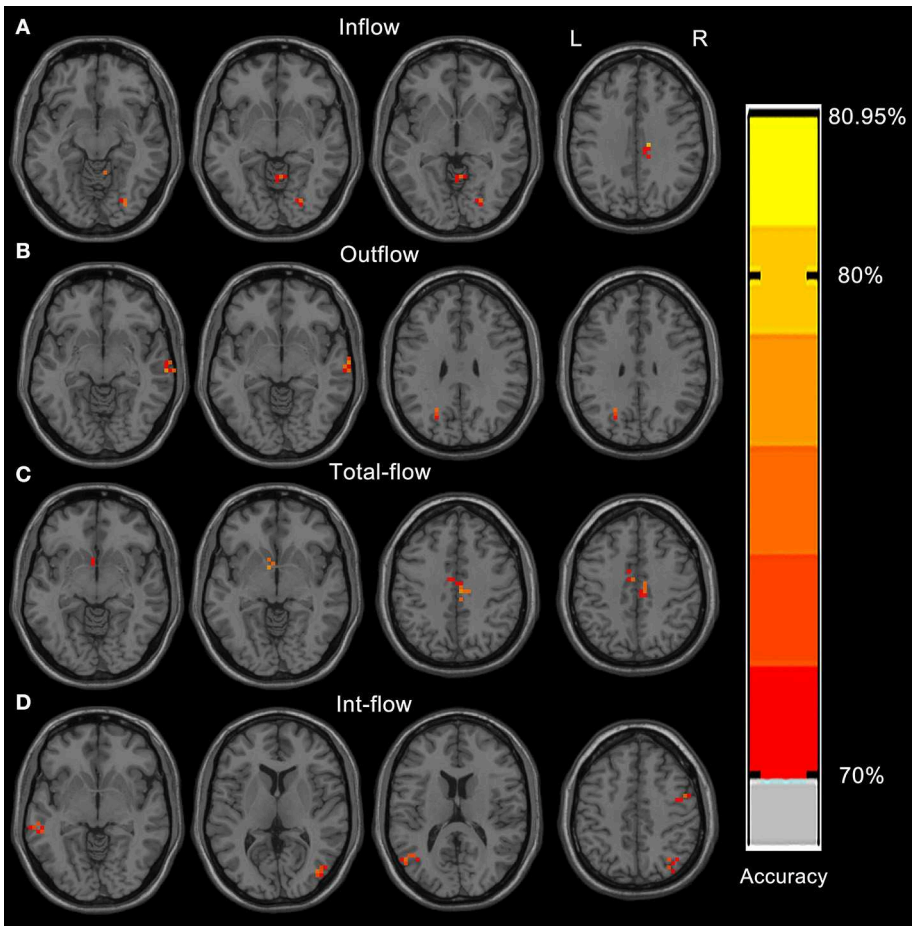

FIGURE 2 | Resulting spatial maps of accuracy for discriminating between IEDs and non-IEDs substates for each of the four GCD metrics. These clusters were identified by setting the threshold of accuracy higher than 70%. Resulting spatial brain areas of accuracy for discriminating between IEDs and non-IEDs substates for Inflow **(A)**, outflow **(B)**, total-flow **(C)**, and int-flow **(D)** connectivity.

TABLE 2 | Most important brain regions discriminating between IEDs and non-IEDs substates.

Conditions	Brain regions of peak coordinates	R/L	BA	Peak accuracy (%)	MNI coordinates		
					X	Y	Z
Inflow	Middle occipital gyrus	R	18	78.57	32	−84	−16
Inflow	Cerebellum anterior lobe	R	N/A	73.81	8	−52	−12
Inflow	Cingulate gyrus	R	23, 24	78.57	12	−28	32
Outflow	Middle temporal gyrus	R	21	78.57	64	−20	−8
Outflow	Precuneus	L	7, 19	76.19	−24	−60	32
Total-flow	Caudate head	L	N/A	76.19	−8	4	−4
Total-flow	Cingulate gyrus	L	23, 24	80.95	−8	−12	36
Int-flow	Cerebellum posterior lobe	L	N/A	78.57	−20	−40	−52
Int-flow	Superior temporal gyrus	R	38	80.95	24	12	−40
Int-flow	Middle temporal gyrus	L	21	80.95	−64	−32	−8
Int-flow	Middle occipital gyrus	R	19	76.19	40	−76	8
Int-flow	Middle temporal gyrus	L	39	78.57	−52	−68	20
Int-flow	Precuneus	L	7, 19	73.81	−28	−64	32
Int-flow	Precentral gyrus	R	6	76.19	44	0	40
Int-flow	Superior parietal lobule	R	7	73.81	32	−72	48

These clusters were identified by setting the threshold of accuracy higher than 70%. IEDs, interictal epileptiform discharges; N/A, not applicable R, right; L, left; BA, Brodmann's area; MNI, Montreal Neurological Institute.

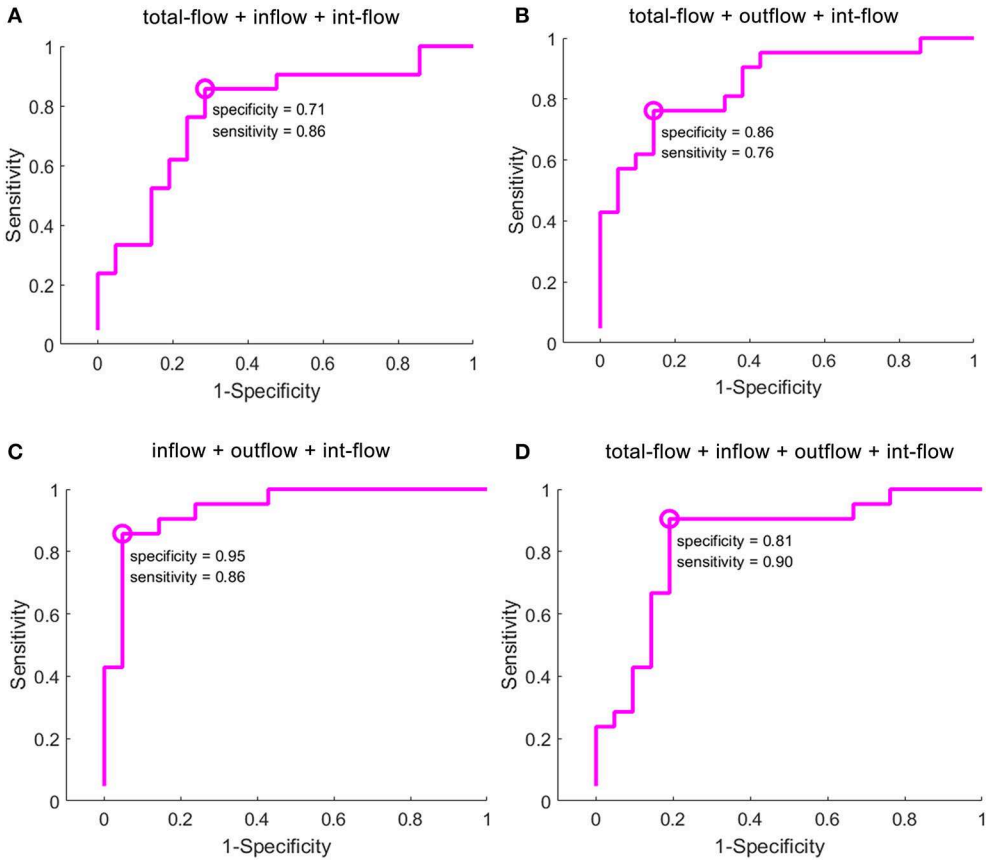

FIGURE 3 | Classification results of GCD maps using selection of the optimal feature dimensions of the SVM-RFE method. GCD, granger causality density; SVM, support vector machine; RFE, recursive feature elimination. The classification accuracy of the combination with total-flow, inflow and int-flow connectivity **(A)**, the combination with total-flow, outflow and int-flow connectivity **(B)**, the combination with inflow, outflow and int-flow connectivity **(C)**, and the combination with total-flow, inflow, outflow and int-flow connectivity **(D)**.

DISCUSSION

BECTS is often associated with clinical syndrome-related specific functional brain impairment (19–24, 28), these impairments not only occur during IEDs substate (29–33), but also non-IEDs substate (33). However, whether the IEDs and non-IEDs substates share the same mechanisms of brain functional impairment remains exploration. The IEDs cannot always be identified by clinical EEG recordings. Thus, the BECTS substate classification has important clinical significance, which may have the potential to early predict IEDs, and assist clinicians for clinical administration. Ji et al. found that both BECTS substates showed consistently abnormal global topology in their functional networks (i.e., decreased global efficiency) relative to that of control subjects, but no differences between the two substates (34). Our study is the first to apply the GCD-SVM model to find a promising model for BECTS substate classification. Our data indicated that the GCD-SVM model achieved extremely high classification performances. Accordingly, although functional connectivity density has been used to characterize abnormal functional connectivity changes in both BECTS substates (35), in the present study, poor performance was observed when the functional connectivity density as the input of the SVM classifier. These findings may suggest that the GCD-SVM model may be served as a sensitive neuroimaging biomarker for BECTS substate classification. In general, the more useful voxel information was entered into the classification procedure, the better the classification performance was. This may explain that: (a) the combinations with more than three GCD metrics could reach up the classification performances relative to single GCD metric; and (b) the classification performance was increased as more numbers of input voxel features ($\geq$750 voxels) were entered into the classification procedure. Specially, some features are uninformative, irrelevant or redundant for classification (36, 37), which may decrease the classification performance. This may explain why the classification performance of the combination with four GCD metrics was decreased relative to the best classification combination. Taken together, our data support our hypothesis.

Machine learning and pattern recognition techniques are being increasingly used in functional MRI data analysis. These methods allow detecting subtle, non-strictly localized effects that

may remain invisible to the conventional analysis with univariate statistics (38, 39). In contrast to the conventional analysis, the machine learning technique takes the full spatial pattern of brain activity into account, measures many locations simultaneously, and exploits the inherent multivariate nature of functional MRI data. The use of machine learning algorithm has been applied to discriminate between the newborns with seizures secondary to hypoxic ischemic encephalopathy and those newborns without seizures (40). Furthermore, non-invasive EEG has been used to identify the presence of seizures in pediatric subjects (41). It has been reported that diffusion tensor imaging based SVM classification method has diagnostic advantage over other T1 based classification in temporal lobe epilepsy (42), and appears promising for distinguishing the children with active epilepsy from those with remitted epilepsy or controls with high sensitivity and specificity (43). Our data indicate that the GCD analysis also can be served as a biomarker for BECTS substate classification. In the present study, the combinations with input and output information flow features (inflow + outflow + int-flow connectivity) received the best classification accuracy of 90.83%, which is close to the EEG classification accuracy (44).

There is a close relationship between the hemodynamic changes and brain neural activity. Since the hemoglobin is an oxygen carrier, the neuronal firings may increase the concentration level of local blood oxygen and oxyhemoglobin (antimagnetic), and decrease the deoxygenated hemoglobin (paramagnetic), and therefore change the blood oxygen level dependence (BOLD) signal of regional brain area. This may change the brain excitatory/inhibition balance. It has been reported that the intrinsic spontaneous BOLD signal and the task-induced functional BOLD signal are linearly superimposed (45). This may help us understand why the proposed GCD method (intrinsic spontaneous BOLD signal) has the potential to reflect the IEDs-induced functional BOLD signal. Relative to the non-IEDs substate, the IEDs-related activation may increase the input and/or output information flow connectivity of the epilepsy-related brain networks, and change the brain network connectivity architecture (edge and/or directions). Consistently, Zhu et al. found that the mapped features of the resting-state functional MRI could distinguish the two BECTS substates (46). These findings may support the high classification performance of the GCD-SVM model in distinguishing the two BECTS substates. The brain regions of the Rolandic area, caudate,

TABLE 3 | Classification performances using combinations of GCD metrics.

Classification indicator	AUC value	Accuracy (%)	Sensitivity (%)	Specificity (%)
Total-flow + inflow	0.703	66.39	62	76
Total-flow + outflow	0.634	66.47	74.67	56
Total-flow + int-flow	0.74	73.61	67	81
Inflow + outflow	0.815	78.61	76	81
Inflow + int-flow	0.9325	75.83	67	95
Outflow+ int-flow	0.8975	83.61	76	90
Total-flow + inflow + outflow	0.675	71.39	62	81
Total-flow + inflow + int-flow	0.758	78.61	86	71
Total-flow + outflow+ int-flow	0.8575	81.11	76	86
Inflow + outflow + int-flow	0.928	90.83	86	95
Total-flow + inflow + outflow + int-flow	0.8175	86.11	90	81

GCD, granger causality density; IEDs, interictal epileptiform discharges; AUC, area under curve.

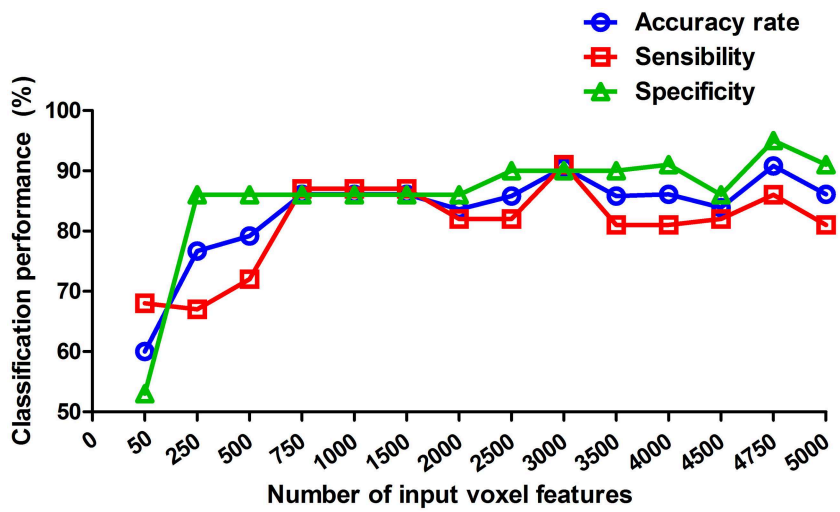

FIGURE 4 | Classification performance at each of reduced data sets. These values reported are of the weighted average of the 5 cross-validation. The reduced data sets were selected by the relief feature selection algorithm. Here, we reported fourteen reduced data sets-50, 250, 500, 750, 1,000, 1,500, 2,000, 2,500, 3,000, 3,500, 4,000, 4,500, 4,750, and 5,000 voxels.

dorsal attention network, visual cortex, language networks, and cerebellum, exhibiting high discriminating value, may be the neurobiological base of the high classification accuracy between the two BECTS substates. These findings suggest that the proposed GCD-SVM model may be helpful for BECTS substate classification by exploiting multitype and multidimensional voxel features with discriminating value.

CONCLUSIONS

To summarize, the proposed GCD-SVM model could be served as a potential neuroimaging biomarker to discriminate between the two BECTS substates, which may expand our understanding of the neurobiological mechanism of BECTS. The performance of the GCD-SVM model has the potential to assist clinicians for early diagnosis, clinical administration, and monitoring the efficacy of disease-modifying therapies. This may promote the clinical management of BECTS.

The strengths of our study are the performance of innovative GCD–SVM method and the invaluable data of the IEDs substate. However, there are several potential limitations that should be noted. First, varying quality of preictal data for different subjects may obtain varying prediction performances. Therefore, small sample size and single center data limited its generality. A larger number of sample sizes and multiple center studies are necessary to corroborate our findings. Second, the small number of IEDs may limit the classification performance. The IEDs substate with more numbers of IEDs may increase the classification accuracy. Third, different types and the density (i.e., the IED number for window length) of the IEDs were not addressed in the present study. Fourth, traditionally, BOLD signal in the white matter (WM) was regarded as noise and was regressed out in the preprocessing step in our study. However, recent research showed that the WM signal was also biologically meaningful. It has structural basis and could be modulated by cognitive state (47). In neurological disease, such as PD, it is of great significance in clinical application (48). In this study, we regressed out the WM signal in the preprocessing step because of unclear biological mechanism. Fifth, the data of non-IEDs and IEDs substates were came from different subjects. However, 8 min MRI scan time are not enough to obtain enough data to divide the data of one subject into non-IEDs and IEDs substates. Therefore, it is equally important to classify the non-IEDs and IEDs substates from different subjects for MRI data. Sixth, twenty BECTS (10 IEDs, 10 non-IEDs) were not first-time visitors and had taken medication before. In the present study, the medication effects were not taken into account.

DATA AVAILABILITY STATEMENT

All datasets analyzed for this study can be found in the article/**Supplementary Material**.

AUTHOR CONTRIBUTIONS

XJ-D, ZZ, and GL conceived and designed the whole experiment. XJ-D, QZ, and YX collected the data. XJ-D and QX take responsibility for the integrity of the data, the accuracy of the data analysis, and the statistical data analysis. XJ-D wrote the main manuscript text and under took the critical interpretation of the data. All authors contributed to the final version of the paper and have read, as well as approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.01201/full#supplementary-material

Supplementary Figure 1 | Classification results of functional connectivity density.

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

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Language Dominance in Patients With Malformations of Cortical Development and Epilepsy

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Background: Language function may be reorganized in patients with malformations of cortical development (MCD). This prospective cohort study aimed in assessing language dominance in a large group of patients with MCD and epilepsy using functional MRI (fMRI).

Methods: Sixty-eight patients (40 women) aged 10–73 years (median, 28.0; interquartile range, 19) with MCD and epilepsy underwent 1.5 T MRI and fMRI (word generation task). Single-subject image analysis was performed with statistical parametric mapping (SPM12). Language lateralization indices (LIs) were defined for statistically significantly activated voxels in Broca's and Wernicke's areas using the formula: $LI = (V_L - V_R)/(V_L + V_R) \times 100$, where V_L and V_R were sets of activated voxels on the left and on the right, respectively. Language laterality was considered typical if LI was between +20 and +100 or atypical if LI was between +19 and −100.

Results: fMRI signal was elicited in 55 of 68 (81%) patients. In 18 of 55 (33%) patients, language dominance was typical, and in 37 of 55 (67%) patients, atypical (in 68%, right hemispheric; in 32%, bilateral). Language dominance was not influenced by handedness, electroclinical, and imaging features.

Conclusions: In this prospective study on a large group of patients with MCD and epilepsy, about two-thirds had atypical language dominance. These results may contribute to assessing risks of postsurgical language deficits and could assist in planning of "cortical mapping" with intracranial electrodes in patients who undergo presurgical assessment.

Keywords: malformations of cortical development, epilepsy, language, functional MRI, epilepsy surgery

INTRODUCTION

Malformations of cortical development (MCD) occur when the normal process of cerebral cortical development including neuronal proliferation, migration, and organization is disrupted (1). The majority of children and adults with MCD have drug-resistant seizures, and epilepsy surgery may render up to 75% of them seizure free (2–6). MCD, however, are often localized in functionally eloquent cortical areas conveying sensory-motor, language, or other higher cognitive functions. Therefore, determining a cortical representation of these functions in the framework of presurgical assessment is necessary to avoid postsurgical deficits. Cortical mapping using intracranial electrodes is still considered the "gold standard" for identifying eloquent cortical areas (7). Functional MRI (fMRI) represents a noninvasive additional tool for lateralizing cortical functions such as language and memory in patients with epilepsy (8). Presurgical fMRI may predict postsurgical language and memory deficits in patients with temporal lobe epilepsy (8). fMRI and electrophysiological studies suggest that cortical functions may be reorganized in patients with MCD. These studies, however, have been performed on relatively small samples of patients with MCD (9–17).

In this prospective cohort study, our goal was to assess language dominance in a large group of patients with MCD and epilepsy using fMRI. A further aim was to perform a correlation analysis between language lateralization and various electroclinical and imaging features.

METHODS

Participants

Seventy-two patients were recruited at the Departments of Neurology and Pediatrics, Medical University of Innsbruck, Austria.

Only patients with epilepsy and an MRI diagnosis of MCD, who had no seizures for at least 48 h before the fMRI study, were included in the study.

Eventually, 68 (40 women) out of 72 recruited patients comprised the study sample, as in four cases, fMRI data could not be analyzed due to massive motion artifacts exceeding 3 mm for translational and 3° for rotational movements.

The median age of patients at the time of fMRI assessment was 28.0 years [interquartile range (IQR) = 19]. Median verbal intelligence quotient (IQ) was 97.0 (IQR = 22). Patients with a verbal IQ lower than 70 were classified as learning disabled (16 patients, 23%). However, all participants were able to perform the tasks. None of patients had aphasia or dysphasia. All underwent prescan training, and the performance of the task was monitored during scanning, as the patients were instructed to whisper the words, which they had to generate. All patients included in the study were compliant and generated the words during the task.

All patients underwent neurological examination and routine electroencephalogram (EEG) recordings using the 10–20 system. EEG video monitoring (EMU) was performed in 65 of 72 patients (90%). The epilepsy side (left, right or bilateral) was determined based on either EMU data or routine EEG and reported seizure semiology. Epileptiform discharges were assessed on interictal routine EEG.

Seizure types and epilepsy syndromes were diagnosed according to the classification of the International League Against Epilepsy (18, 19). Ten patients underwent epilepsy surgery after fMRI study.

We dichotomized our cohort into two groups with regard to the age of seizure onset: those with the onset of seizures at the age of 6 or earlier were categorized as patients with "early onset;" those with the seizure onset later than the age of 6 were categorized as those with "late onset."

Structural MRI

Images were acquired on a 1.5-T MR scanner (Siemens Sonata, Erlangen, Germany) using a Siemens-issued eight-channel head coil. All patients underwent at least two high-resolution MRI using an MRI protocol of our institution for imaging of patients with epilepsy. MRI sequences included T1-weighted spin echo and gradient echo three-dimensional multiplanar reconstruction images with and without intravenous contrast application, axial and coronal T2-weighted turbo spin echo, axial and coronal fluid-attenuated inversion recovery, and diffusion weighted sequences. The thickness of 2 mm was chosen for coronal T2-weighted and fluid-attenuated inversion recovery slices, which were acquired at 90° perpendicular to the long axis of hippocampus. T1-weighted anatomic scans were utilized for each subject as reference in single subject analysis with a spatial resolution of $1 \times 1 \times 1$ mm^3.

Functional MRI

fMRI was acquired using T2*-weighted sequences of echo planar imaging with the following parameters: repetition time = 4 s, echo time = 60 ms, flip angle (α) = 90°, field of view = 250, 25 slices parallel to intercommisural (AC–PC) plane, matrix size = 64×64, thickness = 5 mm, distance factor = 0.25, 98 repetitions, giving a voxel size of $3.91 \times 3.91 \times 6.25$ mm^3 covering the whole brain.

fMRI Task Design

The "word generation" language task was performed: The patients were asked to first generate words belonging to the category "Animals" (active condition 1), then to the category "Tools" (active condition 2), and to rest (resting condition) after each active condition. The task consisted of nine blocks. Every block consisted of active and rest conditions; each condition lasted for 15 s. The instructions were given through earphones.

A series of 98 sequential whole-brain echo planar imaging T2*-weighted scans was acquired, consisting of five volumes during active condition ($A_{1,2}$) alternating with five volumes during rest condition (R) yielding a block order of $RA_1RA_2RA_1RA_2RA_1RA_2RA_1RA_2RA_1R$. Patients underwent a short training immediately before the study. Subjects were asked to whisper the words to monitor the task performance and decrease motion artifacts that could be induced by speaking loudly. All participants were native German speakers.

fMRI Data Analysis

Image analysis for revealing significant brain activation based on changes in blood oxygen level dependent (BOLD) signal (20) was performed on each subject's fMRI data using statistical parametric mapping (SPM12, Wellcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) under MATLAB 7.4 (MathWorks Inc., Natick, MA, USA; http://www.mathworks.com/). The functional data sets of each patient were motion corrected after discarding the first three volumes to allow signal stabilization. Eventually, 95 volumes per series were utilized for data analysis. Anatomical high-resolution images were coregistered to a mean functional image of each subject. Images were not normalized spatially since the majority of patients had MCD, which distorted brain anatomy. Finally, the functional images were spatially smoothed using an 8-mm full width at half maximum Gaussian kernel. A statistical analysis on the basis of the general linear model was conducted as implemented in SPM12. The delta function of the block onsets was convolved with the canonical form of the hemodynamic response function for a duration corresponding to the block length, to generate the model time courses for the three conditions in each task. A high-pass filter (1/288 Hz) was used to remove low-frequency drifts. No global normalization was used. SPM maps of the contrast of voxels with increased intensity during "active" blocks in relation to the resting state ("rest") in the whole brain were computed. Clusters of activation were reported as significant when they surpassed an initial threshold of $p < 0.001$ (uncorrected) and had a family-wise error (FWE) corrected $p < 0.05$ on cluster level.

Language Lateralization

Laterality index (LI) was based on two regions of interest (ROI): (i) a frontal inferior ROI—Broca's area including left inferior frontal gyrus with orbital, triangular, and opercular parts as well as dorsolateral prefrontal cortex (parts of Brodmann's areas 44, 45, 46, and 47), and (ii) a temporo-parietal ROI—Wernicke's area with posterior aspect of superior temporal gyrus, supramarginal, and angular gyri (parts of Brodmann's areas 22, 39, and 40). ROI masks were obtained from Wake Forest University PickAtlas toolbox (21, 22). LIs were defined using the formula: $LI = (V_L - V_R)/(V_L + V_R) \times 100$, where V_L is the set of activated voxels on the left and V_R is the set of activated voxels on the right. LI values between +19 and −19 were classified as bilateral activation; values between +20 and +100 as lateralization to the left hemisphere and values between −20 and −100 as lateralization to the right hemisphere. ROI LI values were calculated using the LI toolbox for SPM12 with bootstrapping, and weighted mean LI values were utilized for the analysis (23). Patients were divided into two groups with regard to their language laterality profile: (i) those with *typical* language laterality (with left dominant hemisphere): LI between +20 and +100; (ii) those with *atypical* language laterality (with right-hemispheric or bilateral language dominance as determined by registered BOLD signal): LI between +19 and −100.

Handedness

Handedness was assessed by Edinburgh Handedness Inventory (EHI) (24). EHI quotient was calculated by the following equation: $EHI\text{-}Q = R - L/R + L \times 100$, where R is a score for the right hand and L is a score for the left hand. In our institution, patients with the score between +60 and +100 are considered right-handed, those with the score between −60 and −100 are regarded left-handed, and scores between −59 and +59 indicate ambidexterity.

Verbal IQ

Verbal IQ was assessed by a multiple-choice vocabulary test (25).

The following electroclinical variables were analyzed in relation to the fMRI activation patterns: age at the time of fMRI study, sex, MCD location and laterality, handedness, epilepsy syndrome, laterality of seizure foci, EEG abnormalities, occurrence of learning disability, motor deficit, lifetime history of status epilepticus, age at seizure onset, epilepsy duration, seizure outcome at the time of fMRI, and seizure frequency during the first year of epilepsy.

MRI Diagnosis of MCD

MCD were diagnosed based on MRI and were classified according to the nomenclature proposed by Barkovich et al. (1). MCD were divided into three categories based on the aforementioned nomenclature: category I—MCD due to abnormal neuronal proliferation [e.g., tuberous sclerosis, focal cortical dysplasia (FCD type II) with balloon cells]; category II—MCD due to abnormal neuronal migration [e.g., periventricular nodular heterotopia (PNH)]; category III—MCDs due to abnormal late migration/cortical organization [e.g., polymicrogyria, FCD without balloon cells (FCD type I)]. Dysembryoplastic neuroepithelial tumor and ganglioglioma were also included in the sample, as they are incorporated in the classification of MCD (1).

Statistical Analysis

Categorical data were analyzed by means of Fisher's exact probability test (two-tailed) for 2 × 2 tables. Either Freeman–Halton extension of Fisher's exact probability test or chi-square test with Yates correction (if all expected cell frequencies were ≥5) was used for tables larger than 2 × 2. In case of significant differences, paired-wise comparisons were carried out by means of 2 × 2 Fisher's exact probability test or 2 × 2 chi-square test with Yates correction. Noncategorical data (e.g., age at seizure onset) were first analyzed by Kruskal–Wallis test. Two-by-two comparisons were performed by means of Mann–Whitney test. Significance was set at $\alpha \leq 0.05$. There were no missing data in the entire analysis.

RESULTS

Statistically significant fMRI activation ($p < 0.05$, FWE corrected at cluster level) in assessed brain regions (Broca's and Wernicke's areas) were registered in 55 of 68 (81%) patients. Task related statistically significant BOLD signal changes were also registered bilaterally in perirolandic areas as well as in the supplementary motor areas in 60% of cases

TABLE 1 | Electroclinical and imaging features of malformations of cortical development and epilepsy.

MCD ($n = 68$)	
Category 1 (abnormal neuronal proliferation)	24 (35%) FCD II ($n = 11$), TS ($n = 7$), GG ($n = 3$), DNET ($n = 2$), HMGE ($n = 1$)
Category 2 (abnormal neuronal migration)	19 (28%) PNH ($n = 16$), SBH ($n = 3$)
Category 3 (abnormal neuronal organization)	25 (37%) PMG ($n = 18$), FCD I ($n = 7$)
Unilateral	39 (57%)
Bilateral	29 (43%)
Temporal	28 (41%)
Frontal	15 (22%)
Multifocal/along lateral ventricles	14 (21%)
Perisylvian	7 (10%)
Frontoparietal	2 (3%)
Frontotemporal	1 (1.5%)
Insular	1 (1.5%)
Epilepsy	
Age at seizure onset, median (interquartile range, IQR) years	12 (15)
Epilepsy duration, median (IQR) years	13 (27)
Medically intractable seizures	47 (69%)
Temporal lobe epilepsy	36 (53%)
Extra- temporal lobe epilepsy	32 (47%)
Febrile seizures	2 (3%)
Status epilepticus	8 (12%)
Diffuse slowing on EEG	26 (38%)
Focal slowing on EEG	53 (78%)
Epileptiform discharges on EEG	35 (51%)
Seizure frequency, 1st year of epilepsy	Daily—8 (12%); weekly—11 (16%); monthly—28 (41%); yearly—21 (31%)

MCD, malformations of cortical development; FCD II, focal cortical dysplasia type II; TS, tuberous sclerosis; GG, ganglioglioma; DNET, dysembryoplastic neuroepithelial tumor; HMGE, hemimegalencephaly; PNH, periventricular nodular heterotopia; SBH, subcortical band heterotopia; PMG, polymicrogyria; FCD I, focal cortical dysplasia type I; IQR, interquartile range.

(this may be attributed to the fact that the patients had to whisper the words). Activated clusters were also found in mesial (55%) and basal (47%) temporal areas, as well as in cerebellum (63%). Clinical and MCD data are detailed in **Table 1**.

It should be noted that language laterality was determined based only on clusters including Broca's and Wernicke's areas. The median LI was −14 (IQR = 67); it varied over a range from a strong left (+77) to strong right (−72) hemisphere dominance. Using dominance categorical classification, in 18 of 55 (33%) patients, language lateralization was typical (LI between +20 and +100), and 37 of 55 (67%) patients had atypical language lateralization (LI between +19 and −100) (**Table S1**, **Figures 1**, **2**). Among patients with atypical language dominance, 12 of 37 (32%) patients had bilateral symmetrical language representation and 25 of 37 (68%) had right-hemispheric dominance (**Table S1**).

In right-handed patients ($n = 46$), the median LI was −15.5 (IQR = 70); 16 of 46 (35%) patients had typical and 30 of 46 (65%) had atypical language dominance. In left-handed patients, the median LI was +1.65 (IQR = 63); two of eight (25%) patients had typical and six of eight (75%) had atypical language representation. The difference between right- and left-handed patients with regard to atypical language dominance was not statistically significant ($p = 0.460$, Fisher's exact test) (**Table 2**). There was only one ambidextrous patient who had right-hemispheric language dominance.

Atypical language lateralization was more common in patients with left- (12/16, 75%) and bilateral (17/24, 71%) MCD compared to those with MCD affecting the right hemisphere (8/15, 53%). The difference, however, did not reach a statistical significance ($p = 0.443$, Fisher's exact test) (**Table 2**).

A higher rate of atypical language dominance was observed in patients with left-hemispheric (15/19, 79%) or bilateral (11/17, 65%) seizure foci compared to those with right-hemispheric seizure foci (11/19, 58%) without reaching statistical significance ($p = 0.370$, Fisher's exact test) (**Table 2**).

The median age of seizure onset in the "early onset" group was 2 years (IQR = 2.25 years) and that in the "late onset" group was 17 years (IQR = 12). Atypical language dominance was observed more frequently in the "late onset" group [27/37 (73%)] compared to the "early onset" group [10/18 (56%)]; the difference, however, was not statistically significant ($p = 0.231$).

Results of further statistical analysis (chi-square, Mann–Whitney test) showed that various types and categories of MCD did not differ with regard to language dominance; they also did not differ with this respect if their lobar location was compared (temporal vs. extratemporal). Atypical language lateralization was not determined either by age at the fMRI study or epilepsy duration. Neither seizure frequency during the first year of epilepsy nor seizure frequency at the time of fMRI influenced language dominance. Patients with temporal lobe epilepsy (TLE) and extra-TLE did not differ with respect to the language lateralization. Motor or cognitive deficits did not have significant relationship to the language dominance. These data are detailed in **Table 2**.

Wada test was performed in nine patients; language dominance determined by Wada test was concordant with the results of fMRI in six of nine patients, with the similarity between fMRI and WADA testing being not statistically significant ($p = 1.0$; McNemar test).

DISCUSSION

The present study aimed at assessing language dominance in a large group of patients with epilepsy and MCD by means of fMRI. We also focused on correlating language lateralization with electroclinical features. The subjects were recruited from outpatient units of a large public hospital representing a broad spectrum of MCD associated with epilepsy and not a highly selective surgical group. The main finding of the study was a high prevalence (67%) of atypical (bilateral or right hemispheric) language dominance in patients with epilepsy and MCD

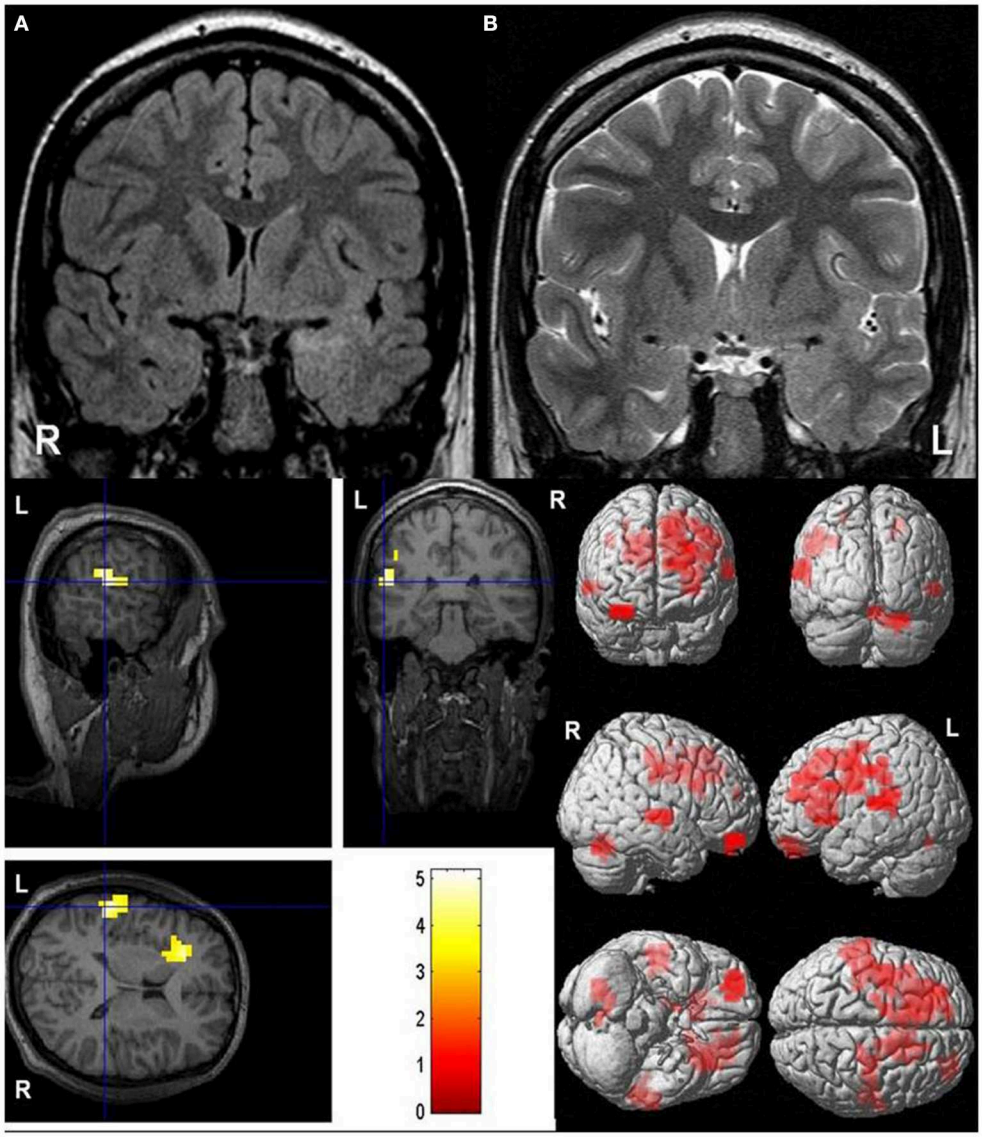

FIGURE 1 | Atypical language dominance in a patient with focal cortical dysplasia type I. **Upper row: (A)** Coronal fluid-attenuated inversion recovery (FLAIR) and **(B)** coronal T2-weighted images show characteristic features of focal cortical dysplasia type I: left (L) temporal lobe is shrunken compared to the right (R) one; there is a higher MR signal in the left temporal lobe (especially in FLAIR sequences) compared to the right one. This patient underwent epilepsy surgery; on histology, focal cortical dysplasia type Ia was diagnosed. **Lower row:** Bilateral language dominance with a lateralization index of +4.9. Blood oxygen level dependent (BOLD) signals are seen bilaterally in Wernicke's areas (threshold $p < 0.05$, family-wise error (FWE) corrected).

determined by fMRI. Atypical language lateralization was not influenced by handedness, electroclinical, and imaging features.

In humans, left-hemispheric language dominance is the most common. However, ∼6% of the general population has atypical language dominance (26). Different genetic, developmental, environmental, and pathological factors may influence language lateralization (26). Several techniques such as Wada test, fMRI, positron emission tomography, or magnetoencephalography have been used for examining language dominance. In epilepsy patients, there is a much greater variability of language dominance compared to healthy subjects, and it ranges from exclusively left-hemispheric dominance to bilateral symmetric and strong right-hemispheric dominance (26–32). About 30% of patients with localization-related epilepsies exhibit atypical language dominance (30). The factors, which may influence language lateralization in epilepsy patients are left-handedness, familial sinistrality, left seizure focus, and early age at seizure onset (26, 27, 33). The activation patterns in native and acquired languages usually overlap in epilepsy patients; however, the second language has a tendency of being represented in both hemispheres (29). Intra- and interhemispheric language reorganization occurs in patients with epilepsy, especially in left-handed individuals (30%) and those with stroke (30%) (34). In a large fMRI study comparing language dominance

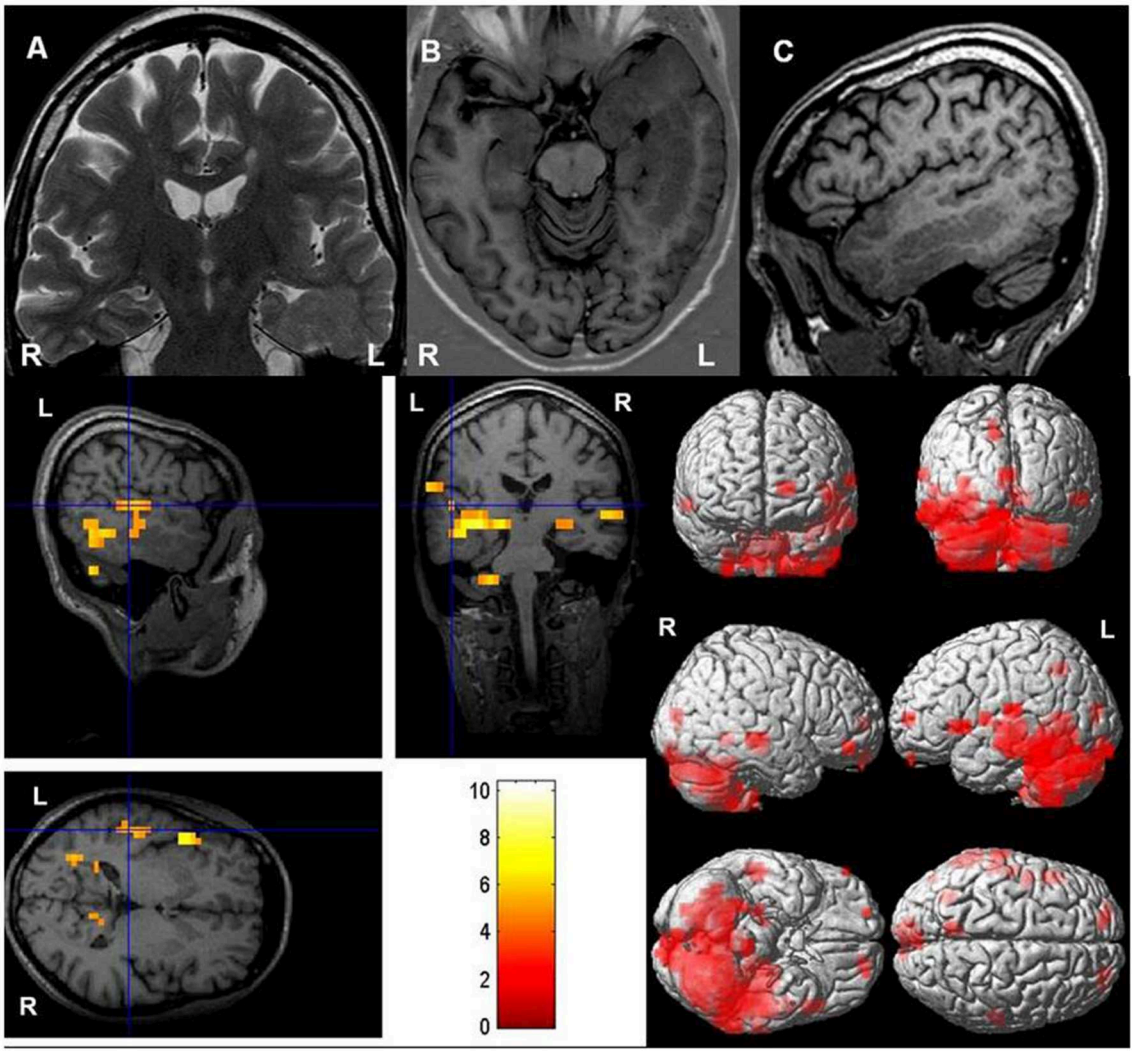

FIGURE 2 | Typical language dominance in a patient with periventricular heterotopia. **Upper row: (A)** Coronal T2-weighted, **(B)** axial T1-weighted inversion recovery, and **(C)** sagittal T1-weighted images show left-sided periventricular heterotopia extending toward cortex. Hippocampus on the left (ipsilateral to periventricular nodular heterotopia) is malrotated. **Lower row:** Left-hemispheric language dominance with a lateralization index of +75. Blood oxygen level dependent (BOLD) responses are mainly in left Wernicke's and Broca's areas [threshold $p < 0.05$, family-wise error (FWE) corrected].

in 220 patients with focal epilepsy and 118 healthy volunteers, 24.5% of patients had atypical language activation patterns compared to 2.5% in healthy controls (27). In this group of patients, atypical language dominance was associated with left-handedness, early seizure onset, and vascular pathology on MRI (27). About a third of this population had a normal MRI, 10% had vascular lesions (stroke, cavernomas, arteriovenous malformations), and other lesions included hippocampal sclerosis, tumors, dual pathology, and FCD (27). As opposed to our study, MCD were underrepresented in this paper.

In a more homogenous group of patients with drug resistant TLE ($n = 162$), the highest incidence of atypical (right-sided) language dominance was determined by a combination of left seizure focus with either nonright-handedness (45%) or with early seizure onset (30%) (31). In this fMRI study, patients had either hippocampal sclerosis (36 had left, 30 had right, and 4 had bilateral hippocampal sclerosis), other pathologies (14 had vascular abnormalities, 8 had low grade tumors, and 1 had FCD), or nonlesional MRI (31). In our cohort, there was a slight preponderance of atypical language dominance in left-handed patients and of those with left-sided seizure foci compared to right-handed patients and right-sided seizure foci, respectively. However, these differences were not statistically significant. These associations may be examined in future studies on larger samples. In our cohort, however, the early seizure onset (before the age of 6 years) was not a determinant of an atypical language dominance. In general, the fMRI studies on language dominance in epilepsy include few patients with MCD. The majority of studies are on patients with TLE, and the most common epileptogenic lesions represented in the studies are hippocampal sclerosis, vascular abnormalities, or tumors.

TABLE 2 | Mapping language system in malformations of cortical development (MCD): language lateralization–demographical and clinical data ($n = 55$).

Demographical and clinical data	Typical ($n = 18$)	Atypical ($n = 37$)	Test	p
Age in years, median (IQR)	31 (12.5)	26 (21)	M-W	0.993
Age at seizure onset in years, median (IQR)	8.5 (12)	15 (19)	M-W	0.398
Age at seizure onset in years, early/late	8/10	10/27	Fischer	0.231
Epilepsy duration in years, median (IQR)	16.5 (20.25)	11 (28.5)	M-W	0.262
Sex, W/M	10/8	23/14	Fischer	0.771
Epilepsy syndrome, TLE/extra-TLE	7/11	13/14	Fischer	0.150
Epilepsy side, R/L/bilat	8/4/6	11/15/11	Fisher	0.370
Seizure frequency during the 1st year of epilepsy, frequent/sporadic	15/3	27/10	Fischer	0.159
Seizure outcome at fMRI time, seizure free/not seizure free	7/11	10/27	Fischer	0.609
Status epilepticus, yes/no	4/14	4/33	Fischer	0.416
Diffuse slowing on EEG, yes/no	10/8	13/24	Fischer	0.244
Focal slowing on EEG, yes/no	13/5	29/8	Fischer	0.738
Epileptiform discharges, yes/no	9/9	22/15	Fischer	0.570
MCD category, 1/2/3	6/6/6	11/10/16	Chi-square	0.775
MCD Location, T/extra-T	5/13	17/20	Fischer	0.249
MCD Side, R/L/bilateral	7/4/7	8/12/17	Chi-square	0.443
Handedness, R/L/ambidexter	16/2/0	30/6/1	Fischer	0.460*
Motor deficit, yes/no	6/12	14/23	Fischer	0.775
Learning disability, yes/no	7/11	8/29	Fischer	0.208

MCD, malformations of cortical development, IQR, interquartile range; W, women; M, men; TLE, temporal lobe epilepsy; T, temporal; R, right; L, left. M-W, Mann–Whitney test; Fischer, Fisher's exact probability test.

*Fisher's exact probability test (two-tailed) for either 2 × 3 or 2 × 2 tables. Chi-square test for 2 × 3 tables if all expected cell frequencies were ≥5. *Fisher's exact probability test was performed for comparison of R- and L-handers.*

fMRI studies have demonstrated a close association of atypical language dominance with early brain injury (26). The incidence of atypical language representation was as high as 50% when patients had both left-hemispheric early brain injury (before the age of 6 years) and left-sided seizure foci; in those with right-sided seizure foci and right-hemispheric early brain injury, the rate of atypical language lateralization was relatively lower-—37.5% (26). There was a greater incidence of atypical language dominance in left TLE patients (33%) in comparison to right TLE patients or healthy subjects, who had exclusively typical, left-hemispheric language dominance (35). Left hemispheric lesions located near language cortical areas increase the likelihood of atypical language lateralization in children (36). In another study, which investigated the location of receptive language areas by means of magnetoencephalography in epilepsy patients, it was demonstrated that atypical language dominance (or interhemisperic language reorganization) was more common in patients with mesial temporal sclerosis as compared to those with nonmesial–temporal lesions (37). The latter, however, had a higher rate of atypical language lateralization indicated by intrahemispheric reorganization compared to those with mesial sclerosis (37). In summary, atypical language dominance is strongly associated with left-hemispheric lesions and seizure foci as well as early brain injury. This is in line with our findings, as all of our patients who showed atypical language dominance had MCDs (early developmental lesions), high incidence of left-hemispheric and bilateral MCD, as well as left-sided or bilateral seizure foci. We presume that the most likely explanation of a high incidence of atypical language dominance in our population is due to early developmental epileptogenic lesions affecting either left or both hemispheres.

The simple language paradigm used in our study resulted in eliciting of an fMRI signal in 81% (55/68) of patients. A similar observation was made in another study, which mapped different functional modalities (motor, language, visual, memory) in patients with MCD and epilepsy (11): Simple tasks (motor and visual) resulted in fMRI activation in 74% (17/23) and complex tasks (language and memory)—only in 40% (4/10). In the study of Janszky et al. (11), a lower rate of fMRI activations compared to our study could be due to a more severe clinical phenotype of the tested population (all patients had drug-resistant epilepsy, 61% had focal neurological abnormalities, and 52% had mental disability) compared to our patients.

Determining language representation is critical in epilepsy patients who undergo epilepsy surgery. fMRI is a common test for assessing presurgical language dominance in patients with drug-resistant epilepsy. In left TLE patients with left-hemispheric language dominance, the larger was the fMRI activation in the left hemisphere, the greater was the postoperative language deficit after anterior temporal lobe resection (28). These patients underwent early postsurgical reorganization of the language function to the contralateral hemisphere as a compensatory

mechanism for regaining language abilities (28). The extent of the resection of the top 10% of the presurgically activated voxels predicted naming decline after temporal lobectomy (32), as it was demonstrated in a study on 35 adult patients with TLE who underwent epilepsy surgery. Right-hemispheric or bilateral dominance were associated with the greater postsurgical language decline (32). In our cohort, till now, only 10 patients underwent epilepsy surgery. The assessment of postsurgical language deficits in this small group and their associations with presurgical fMRI activation patters is not within the scope of this work and is awaiting longitudinal observations. In our study, Wada test was performed only in nine patients who underwent presurgical assessment. Low correlation between the two tests (Wada and fMRI) with regard to language dominance could be due to the mixed population of TLE and extra-TLE patients. It has been shown that patients with extra-TLE may have higher discordance rates between fMRI and Wada test compared to those with TLE (38). In general, congruence of Wada test and fMRI in determining language dominance varies widely from very high—95% (39)—to a relatively low—72.5% in left-sided TLE patients (40). Such variations may be due to sample sizes, patient selection, types of paradigms, lateralization rating, and, eventually, the sensitivity of fMRI for language lateralization.

Language, a cornerstone of human cognition, is a complex, multifaceted mechanism involving dynamic interactions of semantic and syntactic aspects represented in elaborate neural networks (41). In this study, we tested solely an expressive component of the language by utilizing the word generation paradigm, which has also been used by other groups for determining language networks in epilepsy patients (28). Paradigms related to semantic aspects of language, such as picture/auditory naming or semantic decision tasks are also widely used (31, 32, 42–45). Different fMRI tasks, which engage diverse aspects of language, may show either equal or various lateralization patterns (28, 31, 32, 42–45). They may also have different predictive value for postoperative naming decline in epilepsy surgery patients. In a study on 46 patients with temporal lobe epilepsy, preoperative fMRI naming tasks (auditory and picture) were the best predictors of postsurgical naming decline compared to a verbal fluency task (45). Language laterality patterns may also vary in patients with epilepsy and MCD depending on utilized tasks and language components tested. This issue may be addressed in future studies on patients with MCD.

Limitations

The limitations of this study are related to the fact that MCD diagnosis was mainly based on MRI. There was only a small proportion (10/68, 15%) of patients who underwent epilepsy surgery with subsequent histological diagnosis of MCD. Therefore, we cannot make any inferences about the histological features of the brain tissue in the majority of our patients. Another limitation of the study is the restriction of our cohort to patients with MCD and epilepsy. Subclinical seizure or microseizure activity (46) may contribute to the reorganization of cortical function to an unknown extent. Therefore, we cannot extrapolate our results to patients with MCD without epilepsy.

In this study, we did not analyze out-of-scanner language performance. Therefore, we could not determine the associations between fMRI language dominance and neuropsychological measures of language as has been shown in some studies (47).

CONCLUSIONS AND CLINICAL IMPLICATIONS

In this fMRI study on a large group of patients with MCD and epilepsy, we have demonstrated that the substantial proportion of patients had atypical language dominance. In patients with MCD and drug-resistant seizures who undergo presurgical assessment, the results of the present study may help in assessing risks of postsurgical language deficits and could assist in planning "cortical mapping" with intracranial electrodes.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/**Supplementary Material**.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Medical University of Innsbruck, 35, Anichstrasse, 6020 Innsbruck, Austria. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

GK and CS contributed significantly to conception and design of the presented paper, acquisition, analysis and interpretation of the data as well as drafting of the paper. LZ, IU, FK, and EH contributed to acquisition and analysis of data and revising the paper for intellectual content. AI, MD, SF, and ET contributed significantly to conception of the study, interpretation of the results, and gave final approval of the submitted version of the manuscript. MK contributed significantly to the analysis of fMRI data, interpretation of the results, revising the paper, and final approval of the revised manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.01209/full#supplementary-material

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SYSTEMATIC REVIEW
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Epilepsy and Bilingualism. A Systematic Review

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Background: In patients with epilepsy, language abilities and neural language organization have been primarily investigated for the patient's mother tongue. However, in clinical practice, many patients use more than one language or use their second language more than their mother tongue. Yet, information about the linguistic profiles and brain organization of both languages in bilingual epilepsy patients is scarce. The purpose of this study was thus to systematically review the literature on language localization and language abilities in bilingual patients with epilepsy.

Methods: An extensive literature search was performed using various electronic databases, including Embase and Medline. Key aspects of inclusion criteria were the assessment of language abilities and/or the investigation of neural language mapping in bilingual patients with epilepsy.

Results: Our search strategy yielded 155 articles on language in bilingual epilepsy patients. Of these, 12 met final eligibility criteria. The majority of included articles focused on brain mapping of language using fMRI, Wada-test, or electrocortical stimulation in bilingual epilepsy patients, five studies investigated interictal language abilities in this patient group. Study results showed a pronounced heterogeneity of language abilities in bilingual patients, varying from intact language profiles to impairment in several language functions in both languages. However, the mother tongue was most often better perserved than the second language. Furthermore, studies on brain mapping of both languages again revealed heterogeneous findings ranging from identical brain regions for both languages to overlapping, but more distributed cortical areas for the non-native language.

Conclusions: This review underlines the need to evaluate linguistic abilities in both languages, as well as the necessity to preoperatively map both languages in bilingual epilepsy patients. In contrast to the large scientific interest in language abilities and language localization in monolingual epilepsy patients, this review shows that in bilingual patients, the examination of language functions and the identification of brain regions associated with both languages so far played a minor role in epilepsy research. Our review thus emphasizes the need of future research activities in this field.

Keywords: language localization, epilepsy, bilingualism, functional imaging, seizures, language proficiency, second language acquisition

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INTRODUCTION

In the context of globalization and immigration, more and more people are exposed to languages other than their mother tongue. In a survey conducted by the European Commission in 2012, 54 percent of participants are able to hold a conversation in at least one additional language, with increasing rates (1). All over the world, two thirds of children grow up in a bilingual environment (2).

Bilingualism encompasses a heterogeneous typology of speakers. The acquisition of two (or more) languages may occur in different contexts, at different ages, in different situations, with different stimuli and learning environments, and at different proficiency levels. For the present review, we use a broad definition of bilingualism: We define a bilingual person as somebody who can communicate efficiently in both languages. This person may not have an equal proficiency of different language modalities in both languages and may not have a perfect knowledge of their respective cultures, but may be able to express themselves efficiently in two languages.

Several studies in healthy adults suggest that bilingualism is associated with structural brain modulations. Gray matter volume and density studies found significant gray matter increases in bilinguals compared to monolinguals in left inferior temporal and left parietal regions (3, 4), the left anterior cingulate cortex (5), and the cerebellum (6). Increased cortical thickness for bilinguals as compared to monolinguals was observed in the left inferior frontal gyrus (7). In addition, modulations in white matter regions were described: however, whereas some studies found increased fractional anisotropy in parts of the corpus callosum and the inferior fronto-occipital fasciculus in bilinguals (8, 9), others reported decreased fractional anisotropy in these two regions (10, 11). The degree of structural brain alterations in bilinguals has shown to be proportional to second language experience (12).

Functional imaging studies for brain mapping of both languages in healthy bilinguals show controversial findings. Some studies evidenced that second language processing used the first language's functional brain networks located predominantly in inferior frontal, middle and superior temporal, and parietal areas of the left hemisphere (13–15). Activations in these areas have often found to be higher in bilinguals as compared to monolinguals, which has been explained with higher processing demands to monitor both languages (16–18). On the contrary, other studies proved that processing of a second language involved additional functional brain areas in bilinguals (19–22). These additional functional brain areas were predominantly located in homologous areas of the right hemisphere, resulting in a weaker language lateralization in bilinguals as compared to monolinguals. Two studies furthermore examined both, structural and functional relationships between gray matter regions in bilingual healthy adults and pointed to the important role of the left inferior frontal gyrus and its stronger functional connections to temporo-parietal brain regions in bilinguals as compared to monolinguals (9, 23).

In healthy individuals, several factors have been identified that may play a role in determining whether both language networks overlap or differ, among them the age of acquisition (24, 25), second language learning strategies (26), the level of proficiency (27), and the orthographic transparency of the second language, i.e., the systematicity in the mapping between graphemes and phonemes (25).

Many epilepsy patients exhibit language deficits, with naming and spontaneous speech being most often affected (28). These deficits may increase with longer duration of epilepsy (29). Epilepsy surgery is widely accepted as an effective therapeutic alternative in patients with medically refractory epilepsy. Surgical therapy has shown to result in favorable outcomes, concerning seizure activity as well as cognitive aspects. Hereby, knowledge about preoperative language abilities and preoperative language localization plays a major role. However, despite the global predominance of multilingualism, much remains unknown regarding functioning and brain mapping of both languages in bilingual epilepsy patients. Most studies so far have concentrated on language abilities and language mapping in monolingual epilepsy patients, or have neglected the fact that their patients used a second language besides their mother tongue. Nevertheless, for an optimal outcome, presurgical brain mapping has to take into account both languages. We therefore aimed to conduct a systematic review of studies investigating abilities and brain mapping of both languages in bilingual patients with epilepsy to offer the current state of research and potentially initiate further research activities in the field of language assessment in bilingual epilepsy.

METHODS

We conducted a comprehensive search for empirical studies that investigated language localization or language abilities in bilingual epilepsy patients. Publication year and language were not restricted. Studies were identified by searching the following electronic databases up to the 17th of January 2019: Arts and Humanities Citation Index, Biosis Previews, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Conference Proceedings Citation Index—Science, Conference Proceedings Citation Index—Social Science and Humanities, Current Contents Connect, EMBASE, ERIC, MEDLINE, PsycINFO, PSYNDEXPlus, Science Citation Index Expanded, and Social Sciences Citation Index. The following search terms were used: (bilingual* OR second language* OR two language* OR dual language* OR (L2 AND (language* OR proficien* OR learn*))) AND (epilep* OR seizure*).

Articles were included if (a) they provided original data on interictal language abilities and/or language mapping in bilingual epilepsy patients, and (b) studies described quantitative results in form of counts or numbers (ref chapter Data Extraction). Eligibility assessment was performed independently in an unblinded standardized manner by both authors. Disagreements between reviewers were resolved by consensus.

Data Extraction

One reviewer (LBD) extracted information from the included papers, the second author checked the extracted data. Disagreements were resolved by discussion between the two

review authors. Data items compromised (1) characteristics of epilepsy patients (including age, education, seizure lateralization, age at epilepsy onset, duration of epilepsy, MRI findings, drug resistence); (2) characteristics about their languages (L1, L2, age at first exposure to L2, duration of exposure to L2, L2 proficiency); (3) information about controls; (4) languages used during testing; (5) interictal language abilities tested; (6) interictal language tests used; (7) methods used to map language functions; (7) language mapping test paradigm; and (8) results.

Due to the large variation in methodology and the limited amount of data, a quantitative meta-analysis of study results was not feasible. We therefore analyzed these data qualitatively. The PRISMA guidelines were used as a framework for this review (30).

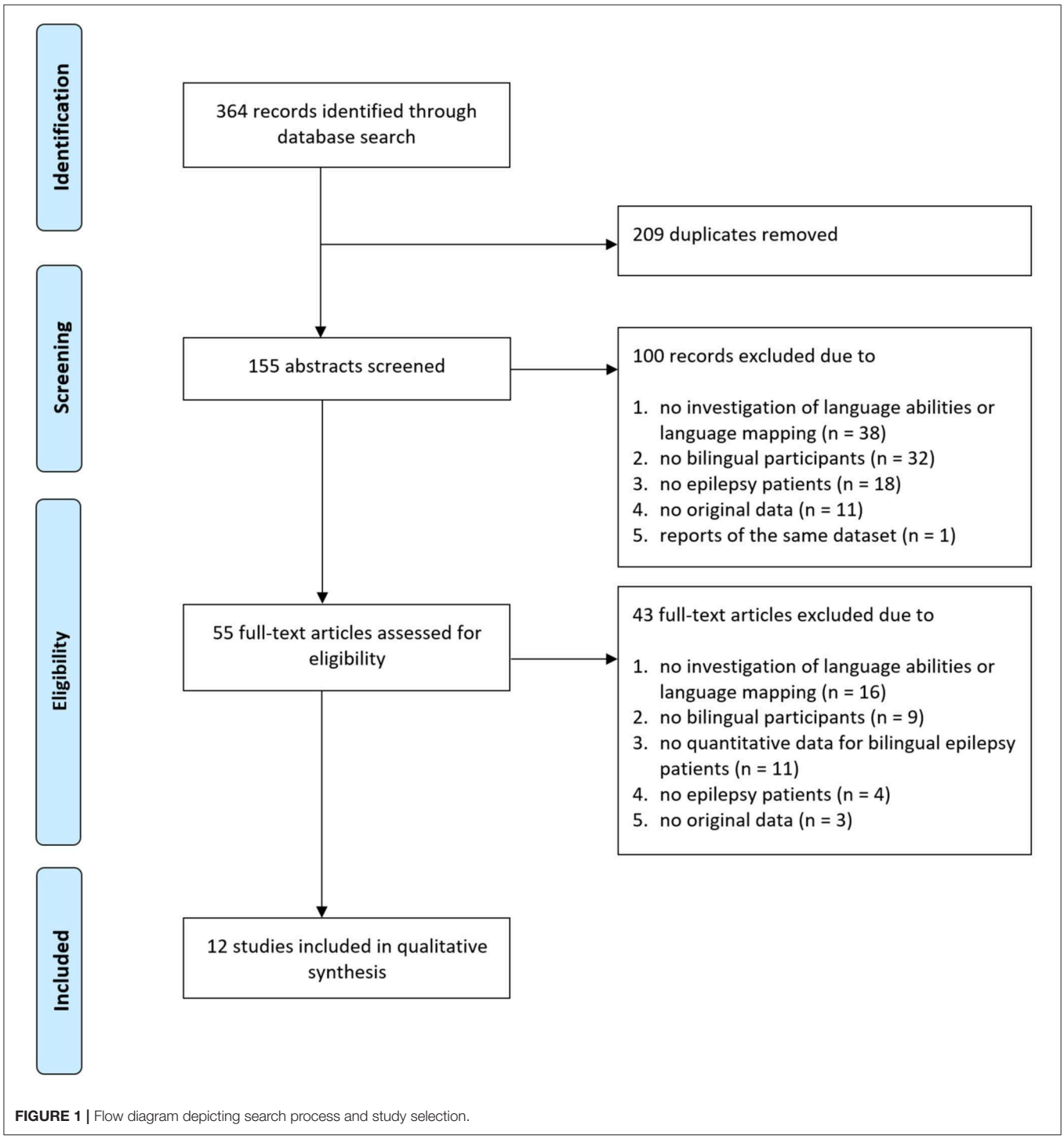

FIGURE 1 | Flow diagram depicting search process and study selection.

RESULTS

Literature search yielded, after elimination of duplicates, 155 articles (**Figure 1**). After screening of all abstracts, 100 records were excluded. Thus, 55 articles were included in the full-text analysis. Of these, 43 full-text articles were excluded (**Figure 1** depicts reasons for exclusion per screening step). Overall, articles were excluded due to the following exclusion criteria[1]: no investigation of interictal language abilities or language mapping described ($n = 54$), no bilingual participants included ($n = 41$), no epilepsy patients included ($n = 22$), no original data reported ($n = 14$), no quantitative data for bilingual epilepsy patients presented ($n = 11$), or reporters of the same dataset ($n = 1$). Finally, 12 studies were identified meeting inclusion and not meeting exclusion criteria.

Study Participants

Epilepsy Patients

Overall, 129 bilingual epilepsy patients were investigated, including six participants younger than 18. Sample size varied between studies from 1 to 56 epilepsy patients with ages from 13 to 53 years (overall mean age 30.52, *sd* 9.48; **Table 1**). Seizures were left lateralized in 79 patients and could be further localized to the temporal lobe in 24, to the frontal lobe in two, and to the occipital lobe in one of them. Seizures were right lateralized in 28 epilepsy patients, with 12 of them originating from the right temporal lobe and one from the frontal lobe. In addition, seven participants experienced bilateral seizure activity, six patients suffered from generalized seizures, and nine bilingual epilepsy patients had an unknown seizure lateralization. The majority of patients in the studies that provided information on clinical and demographic variables had a mean epilepsy duration of more than 10 years and resistance to antiepileptic drugs in their population (overall mean age at epilepsy onset 15.11 years, *sd* 9.86, range 0.4–47; overall mean duration of epilepsy 15.28 years, *sd* 12.45, range 1–50). MRI findings were heterogeneous. In sum, 36% of patients across all studies with MRI examinations displayed mesiotemporal/hippocampal sclerosis, 22% suffered from tumors, 40% had other structural findings including dysplasia and cavernoma, and 2% presented with a normal MRI scan.

Control Groups

The majority of studies did not compare findings in bilingual epilepsy patients to a control group, only three studies investigated group differences. One of them compared bilingual epilepsy patients to monolingual epilepsy patients (31), one compared bilingual epilepsy patients to bilingual healthy controls (39), and one compared a bilingual epilepsy patient with monolingual healthy controls (33). All studies that investigated language abilities in their patients interpreted their findings in relation to normative test control data, though not for all language abilities tested.

[1]Records meeting more than one exclusion criteria were only counted once.

Information About the Patients' Languages

First Language (L1)

In 78 epilepsy patients, L1 was an Indo-European language. Within these, Iberian languages (Spanish, Portuguese) were the ones most often learned as first language ($n = 32$). Further languages within the Indo-European language family comprised Germanic (English, Dutch, Yiddish), Romance (Italian, French, Romanian), Hellenic (Greek), Italic (Welsh), Balto-Slavic (Polish, Serbian, Russian), and Indo-Iranian languages (Urdu, Hindi, Gujarati, Bengali, Farsi). In 26 participants, L1 belonged to the Sino-Tibetian language family (Chinese, Mandarin, Cantonese), and four patients spoke Korean as L1. Further L1 belonged to the Tai Kadai (Lao), Turkic (Turkish), Niger-Congo (Shona, Igbo), Japonic (Japanese), Dravidian (Telugo, Malayan, Tamil), and Afro-Asiatic (Arabic, Eritrea) language families, and not further specified Creol languages.

Second Language (L2)

Most often, L2 of study participants was English ($n = 109$). Further language families of L2 within the Indo-European languages comprised Romance (Italian, French), Iberian (Spanish), Hellenic (Greek), Uralic (Finnish), and other Germanic languages (German), besides English. There were only few study participants with their L2 belonging to a language family other than Indo-European ($n = 5$), including Korean, Sino-Tibetian (Cantonese), Aftro-Asiatic (Hebrew), and Austro-Asiatic (Vietnamese) language families.

Ten studies specified the age of the first exposure to L2 in overall 48 participants. Twenty-eight of them acquired their L2 before the age of six, 20 patients were first exposed to L2 with 6 years of age or later. Years of exposure to L2 was described in eight studies and in overall 31 participants, with 29 of them having more than 10 years of L2 exposure. Eight studies furthermore informed about L2 proficiency and described low and medium proficiency, respectively, in six participants each, and high proficiency in 35 study participants (75%).

Overall, study participants most often spoke Indo-European languages. However, the whole study sample in this review comprises a wide variety of languages, especially for L1. In about 1/3 of study participants, more detailed information was available about age at first exposure to L2 and years of exposure to L2. Most of them had more than 10 years of exposure to L2 and spoke this second language with high proficiency.

Interictal Language Abilities

Five studies investigated the interictal language abilities of bilingual epilepsy patients, and overall, 63 patients were tested with language tests tapping different language functions (31–33, 35, 41); **Table 2**. In four studies, language abilities were tested in both L1 and L2, one study examined linguistic functions in L2 only (31). One study (41) reported post-operative language abilities in a single patient, whereas the other four studies investigated language abilities in non-operated patients.

Most often, visual naming was investigated. Studies found naming in L1 better than in L2 in most, but not all patients (33, 35, 41). Furthermore, visual naming in L2 was significantly worse in bilingual epilepsy patients compared to monolingual

TABLE 1 | Study characteristics.

References	Sample	Seizure lateralization (patients, *n*)	Age, y	Education	Age at epilepsy onset, y	Duration of epilepsy, y	MRI findings (patients, *n*)	Drug resistance (*n*)	L1 (patients, n)[a]	L2 (patients, n)	Age at L2 first exposure, y	Duration of exposure to L2, y	L2 proficiency (patients, *n*)
Gooding et al. (31)	56	L (23) R (14) BL (5) GEN (6) UNKN (8)	36.9 (14.3)	15.7 y (2.5)	22.7 (1.8)	Not spec	Not spec	Not spec	Spanish (22) Creole (3) Italian (3) Korean (3) Yiddish (3) French (2) Greek (2) Telugu (2) other (16)[a]	English (56)	Not spec	Not spec	Not spec
O'Grady et al. (32)	1	R	33	5 y	5	28	Normal	Not spec	Urdu	English	8	25	Not spec
Tomasino et al. (33)	1	L	30	17 y	25	5	Glioma grade II	na	Serbian	Italian	28	2	High[b]
Centeno et al. (34)	16	LT (5) RT (3) T (2) LF (2) RF (1) LOC (1) L (1) UNKN (1)	34.3 (7.8)	Not spec	13.8 (9.8)	21.0 (15.3)	HS (6) Cryptogenic (4) Cavernoma (3) FCD (1) Unclear (1) Dual pathology (1)	16	Portuguese (3) Urdu (2) Polish (2) Turkish (2) Other (7)[a]	English (16)	Before 6 (5) After 6 (11)	Not spec	Low (5)[c] Medium (6) High (5)
Cervenka et al. (35)	4	LT (4)	39 (11.1)	Not spec	22.2 (10.0)	16.8 (16.3)	Gangliocytoma (1) MTS (1)	4	Igbo (1) Italian (1) Spanish (1) Greek (1)	English (4)	12.0 (4.9)	27.0 (11.1)	Not spec
Wang et al. (36)	1	L	25	Graduate student	Not spec	Not spec	Glioma	Not spec	Chinese	English	13	12	High
Serafini et al. (37)	1	LT	13	Student	11	2	Astrocytoma	1	English	Hebrew	Infancy	Not spec	Raised bilingual since infancy
Navarro et al. (38)	1	RT	34	At least 12, not further spec	8	26	HS	1	French	English	11	8	Low
Cheung et al. (39)	21	LT (13) RT (8)	26.3 (9.1)	LT: 11.3 y (2.7) RT: 10.6 y (3.0)	15.0 (9.2)	11.3 (7.9)	MTS (8) Glioma (4) Cyst (3) Hemangioma (2) DNET (1) Astrocytoma (1) Lesion (1)	21	Chinese (21)	English (21)	Before 6	At least 10	Not spec

(Continued)

TABLE 1 | Continued

References	Sample	Seizure lateralization (patients, *n*)	Age, y	Education	Age at epilepsy onset, y	Duration of epilepsy, y	MRI findings (patients, *n*)	Drug resistance (*n*)	L1 (patients, n)[a]	L2 (patients, n)	Age at L2 first exposure, y	Duration of exposure to L2, y	L2 proficiency (patients, *n*)
Lucas et al. (40)	25	L (24) R (1)	31.0 (8.9)	Not spec	Not spec	Not spec	Not spec	Not spec	English (14) Spanish (3) Other (5)[a] Missing (3)	English (8) Spanish (6) Korean (2) Other (6)[a] Missing (3)	Not spec	Not spec	>65%[d]
Trudeau et al. (41)	1	L	17	Not spec	5	12	Rasmussen encephalitis	1	English	French	0	17	Raised bilingual from birth on
Pouratian et al. (42)	1	LT	43	Not spec	39	4	Low grade tumor	1	Spanish	English	6	37	Language at home and work

BL, bilateral; DNET, dysembryoplastic neuroepithelial tumor; FCD, focal cortical dysplasia; GEN, generalized; L1, mother tongue; L2, second language; L, left hemisphere; LF, left frontal; LOC, left occipital; LT, left temporal; HS, hippocampal sclerosis; MTS, mesial temporal sclerosis; na, not applicable; Not spec, not specified; R, right hemisphere; RF, right frontal; RT, right temporal; SD, standard deviation; T, temporal; UNKN, unknown.

[a]*Languages with just 1 speaker are presented as "other."*

[b]*As administered by the Bilingual Language History Questionnaire (43).*

[c]*Self-rated.*

[d]*Proficiency score.*

epilepsy patients (31). Overall, 31% of bilingual epilepsy patients across all studies revealed impaired naming performance in L1, 84% of all patients exhibited impaired naming performance in L2.

Verbal fluency was investigated in four studies and in overall 62 patients. Cervenka et al. (35) found L2 verbal fluency below the 5th percentile in one out of four patients, and Gooding et al. (31) described the group performances of phonemic and semantic fluency in L2 in bilingual epilepsy patients not significantly different to monolingual epilepsy patients. Verbal fluency in L1 was only investigated in two single-case studies and reported to be at borderline in one patient (32) and severely impaired in the second patient who suffered from Rasmussen encephalitis and had a hemispherectomy (41).

Four studies investigated reading abilities of their bilingual patients and investigated overall 62 patients (31, 32, 35, 41). Only one study reported impaired reading abilities in both L1 and L2 in their patient with Rasmussen encephalitis and hemispherectomy (41), the other studies found intact reading abilities in both languages (33, 35) and no differences between L2 reading in bilingual epilepsy patients compared to monolingual epilepsy patients (31).

Only two studies investigated writing abilities of their patients. The single case with Rasmussen encephalitis and hemispherectomy showed severe writing deficits for both languages, whereas group comparisons between L2 writing in bilingual vs. L1 writing in monolingual epilepsy patients did not yield significant differences (31).

Auditory comprehension for L1 was investigated in two bilingual epilepsy patients, and comprehension for L2 was examined in five bilingual epilepsy patients only. Tomasino et al. (33) found both L1 and L2 comprehension intact in their case of bilingual epilepsy, whereas Trudeau et al. (41) described auditory comprehension impaired for both languages in their patient after hemispherectomy. Overall, comprehension of L2 was impaired in 3/5 epilepsy patients (32, 33, 35, 41).

In sum, in non-operated epilepsy patients, linguistic abilities in L1 were often better preserved than in L2, however, only few studies investigated the interictal language abilities of bilingual epilepsy patients, and heterogeneous findings were presented.

Brain Mapping of Languages

Ten studies performed language mapping in bilingual epilepsy patients, three of them with multiple methods. Language regions were investigated for both languages in all studies (though one study only reported results of L2 mapping) and in overall 71 bilingual epilepsy patients. Six studies used functional magnetic resonance imaging (fMRI) (32–34, 38, 39, 42), four studies performed language mapping with intraoperative electrocortical stimulation during awake surgery (33, 36, 40, 42), two studies investigated languages sites using subdural electrocortical stimulation extraoperatively (35, 37), one study used electrocorticography to detect task-specific spectral perturbations (35), one study used intraoperative optical imaging (42), and one study measured language lateralization with a Dichotic Listening Test (32).

The fMRI paradigms used in the included studies were heterogeneous. Tasks of reading, comprehension, fluency,

TABLE 2 | Interictal language abilities and/or language localization in bilingual epilepsy patients.

References	*N*	Controls	Test language	Interictal language abilities tested	Interictal language tests used	Language localization methods	Language localization test paradigm	Results
Gooding et al. (31)	56	186 ML E	L2	Visual naming, auditory naming, phonemic fluency, semantic fluency, word reading	AVNT BNT WTAR COWAT	–	–	BLING epilepsy patients scored significantly worse in L2 (English) naming compared to native English speaking ML epilepsy patients. No differences between groups were found in other language abilities. An association between seizure laterality and naming abilities was only significant within the ML group
O'Grady et al. (32)	1	0	L1 L2	Comprehension, visual naming, semantic fluency	NAB PPVT	fMRI, dichotic listening	Sentence reading and comprehension, letter fluency, antonym generation, object naming, word perception (Dichotic Listening)	This patient with right hemisphere epilepsy showed reduced language abilities in both L1 and L2. FMRI revealed left lateralized, but bilateral activations in frontal, temporal, and parietal areas for both languages. Dichotic listening showed a left ear advantage for receptive language processing. These findings point to a right hemisphere involvement for both languages
Tomasino et al. (33)	1	18 ML HC	L1 L2	Comprehension, phonemic discrimination, visual naming, word and pseudoword reading, word and pseudoword repetition	Token Test BADA	Electrocortical intraoperative stimulation, fMRI	Counting, object naming, silent object naming, verb generation	The patient had intact language abilities in both L1 and L2, only naming was worse in L2 compared to L1. Electrocortical intraoperative stimulation in the left superior temporal gyrus induced involuntary language switching from L2 to L1, stimulation in inferior frontal gyrus induced speech arrest. In fMRI, L1 and L2 both activated the left superior temporal gyrus and the left supramarginal gyrus. Thus, this epilepsy patient showed overlapping language areas for L1 and L2
Centeno et al. (34)	16	0	L1 L2	–	–	fMRI	Verbal fluency, verb generation	At the group level, L2 revealed overlapping language areas with L1, but larger clusters and a more bilateral distribution. At the individual level, language laterality indices were concordant between L1 and L2 except in one participant
Cervenka et al. (35)	4	0	L1 L2	Naming, spontaneous speech, writing, reading, comprehension	BNT WRAT Token Test	Subdural electrocortical stimulation, electrocorticography	Object naming	L1 and L2 language assessment revealed borderline to average language abilities in all patients, no language impairment. Electrocortical mapping during naming in L1 and L2 revealed both shared and distinct areas in three patients. More language sites in L2 than in L1 were found in two patients
Wang et al. (36)	1	0	L1 L2	–	–	Electrocortical intraoperative stimulation	Object naming, naming of colors or shapes	Stimulation of the left caudate induced difficulties in language switching
Serafini et al. (37)	1	0	L1 L2	–	–	Subdural electrocortical stimulation	Object naming, sentence completition, reading	This patient showed distinct but also overlapping cortical areas for L1 and L2
Navarro et al. (38)	1	-	L1* L2	–	–	fMRI	auditory semantic decision	FMRI in L2 activated a bihemispheric, but right lateralized language network in frontal, temporal, and parietal regions, including the right hippocampus. Seizures affecting the right hippocampus elicited L2 ictal speech automatisms

(Continued)

TABLE 2 | Continued

References	*N*	Controls	Test language	Interictal language abilities tested	Interictal language tests used	Language localization methods	Language localization test paradigm	Results
Cheung et al. (39)	21	23 BLINGE HC	L1 L2	–	–	fMRI	Reading words	RTLE and HC showed left lateralized activations in reading English words (L2) and bilateral activations in reading Chinese characters (L1). LTLE revealed bi-hemispheric involvement during reading in both languages
Lucas et al. (40)	25	–	L1 L2	–	–	Electrocortical intraoperative stimulation	Object naming	Intraoperative cortical stimulation in the dominant hemisphere revealed distinct language-specific sites, but also shared language sites. L2-specific sites were located exclusively in the posterior temporal and parietal lobes, whereas shared sites and L1-specific sites were located throughout the mapped cortical areas
Trudeau et al. (41)	1	–	L1 L2	Comprehension, repetition, naming, fluency, reading, writing	BDAE Token Test TLDD EVIP-A	–	–	After left hemispherectomy, the patient showed severe language deficits in most language abilities in both L1 and L2. However, linguistic profiles of L1 and L2 were not identical
Pouratian et al. (42)	1	–	L1 L2	–	–	fMRI, electrocortical intraoperative stimulation, intraoperative optical imaging	Object naming	Cortical language representations of L1 and L2 consisted of both overlapping and distinct language areas

**Results were only reported for L2.*

AVNT, Auditory and Visual Naming Tests; BADA, Battery for the Analysis of Aphasic Deficits; BDAE, Boston Diagnostic Aphasia Examination; BLING, bilingual; BNT, Boston Naming Test; COWAT, Controlled Oral Word Association Test; EVIP-A, Échelle de Vocabulaire en Image Peabody; HC, healthy controls; L1, mother tongue; L2, second language; LTLE, left temporal lobe epilepsy patients; ML, monolingual; E, epilepsy patients; fMRI, functional magnetic resonance imaging; NAB, Neuropsychological Assessment Batteries; PPVT, Peabody Picture Vocabulary Test; RTLE, right temporal lobe epilepsy patients; TLDD, Tests de Langage Dudley-Delage; WTAR, Wechsler Test of Adult Reading; WRAT, Wide Range Achievement Test.

generation of verbs or antonyms, naming, and auditory semantic decision were requested during scanning. During intraoperative electrocortical stimulation, object naming was examined in all studies. Tomasino et al. (33) tested counting in addition, Wang et al. (36) investigated naming of colors and shades in addition to object naming intraoperatively. Object naming was also investigated in all three studies that used extraoperative subdural stimulation. Serafini et al. (37) furthermore tested sentence completion and reading. Cervenka et al. (35) measured intraoperative electrocorticography and Pouratian et al. (42) used intraoperative optical imaging during naming in addition to intraoperative cortical stimulation. O'Grady et al. (32) examined ear advantages during word perception besides several fMRI paradigms.

Overlapping cortical areas for L1 and L2 were described in two patients (32, 33). In further two single cases (35) and a group study of 16 patients (34), a larger and more bihemispheric distribution for L2 was reported. The latter study, however, found concordant lateralization indices between the two languages in 15/16 study participants. Four single cases (35, 37, 42) and a group of 25 patients (40) exhibited some shared, but also distinct language areas for L1 and L2. Within this group of 25 study participants, L2-specific sites were exclusively located in posterior temporal and parietal regions, whereas shared language sites and L1-specific cortical areas were found to be more distributed.

Influence of Seizure Lateralization on Language Lateralization

Most of the reviewed studies did not analyze their data according to seizure lateralization. However, Cheung et al. (39) reported the impact of seizure laterality on language lateralization: Whereas eight right temporal lobe epilepsy patients showed bilateral language representations for L1 during reading of Chinese characters and left language lateralization for L2 during English reading, 13 left temporal lobe epilepsy patients exhibited bilateral language areas for both L1 and L2.

Influence of Age of L2 Acquisition on Language Regions in the Brain

Centeno et al. (34) showed that late L2 acquisition (after 6 years of age) was associated with increased right hemisphere activation in L2. No other study investigated the influence of age of L2 acquisition on language regions in the brain.

Overall, the studies included in the present review used various methods to map different language functions in the brain. Findings were heterogeneous, results varied from identical brain regions to overlapping, but also distinct brain areas for L1 and L2.

DISCUSSION

To our best knowledge, this study is the first to report interictal language abilities and language mapping in bilingual epilepsy patients based on a systematic review of the literature. Studies differ substantially in patients and controls selection, types of epilepsy, language families tested, number and types of language measures employed, and brain mapping methods applied. Overall, in non-operated epilepsy patients, linguistic abilities in L1 were often better preserved than in L2, but individual results varied from intact language profiles to impairments in several language functions. Results for language mapping varied from identical brain regions for both languages to overlapping, but also distributed cortical areas for L1 and L2.

Language Abilities in Bilingual Epilepsy Patients

Linguistic abilities in L1 were often better preserved than in L2, however, only few studies investigated the interictal language abilities of their bilingual epilepsy patients.

Naming was the language function most often investigated, and whereas 69% of bilingual epilepsy patients across all studies exhibited intact naming performance in L1, only 12% of them revealed intact naming performance in L2. Two reasons may underly these findings. First, weaker naming abilities in L2 compared to L1 may reflect lower (premorbid) overall language proficiency in L2 compared to L1. Most studies that provided information about language proficiency investigated patients with more than 10 years of exposure to L2 and high proficiency in L2, however, many studies did not present proficiency levels. Furthermore, naming performances in both languages were not controlled for respective proficiency levels, and quantitative information about possible discrepancies between L1 and L2 proficiencies was not given in any study. Second, in chronic epilepsy, neuronal cell loss and deafferentation may affect language associated brain regions, and "weaker" language networks that need to recruit additional neural resources may be more affected than "stronger" networks. In fact, studies on healthy bilinguals have shown that compared to L1, the use of L2 increases activation in language control networks. Explanations for these findings include compensation for lower efficiency in L2, the requirement of more neurons to perform the task (44), and the need to inhibit the "stronger" language in order to access L2 (17).

Besides naming, verbal fluency, reading, writing, and auditory comprehension were investigated, yet just in a small number of patients and with heterogeneous findings. Overall, this systematic review shows that compared to studies in monolingual epilepsy patients, language function in bilingual patients with epilepsy has received far less formal investigation. It therefore underlines the need for a broader range of language assessment and more detailed, standardized information about the proficiency levels in both languages in bilingual epilepsy patients.

Language Regions in Bilingual Epilepsy Patients

Ten studies were included that investigated language mapping in bilingual epilepsy patients. In bilingual epilepsy patients, the heterogenous picture of language network distributions previously found in bilingual healthy adults was replicated. Whereas, some studies in bilingual patients described overlapping cortical areas for both languages, other studies reported a larger and more bihemispheric distribution for the second language, and again other studies in bilingual epilepsy patients described some shared, but also distinct language areas for both languages.

One study furthermore showed that late age at L2 acquisition was associated with increased right hemispheric involvement

(34). This finding is comparable to data in healthy subjects and supports the so-called "critical period hypothesis" which claims that there is an ideal time window to acquire language in a linguistically rich environment, and acquisition of language after that period becomes more effortful and thus needs the recruitment of more brain regions (45). However, the factor age of acquisition is often confounded with the level of proficiency, with earlier age of acquisition being associated with a higher proficiency level. Perani et al. (46) compared two groups of healthy late bilinguals who were either low or high proficient in L2. They found that the proficiency levels were more important than the age of acquisition as determinants of the cortical representation of L2. The influence of both, proficiency levels and age of acquisition seems to vary for different linguistic systems: Wartenburger et al. (47) showed that L2 proficiency predominantly influenced the brain regions involved in semantic decisions in healthy bilinguals, while the age of acquisition of L2 mainly affected the brain regions involved in grammatical processing. In addition to age of acquisition and proficiency, the amount of daily language exposure has also proven to affect the organization of L2 regions in the brain (48). However, none of these language-related factors were investigated in the studies on bilingual epilepsy patients. Moreover, the degree of linguistic relatedness of both languages, i.e., the extend to which first and second languages share semantic, syntactic, and phonological features, may further influence the neural organization in the bilingual's brain. The study sample in this review comprises a wide variety of languages, especially for L1. Whereas some patients spoke two Germanic languages (e.g., Yiddish-English) which share many linguistic features, others spoke two languages which stem from very different language families (e.g., Chinese-English) that have profound differences in their language structures. We hypothesize that the linguistic relatedness of two languages further impacts their neural language organization, though we are not aware of any respective study in healthy bilinguals.

Besides language-related factors, epilepsy-related factors may also influence the organization of two languages in the brain. Cheung et al. (39) showed that left seizure onset lateralization was significantly associated with a more right hemispheric language involvement. No other study included in this review investigated the possible influence of seizure laterality on neural language organization or of other clinical variables. Studies investigating monolingual epilepsy patients demonstrated a significant impact of clinical features inherent in epilepsy that contribute to the neural organization of language in epilepsy, among them seizure frequency, seizure type, age of seizure onset, duration of epilepsy, extent of interictal epileptiform activity, and brain pathology [for review, see Hamberger and Cole (49)]. Thus, it may be hypothesized that these clinical variables add to language-related factors influencing the organization of two languages in the brain and thus add to form the heterogeneous picture found in this review.

Overall, many factors seem to influence the neural language network in bilingual epilepsy patients, and the degree of overlap of two language's brain areas in bilingual individuals planned to undergo epilepsy surgery cannot be predicted to date.

Limitations

Though broad inclusion criteria, only few studies were identified. Some of them were even more single case studies which did not claim to provide representative data but just presented interesting investigations in single cases. These few studies with an overall low number of participants, however, have used very different methods to map languages in the brain and to examine language abilities in participants with different languages and different proficiency levels. Overall, these factors limit the representativeness of the results of this review and impede to form a consistent picture of neural language organization in bilingual epilepsy patients.

CONCLUSIONS

This review emphasizes the clinical need to individually investigate and map both languages in bilingual epilepsy patients prior to epilepsy surgery. Future research in the field of bilingualism in epilepsy patients should take into account both, language-related and clinical, epilepsy-related variables. Functional brain imaging studies in bilingual epilepsy patients underline the brain's great ability to change and adapt the cortical representation of two languages in the brain.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. All data used in this systematic review were published in articles (please see references).

AUTHOR CONTRIBUTIONS

LB-D: concept and design, data extraction, analysis and interpretation of data, and drafting of the manuscript. SB: concept and design, data extraction, analysis and interpretation of data, and critical review of the manuscript. All authors approved the submitted version of the article.

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Mapping the Effect of Interictal Epileptic Activity Density During Wakefulness on Brain Functioning in Focal Childhood Epilepsies With Centrotemporal Spikes

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Childhood epilepsy with centrotemporal spikes (CECTS) is the most common type of "self-limited focal epilepsies." In its typical presentation, CECTS is a condition reflecting non-lesional cortical hyperexcitability of rolandic regions. The benign evolution of this disorder is challenged by the frequent observation of associated neuropsychological deficits and behavioral impairment. The abundance (or frequency) of interictal centrotemporal spikes (CTS) in CECTS is considered a risk factor for deficits in cognition. Herein, we captured the hemodynamic changes triggered by the CTS density measure (i.e., the number of CTS for time bin) obtained in a cohort of CECTS, studied by means of video electroencephalophy/functional MRI during quite wakefulness. We aim to demonstrate a direct influence of the diurnal CTS frequency on epileptogenic and cognitive networks of children with CECTS. A total number of 8,950 CTS (range between 27 and 801) were recorded in 23 CECTS (21 male), with a mean number of 255 CTS/patient and a mean density of CTS/30 s equal to 10,866 ± 11.46. Two independent general linear model models were created for each patient based on the effect of interest: "individual CTS" in model 1 and "CTS density" in model 2. Hemodynamic correlates of CTS density revealed the involvement of a widespread cortical–subcortical network encompassing the sensory-motor cortex, the Broca's area, the premotor cortex, the thalamus, the putamen, and red nucleus, while in the CTS event-related model, changes were limited to blood–oxygen-level-dependent (BOLD) signal increases in the sensory-motor cortices. A linear relationship was observed between the CTS density

hemodynamic changes and both disease duration (positive correlation) and age (negative correlation) within the language network and the bilateral insular cortices. Our results strongly support the critical role of the CTS frequency, even during wakefulness, to interfere with the normal functioning of language brain networks.

Keywords: CECTS, epileptic discharges frequency, language network, BOLD, cognition, centrotemporal spikes

INTRODUCTION

Epileptic disorders of childhood and adolescence are challenging conditions, as the repetition of seizures and epileptic discharges (EDs) can have tremendous impact on the developing brain. Childhood epilepsy with centrotemporal spikes (CECTS) is the most common type of "self-limited focal epilepsy" (1), also known as benign epilepsy with centrotemporal spikes (BECTS) or Rolandic epilepsy, representing between 15 and 20% of epilepsies in children between 5 and 14 years of age (2). The prevalence of CECTS is estimated to be ∼2% in children, and it is four times more common than typical absence epilepsies (3). It is known to be age dependent, presumably genetic, and mainly occurs at developmentally critical ages. Generally, CECTS is characterized by infrequent focal sensorimotor seizures involving the face during sleep, which may secondarily generalize, reflecting non-lesional cortical excitability from Rolandic and perysilvian regions (4). The prognosis is usually considered to be excellent. Nevertheless, over the past years, some investigators have questioned whether BECTS is indeed benign, considering the variety of different presentations associated with the disorder, thus renamed it CECTS instead of BECTS. It is not uncommon for CECTS to be associated with neuropsychological deficits, especially in visuospatial and verbal fluency tests, language (5) and memory (6) and behavioral problems, such as aggressive behavior, social problems, depression, and attention deficits (7–9). Location of spikes seems to be related to the different selective cognitive deficits in children with CECTS, suggesting an overlap between cortical areas subserving complex cognitive functions and interictal abnormalities sources (10). Different aspects of CECTS were reported to influence cognitive abilities, namely, the age at onset, duration of disease, number of seizures, and antiepileptic drugs (10–12). Nowadays, a causative role of ED is gaining prominence as the predominant mechanism by which epilepsy interferes with the normal organization of oscillatory brain networks, hence causing cognitive deficits (13, 14). A recent electroencephalophy (EEG)-functional MRI (fMRI) study dynamically captured changes in networks' synchronization across different EEG discharge periods in children with CECTS, highlighting the effect of interictal epileptiform activity [represented by centrotemporal spikes (CTS)] "per se" on cognitive functions (15). More than the single ED event, abundance (or frequency) of ED in CECTS is considered a risk factor for epileptogenesis (16) and deficits in cognition processing (17), especially during sleep. Recently, altered widespread functional connectivity patterns were observed in CECTS with spike-wave index during non-rapid eye movement sleep ≥50% compared with the spike-wave index ≤50% group, and these alterations were associated with a worse cognitive profile, while no relationship was detected with age of epilepsy onset, disease course, years of education, and total number of seizures (18). For epileptiform activity in wakefulness, it is shown that reading cognitive performances in children with CECTS were higher disrupted when the awake EEG showed high density of spikes than when the EEG was spike free (19). Moreover, previous EEG-fMRI studies documented that ED are associated with the involvement of cortico-subcortical circuits even remote from the seizure onset zone, relevant for the occurrence of the neurodevelopment and neurocognitive impairments (13–15, 20, 21). Despite these premises, the metabolic effect of the ED density measure (i.e., the number of ED for time bin) on the brain function in CECTS has not been explored to date, either in sleep and awake. In this work, we aim to fill this gap by investigating, specifically, the BOLD correlates of the diurnal ED density in a cohort of patients with CECTS and to correlate the revealed hemodynamic patterns with patients' clinical and cognitive measures. We hypothesized that, in case of higher ED frequency, the metabolic counterpart of this quantitative parameter would be able to explain, even partly, the worse clinical and cognitive functioning observed in some CECTS patients by means of the involvement of critical brain hubs and networks.

METHODS

Study Population

Twenty-seven patients with CECTS [21 male; mean age, 9.7 ± 2.83 years; median age, 9 years (range, 6–17); mean age of epilepsy onset, 7.8 ± 2.6 years; median age, 7 years (range, 2–13)] were selected. Among these, 16 patients age between 7 and 9 years old, 6 patients between 10 and 12 years old, and the remaining 5 patients between 13 and 17 years old. The human ethic committee of the University of Modena and Reggio Emilia approved this study, and written informed consent was obtained from parents and assent from patients. Patients were required to have a clinical diagnosis of CECTS in accordance with the International League Against Epilepsy classification (22) with a history of at least two clinical seizures characterized by simple partial, often facial, and motor or tonic–clonic seizures during sleep and an EEG showing sleep-activated CTS.

The exclusion criteria were (a) any other epilepsy than CECTS, (b) pathological abnormality on conventional MRI, (c) other accompanying neurologic disorders such as cerebral palsy, brain tumor or neurometabolic diseases, and intellectual disability, and (d) head motion while scanning exceeding 3 mm in translation or 3° in rotation.

Before the EEG-fMRI study, within a 15-day window time, the patients were visited by the referring epileptologist and their clinical and EEG features updated. With the exception of two boys (patients 4 and 23) with left-handedness, all patients were right-handed (23).

EEG-fMRI Protocol

All the recruited patients were scanned in the early afternoon, without sleep deprivation; no sedation was used.

Scalp EEG has been recorded by means of a 32-channel MRI-compatible EEG recording system (Micromed, Mogliano Veneto, Italy). Electrodes were placed according to conventional 10–20 locations. Before in-magnet EEG recording, 10 min of out-of-magnet EEG was collected in a room beside the scanner. Foam pads were used to help secure the EEG leads, minimize motion, and improve patient comfort. Data were transmitted via an optic fiber cable from the amplifier (1,024 Hz sampling rate) to a computer located outside the scanner room. To avoid saturation, the EEG amplifiers have a resolution of 22 bits with a range of ± 25.6 mV.

Patients' behavior has been constantly observed and recorded by means of a small camcorder positioned on the head coil inside the scanner pointing to the patients' face to obtain a split-screen video-EEG documentation during the fMRI recording. Patients were asked to remain still during the scanning with eyes closed and do not fall asleep.

Functional data have been acquired using a Philips Intera system at 3 T and a gradient-echo echo-planar sequence from 30 axial contiguous slices (TR = 3,000 ms; in-plane matrix = 64 × 64; voxel size, 4 × 4 × 4) over one 10-min session (200 volumes) with continuous simultaneous EEG recording. A high-resolution T1-weighted anatomical image has been acquired to allow accurate anatomical localization of activations/deactivations. The volume consisted of 170 sagittal slices (TR = 9.9 ms; TE = 4.6 ms; in plane matrix = 256 × 256; voxel size = 1 × 1 × 1 mm).

EEG Processing

BrainQuick System Plus software (Micromed) was used for offline correction of the gradient artifacts (24) and filtering of the EEG signal. In addition, the EEG data were exported in the .edf format and reviewed and analyzed by means of the BrainVision Analyzer 2.0 software (Brain Products, Munich, Germany). After removing the gradient and mean ballistocardiographic artifacts, an independent component analysis was performed on EEG data to isolate IEDs from physiological and artifactual activities.

Two experienced electroencephalographers reviewed the preprocessed EEG recordings independently (AEV, AR) to identify interictal epileptiform abnormalities (i.e., CTS) based on both spatial distribution and topography. When recognized, CTS were marked at peak. We classified patients as unilateral (right or left) in case of only one spike focus without migration; bilateral in the case that both foci were active. In this latter condition, left and right CTS were considered as independent in further analyses. The presence of sleep during fMRI recordings was checked by video recordings and by the presence of sleep spindles and K complexes.

fMRI Data Preprocessing

The Matlab 7.1 and SPM12 (Wellcome Department of Imaging Neuroscience, London, UK) software was used for fMRI data preprocessing and analysis. All functional volumes were slice time corrected, realigned to the first volume acquired and smoothed with a 8 × 8 × 8 mm full width at half maximum Gaussian kernel. The six motion parameters derived from the fMRI preprocessing (translation and rotation in the *X*, *Y*, and *Z* direction, respectively) and a Volterra expansion of these (25) were used as covariates in the general linear model (GLM). Movement artifacts individuated by the analysis of EEG and video recordings (eye blink, deglutition, head movements, etc.) were considered as confounders in the model (26).

EEG-fMRI Data Modeling

After preprocessing, for each patient, EEG and fMRI data were analyzed according to two different procedures:

(a) CTS were treated as single event and their onset exported in .mat file that describes the exact timing (in seconds) of CTS for fMRI time bin (TR = 3 s). The resulting timing files served as onsets for a GLM convolved with the standard hemodynamic response function (HRF) and its temporal derivatives (TDs). This analysis reflects the standard procedure generally adopted in previous works from our group and others (27–29) and will be named in the following paragraphs as "individual CTS."

(b) Instead of treating CTS as single event, we computed the spike density, i.e., the number of ED for each time bin. As the aim was to use this information as regressor into the GLM model, we fixed the time bins equal to the TR, i.e., 3 s. Each spike density signal was then convolved with the standard HRF and its temporal first derivative (TD).

According to the EEG data analyses, two independent GLM models were created for each patient based on the effect of interest: "individual CTS" in model 1, "CTS density" in model 2. For both models, we specified as regressors of no interest the 24 realignment parameters (six scan realignment parameters from image preprocessing and a Volterra expansion of these) and the video based physiological facial movements. The resulting fMRI results [F-contrast or T-contrast as appropriate] were thresholded at $p < 0.05$, corrected for multiple comparisons [familywise error rate (FWE)] or at $p < 0.001$, uncorrected, if the subsequent BOLD maps did not reveal any changes at the more conservative threshold. In this latter case, an extent threshold of 10 contiguous voxels was applied to check for scattered BOLD changes. The statistical parametric maps were superimposed on the coregistered patients' anatomical MRI scans for localization purposes.

We choose not to merge the two regressors reflecting different CTS models in a common matrix as they would have been highly intercorrelated. We decided to employ two separate GLM to optimize the sensitivity of the first level analysis and the interpretation of the results (30).

Group-Level Analysis

Using the parameter estimates obtained by single-subject analyses, we performed two second level (group) random-effect

analyses, one for each CTS model. To this end, the patients' realigned fMRI data were spatially normalized to a standard EPI template and smoothed again. A full factorial design was used, with hemodynamic shapes (HRF, TD) as factors. Subjects' age and gender were included in the model as covariates.

The threshold for statistical significance was set at $p < 0.001$ (uncorrected) and cluster extent of 10 voxels. The resulting statistical maps were displayed in MNI space and warped to the Population-Average, Landmark-, and Surface-based [PALS-B12 atlas in Caret (Caret, http://brainvis.wustl.edu/wiki/index.php/Caret:About; (31)].

Furthermore, we explored the differences by applying an exclusive masking procedure between the random analyses generated contrasts each related to the specific CTS model. In details, to isolate the brain regions that were significantly involved in the main effect "CTS density" but not in the main effect "individual CTS," the contrast "CTS density > baseline" was exclusively masked by the contrast "individual CTS" and vice versa. SPM exclusive masks were thresholded at $p < 0.05$ uncorrected, whereas the contrasts to be masked were thresholded at $p < 0.001$. In this way, those voxels that reached a level of significance at $p < 0.05$ in the mask contrast were excluded from the analysis.

Neuropsychological Assessment

General intelligence (IQ)—including verbal IQ (VIQ), performance IQ (PIQ), and full scale total IQ (TIQ)—was assessed using the Italian version of the Wechsler Intelligence Scale for Children (WISCIII and WISCIV). All scores were standardized for age and sex. For children with WISC III results, VIQ, PIQ, and TIQ where considered, whereas only WISC IV TIQ was analyzed.

Clinical Correlation Analyses

We then further explored the potential relationship between CTS density BOLD changes and disease characteristics and neuropsychological scores in CECTS.

A whole-brain correlation analyses was used to test for a linear relation between BOLD signal changes relative to CTS (either individual event or density) with the disease features and neuropsychological scores. The following measures were considered: age at epilepsy onset, age at fMRI study, disease duration (in months), and neuropsychological parameters (verbal IQ, performance IQ, and full-scale total IQ). For this latter correlation, we limited the analysis to 16 CECTS being the neurophysiological evaluation available not for all patients (see below). The statistical significance level was set at $p < 0.001$ (uncorrected), with a cluster extent of 10 voxels.

RESULTS

Clinical and Cognitive Findings

All the recruited patients completed the EEG-fMRI protocol. No subject's head motion exceeding 3 mm of translation or 3° of rotation. All EEG studies were recorded during resting quite wakefulness. No spindles and/or K complexes were observed. All patients except four (patients 2, 3, 8, and 19) demonstrated CTS during fMRI sessions. Of those, QI measures (TIQ, VIQ, PIQ) tests were available in 16 patients. The time lag between the neuropsychological tests and the fMRI experimental sessions ranged between 1 and 6.3 months. Disease's duration (in months) ranged between 0 and 103 months (mean, 24.8 months; median, 17.2 months). **Table 1** summarizes the demographic and electroclinical data of the studied population. Neuropsychological data are reported in **Table 2**. The mean full-scale IQ was equal to 96.5 ± 14.6 (range, 71–124), mean PIQ = 100.88 ± 16.01 (range, 71–128), and mean VIQ = 99 ± 17.7 (range, 66–124). We did not observe any significant correlation between the cognitive measures and the total number of ED recorded during the fMRI experimental session ($p = 0.063$ Pearson's correlation), the ED density parameter ($p = 0.065$), as well as duration of epilepsy ($p = 0.760$) and age at seizures' onset ($p = 0.864$).

TABLE 1 | Demographic and electroclinical data of CECTS.

ID pt.	Disease's duration (mo)	Seizures type	AED	Spikes during fMRI (n)
#1	1	FOS	Naive	P4 (560)
#2	5	FOS	Naive	–
#3	12	FOS	Naive	–
#4	2	FOS	Naive	F4 (250)
#5	30.8	FOS	Naive	T4 (90)
#6	0.15	FOSa	Naive	T4 (176) T3 (140)
#7	19.3	FOSa, GTCS	LEV	Pz P3 (67)
#8	32	FOS	OXC	–
#9	27.22	FOSa	LEV	T3, CP5 (511)
#10	7.28	FOS	Naive	T4 (92)
#11	0.16	FOS	Naive	T4 (641) F7 (525)
#12	32	FOSa	VPA	FC6 T4 (562) C3 (785)
#13	25.18	FOS	Naive	T4 (126)
#14	44.9	FOSa, GTCS	LEV	CP5 (52)
#15	9	FOSa	ETS + VPA	AF4 (26)
#16	3.9	FOSa	OXC	C4 (51)
#17	24.28	FOS	Naive	T4 (440) C3 (496)
#18	77	FOS	VPA	F8 (801) C3 (406)
#19	36	FOSa	VPA	–
#20	15.14	FOSa	CBZ	T4 P4 (693) Cz (279)
#21	12	FOS	Naive	T3 (84)
#22	1	FOS	Naive	C3 (185)
#23	11	FOS	Naive	C4 (47)
#24	45.9	FOSa, GTCS	Hydr + VPA + CBZ	P4 T6 (504)
#25	9.22	FOS	Naive	C4 (83)
#26	103	FOS	Naive	C4 (140)
#27	64	FOSa	VPA + LEV	C3 T3 (27)

M, male; F, female; Y, yes; N, no; n, number; mo, months; FOS, focal onset seizures; FOSa, focal onset seizures with impaired awareness; GTCS, generalized tonic-clonic seizures; VPA, valproic acid; LEV, levetiracetam; OXC, oxcarbazepine; ESM, ethosuximide; Hydr, hydrocortisone; CBZ, carbamazepine. Spikes during fMRI sessions are described based on their topography and total number.

TABLE 2 | Neuropsychological measures of CECTS.

ID pt.	TIQ	VIQ	PIQ
#1	120	124	110
#4	97	97	97
#5	106	103	107
#6	81	89	77
#7	109	123	93
#9	110	91	109
#11	124	115	128
#14	101	110	128
#15	79	78	85
#16	104	101	106
#20	89	75	106
#23	84	77	93
#24	84	102	71
#25	100	108	92
#26	100	102	104
#27	75	66	95

TIQ, full-scale total IQ; VIQ, verbal IQ; PIQ, performance IQ.

EEG During fMRI

A total number of 8,950 CTS (range between 27 and 801) were recognized, with a mean number of 255 CTS/patient and a mean density of CTS/30 s equal to 10,866 ± 11.46. Of those, 5,419 CTS mapped over the right hemisphere and 3,557 were left sided. CTS were classified as unilateral in 17 patients and bilateral in the remaining 6 cases (**Table 1**). Of those unilateral, 11 patients showed right CTS, while 6 left CTS. For each patient, the interictal events selected during scanning were similar to their routine EEG recordings; topography was checked for each patient and mapped over the centrotemporal and centroparietal leads in all cases (see **Supplementary Figure 1**).

fMRI Findings

"Individual" CTS Analysis

At group level, the regions that showed positive BOLD signal changes time locked to CTS are summarized in the **Table 3** and **Figure 1A**. BOLD signal increases were observed at the bilateral postcentral gyrus (more on the right side) and bilateral insula. No decreases in BOLD signal were detected.

"CTS Density" Analysis

At single-subject level, we observed a good correlation between the BOLD response and the time course of the "density" regressor (see **Supplementary Figure 2** for a representative example). CTS density random-effect analysis reveals the involvement of a more widespread cortico-subcortical network that encompasses the bilateral insula (BA13, global maxima over the right insular cortex), the bilateral sensory-motor cortex (BA4), more lateralized on the right side, the left inferior frontal gyrus (BA44), the right cingulate cortex (BA24), the right supplementary motor area (SMA) (BA6), the bilateral temporal cortex (BA22), the bilateral thalamus, and the putamen and red nucleus lateralized on the left side (**Table 3, Figure 1B**). No decreases in BOLD signal were detected.

TABLE 3 | Group level CTS-related BOLD findings.

	Side	MNI coordinates			*Z* score
	L/R	*x*	*y*	*z*	
Individual CTS					
Insula-BA13	R	38	−16	8	4.65
Postcentral gyrus-BA3	R	64	−16	32	3.78
Insula-BA13	L	−52	−10	8	3.73
Postcentral gyrus-BA40	L	−54	−22	16	3.44
CTS density					
Insula-BA13*	R	36	−20	6	4.76
Precentral gyrus-BA4	R	54	−8	46	4.33
Insula-BA13	L	−38	−18	14	3.95
Superior temporal gyrus-BA22	L	−58	−4	8	3.60
Putamen	L	−32	−10	0	3.58
Inferior frontal gyrus-BA44	L	−50	14	2	3.49
Brain stem-red nucleus	L	−6	−24	−8	3.49
Cingulate gyrus-BA24	R	10	−2	44	3.49
Superior frontal gyrus-BA6	R	8	−14	66	3.49
Precentral gyrus-BA44	L	−60	10	8	3.45
Middle temporal gyrus-BA22	R	50	−42	6	3.30
Inferior frontal gyrus-BA45	R	54	26	12	3.20
Thalamus	L	−8	−14	−10	3.18
Thalamus	R	14	−24	0	3.14

List of brain regions showing BOLD signal increases related to CTS either treated as single events either as density for time bin ($p < 0.001$ uncorrected, 10 voxels extent threshold).
**$p < 0.05$ corrected for FWE.*
BA, Brodmann area; L, left; R, right.

CTS Density vs. Individual CTS

Figure 2A displays the spatial overlap of the BOLD changes constrained to the two CTS models warped to PALS-B12 atlas, flat view. CTS density model reveals increased neuronal activity in the red nucleus, left putamen, left inferior frontal gyrus, left perisylvian cortex, and bilateral SMA, while CTS individual model does not (**Figure 2B**, **Table 4**). On the contrary, CTS single-event-exclusive BOLD correlates were observed at the bilateral (more right) sensory-motor cortex and right insula (**Supplementary Figure 3**).

Correlations Between BOLD Signal and Clinical Measures

Whole-brain correlation analyses using individual clinical characteristics of the CECTS patients disclosed a linear positive relationship between the interictal discharge-related BOLD changes (CTS density model) and disease duration at the bilateral insula (BA13), bilateral cingulate cortex (BA31, BA24), bilateral auditory cortex (BA41–42), the left supramarginal gyrus (BA40), left middle temporal gyrus (BA22), left dorsolateral prefrontal cortex (BA46), left inferior frontal gyrus (opercular and triangular part) (BA44–45), and left superior frontal gyrus (BA6). Interestingly, these BOLD changes survive at a more conservative

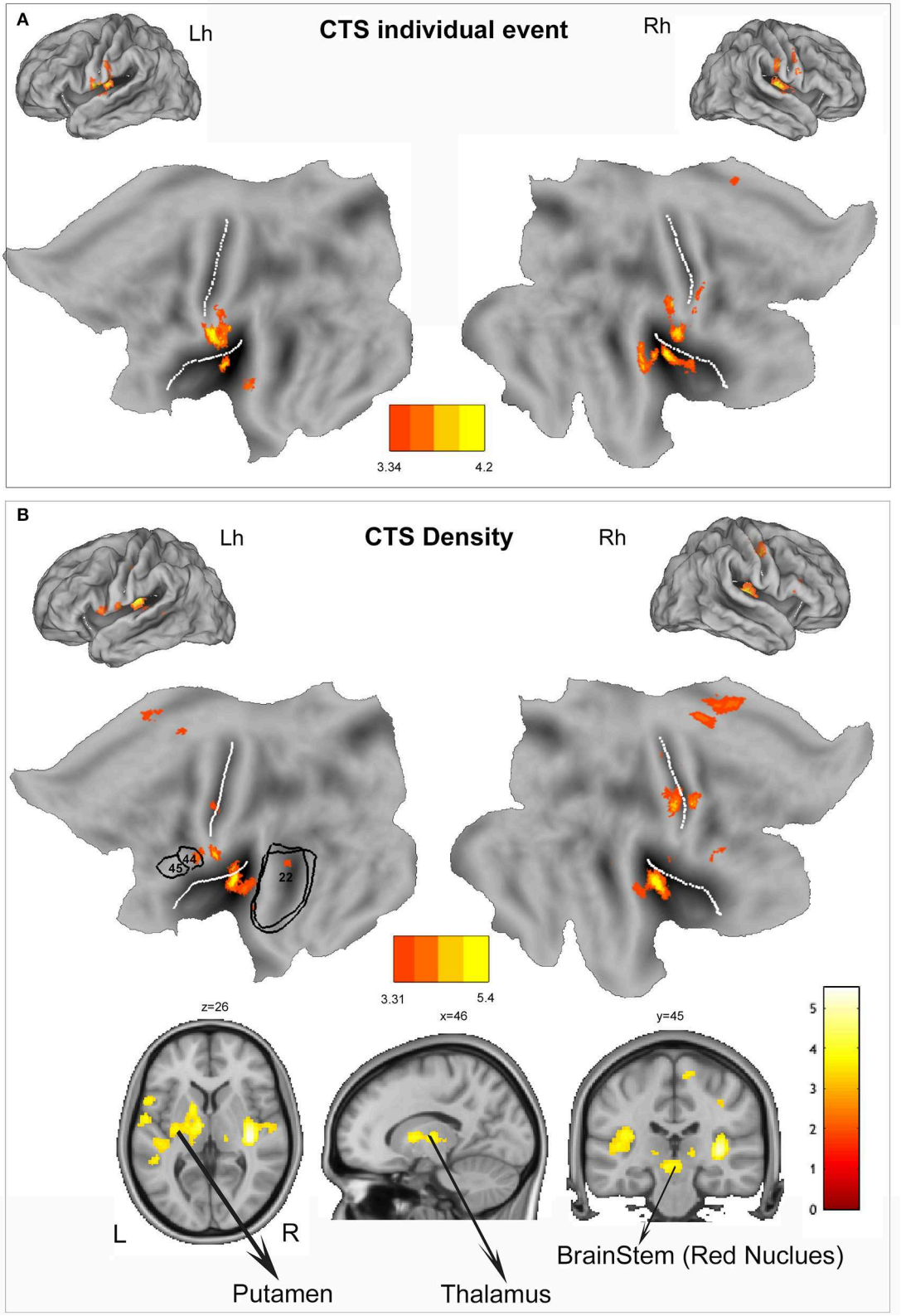

FIGURE 1 | (A) Group-level individual centrotemporal spike (CTS) model ($p < 0.001$, 10 voxels extent). The functional maps are warped to the PALS-B12 atlas in caret (lateral view) for right (Rh) and left (Lh) hemisphere and to flat template. **(B)** Group-level density CTS model ($p < 0.001$, 10 voxels extent). The functional maps are warped to the PALS-B12 atlas in Caret (lateral view) for right (Rh) and left (Lh) hemisphere and to flat template. For localization purposes, functional results on the

(Continued)

FIGURE 1 | left hemisphere were plotted and compared against Brodmann areas of language areas (BA44, BA45, and BA22) indicated by the black numbers. In addition, to show the subcortical findings, BOLD changes have been overlaid into the canonical T1 0.5 mm image (coronal, axial, and sagittal slices) as implemented in FSL (FMRIB Software Library). L, left; R, right. The white lines on the PALS-B12 atlas and flat template show the central and sylvian fissure surface landmarks as implemented in Caret. The yellow-red color identifies positive BOLD changes. Negative BOLD changes were not observed. See text for details.

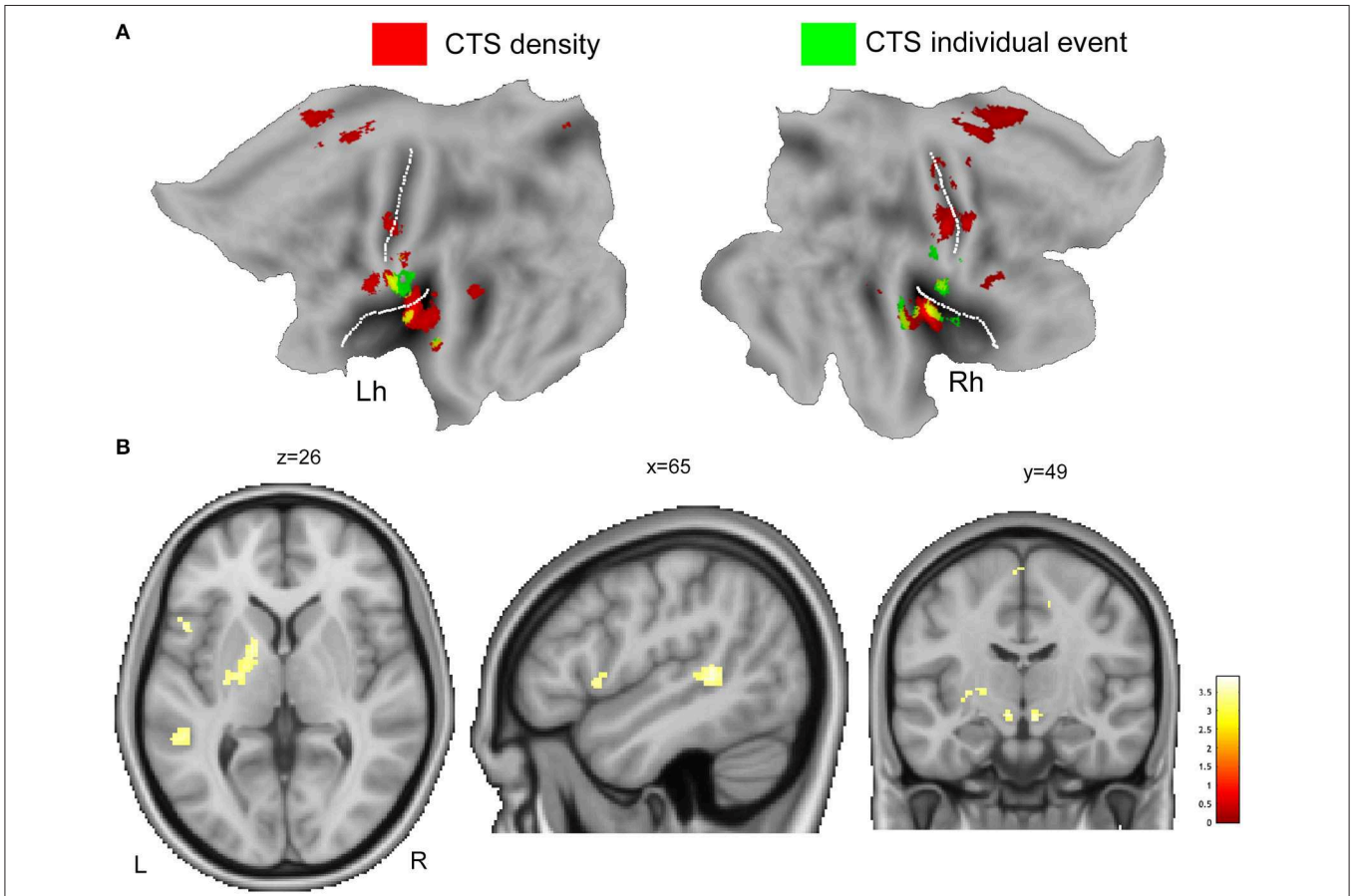

FIGURE 2 | (A) The overlaid of individual CTS model (green color) and CTS density model (red color) is displayed onto the flat template as implemented by Caret for left (Lh) and right hemisphere (Rh). **(B)** The main effect contrast derived from group-level density CTS > baseline analysis was exclusively masked by the mask contrast "individual CTS > baseline," at a threshold of $p < 0.05$, uncorrected for multiple comparison. See text for details. Clusters of activations are overlaid into the canonical T1 0.5-mm image (coronal, axial, and sagittal slices) as implemented in FSL (FMRIB Software Library). R, right; L, left.

threshold of $p < 0.05$ corrected for FWE (**Figure 3A**). A similar hemodynamic map was obtained by correlating CTS density BOLD changes with patients' age (at fMRI study) although of the opposite sign: a negative relationship was indeed observed at the bilateral insula, bilateral cingulate cortex (BA24), bilateral auditory cortex (BA41–42), left supramarginal gyrus (BA40), left middle temporal gyrus (BA22), left inferior frontal gyrus (BA44), and left superior frontal gyrus (BA6) (**Figure 3B**). In other words, the younger the patient and the longer the disease, the higher was the metabolic gain of the perisylvian and the language circuitry of the brain in case of very frequent CTS. Intriguingly, the individual event CTS analyses did not reveal any linear correlation with patients' age, while a positive relationship was detected between the disease's duration and CTS-related BOLD map at the right posterior cingulate cortex and right precuneus (data not shown). Correlation between CTS BOLD changes and neuropsychological measures as well as CTS BOLD changes and age at epilepsy onset did not revealed any significant relationship for both the specified GLM models.

DISCUSSION

The present study is innovative for different aspects. First, we explore the hemodynamic counterpart of the ED density measure during wakefulness in a cohort of patients affected by CECTS. Using EEG-fMRI, instead of individual events, we modeled the number of ED for time bin. The resulted continuous regressor expresses the frequency (i.e., density) of ED for time window along the entire fMRI session at single-subject level. The rationale behind this approach is not trivial

as abundance of ED is recognized as a prognostic factor of the neurocognitive outcome in CECTS (16, 31) and often influences the clinicians' decision tree including treatment (32, 33). Second, our analyses provide a significant contribution within the "puzzle" of evidences that try to explain the complex relationship between epilepsy and cognition in CECTS. With respect to the individual spike analysis, the ED density model BOLD maps reveal the engagement of brain hubs beyond the epileptogenic zone demonstrating how individual ED affects a limited territory, but at the same time, their number can influence the activity of a broader network, comprising nodes of relevance for cognitive functions, and in particular for language. This effect appears to be greater in youngest patients and in those with longer disease's duration, thus confirming the hypothesis of an age-dependence effect of ED on the cognitive development (34) and further supporting the necessity of an early and patient's tailored neuropsychological assessment in CECTS, especially in case of high frequency, even diurnal, ED (34, 35).

TABLE 4 | Exclusive masking findings CTS density vs. individual CTS model and vice versa.

	Side	MNI coordinates			*Z* score
	L/R	*x*	*y*	*z*	
CTS density > individual CTS					
Brain stem, red nucleus	L	−6	−22	−8	3.77
Middle temporal gyrus-BA22	L	−52	−42	4	3.66
Putamen	L	−32	−10	0	3.58
Inferior frontal gyrus-BA47	L	−50	14	2	3.49
Medial frontal gyrus-BA6	R	12	−20	48	3.49
Medial frontal gyrus-BA6	L	−2	−12	66	3.23
Individual CTS > CTS density					
Postcentral gyrus-BA3	R	60	−18	32	3.91
Insula-BA13	R	46	−4	10	3.60
Precentral gyrus-BA4	L	−60	−14	38	3.49

List of brain regions showing BOLD signal increases related to the CTS density vs. individual CTS model and vice versa ($p < 0.001$ uncorrected, 10 voxels extent threshold). BA, Brodmann area; L, left; R, right.

The ED Density Effect on Cognition in CECTS

The importance of ED density parameter and its impact on cognition have been largely discussed in relation to the non-rapid eye movement sleep ED activation, phenomenon described in different epileptic conditions of the same spectrum that includes CECTS as the mildest extreme (36). It has been argued that the negative effect of epileptic discharges during sleep might reflect the impairment of the physiological sleep-related synaptic homeostasis processes (37, 38) that, if occurring in the critical period of development, may disrupt cognitive functions and behavior, hence interfering with the learning process occurring in wakefulness (17). By converse, the effect of diurnal ED

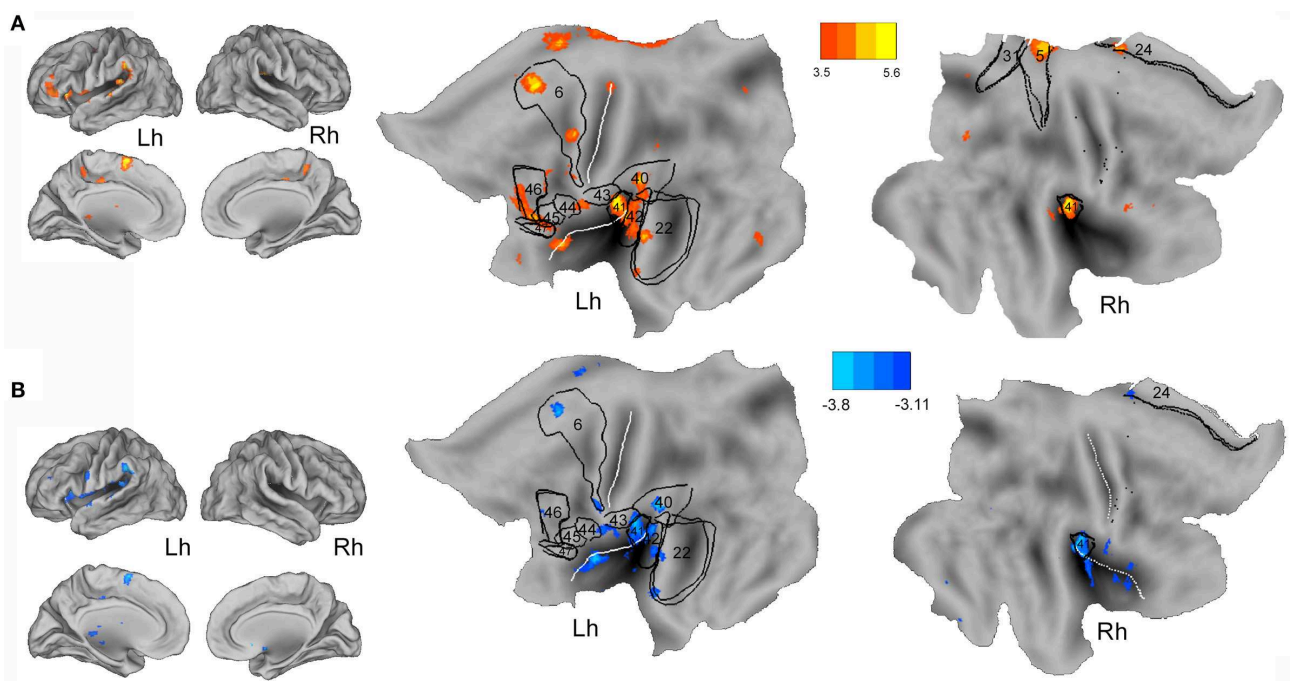

FIGURE 3 | Whole-brain correlation analysis between CTS density-related BOLD changes and disease's duration **(A)** and age at fMRI **(B)** are warped to the PALS-B12 atlas in caret (lateral and mesial view) for right (Rh) and left (Lh) hemisphere and to flat template. See text for details. For localization purposes, functional results were plotted and compared against Brodmann areas indicated by the black numbers. The white lines on the PALS-B12 atlas and flat template show the central and sylvian fissure surface landmarks as implemented in Caret. The yellow-red color identifies the positive correlations, the light-blue color the negative correlations.

density has been poorly investigated, especially in CECTS, and to our knowledge, the present report is the first study that addresses this issue specifically using a functional neuroimaging protocol. Previous clinical studies support the existence of a relationship between the number of spikes on awake EEG and neuropsychological performances. Although in a limited number of patients, the visual discrimination between words and pseudo-words in a reading test has been confirmed to be impaired in patients with frequent diurnal CTS (19). Children affected by different epilepsy syndromes (including CECTS) with diurnal ED in ≥10% of the EEG record showed impaired central information processing speed, short-term verbal memory, and visual-motor integration (39). This effect was seen independently from other EEG-related and epilepsy-related characteristics and from epilepsy syndrome diagnosis (39). Previous EEG-fMRI and magnetoencephalography-fMRI studies demonstrated that diurnal ED in focal childhood epilepsies (including CECTS) may affect the oscillatory synchrony, and the organization of spontaneous network connectivity in the developing brain and changes in the network topology might account for cognitive impairments (13, 15). Interestingly, children with less resilient (or highly vulnerable) networks were found to be prone to a greater frequency of ED and that the combined contribution of network changes and ED is strongly associated with IQ (13). Functional neuroimaging studies in epileptic encephalopathies including electrical status epilepticus during sleep (ESES), a condition characterized by an elevated amount of ED, demonstrated a reliable pattern of network activation including the perisylvian region, temporal, parietal, and cingulate cortex. In addition, besides the network related to epileptiform discharges, there are changes in brain regions pertaining to of the default mode network (28, 40, 41). This latter finding was explained as a remote diurnal ED effect able to explain cognitive deficits in patients with ESES (41). The results of our current report confirm and expand these previous observations. Either the ED density and the ED individual models revealed the involvement of the pericentral and the perisylvian regions, particularly of insula (**Figure 1**). Both these areas can be regarded as key zones for the CTS generation (42) and similar EEG-fMRI findings in CECTS (15) and even in other conditions of the spectrum (ESES, Lennox-Gastaut) (28, 43) point in this direction. A recent ictal source imaging study in CECTS showed the activation of the operculo-insular area time locked to the contralateral focal myoclonic jerks, emphasizing the role of this network for seizures generation (44). Nevertheless, it has been argued that the insular and, in general, the perisylvian involvement reflects the propagation of ED, and they might contribute to cause specific neuropsychological deficits (28). The ED density model, but not the ED individual model demonstrated a diffuse cortical frontal and temporal activations including the right anterior cingulate cortex, the bilateral SMA, and the anterior and posterior speech cortex [the left inferior frontal gyrus (Broca's area) and the left superior temporal gyrus (Wernicke's area)] (see **Figure 1B**). Even the SMA involvement can be linked to a functional disruption and hence reorganization of the language network (45). A direct effect of CTS on the language-related areas has been largely documented either as a transient disturb (15, 46, 47) and more long-lasting morphological changes (48–50). As far as the anterior cingulate (ACC) involvement, it probably reflects attentional difficulties as frequently documented in CECTS even at onset and free of medication (35). Interestingly, altered cortical thickness in CECTS patients with comorbid attention-deficit/hyperactivity disorder involved the cingulate gyri (51). Beside cortical involvement, ED density measure was associated with increase in BOLD signal of putamen, thalamus, and red nucleus. The putamen is of particular interest given the growing evidence for its selective anomaly in CECTS (14, 52). Previous findings observed an increase variability (calculated based on functional connectivity measure) in the striatal (dorsal putamen)–sensorimotor circuits during CTS, and this excessive variability was related to highly frequent ED (14). Our results point in the same direction and support the hypothesis that the dynamic characteristics of interictal epileptic activity act as modulator of the oscillatory dynamics in the striatal–sensorimotor epileptogenic circuitry. Interestingly, the left putamen and motor cortex have been associated with the initiation and execution of overt relative to covert speech (53). Taken together, the BOLD map revealed by the density model provide further information within the complex interaction between the (diurnal) epileptic activity and the brain functionality, highlighting the involvement of core node (putamen, SMA, anterior cingulate cortex) and networks (language, attentional) likely interfering on the cognitive profile of these children.

The Age-Dependence Effect of ED Density on Normal Neurodevelopment

We demonstrated a linear relationship between the BOLD ED density-related changes and both the patients' age (negative correlation) and disease duration (positive correlation). In details, the longer the disease and the younger the patient, the higher is the engagement of the bilateral perisylvian cortex (insula) and a complex network of brain hubs pertaining to the language processing stream (**Figure 3**). In details, ED density measure interferes on regions responsible for the verbal fluency (Broca's area) (53), speech comprehension (Wernicke's area) (54), phonological retrieval and articulatory words processing (supramarginal gyrus) (53, 54), and auditory speech processing (Heschl's gyrus) (53). Even the cingulate and the insular cortex involvement could be regarded in the contest of their participation in words production, especially articulatory planning (insula) and lexical decision (anterior cingulate cortex) (53). Of interest, the individual spike model did not end with similar results, but rather, it shown a positive relationship between the ED-related metabolic activity of the posterior default mode network (precuneus and posterior cingulate cortex) and the disease's duration variable. CECTS is an age-dependent epileptic condition and is therefore clear that maturational factors are important in the development and expression of the disease (34, 55). Recurrent epileptic activity in critical period of life would likely influence and interfere with brain development, aided by the greater neuroplasticity and less functionally specialized

neural networks (56). In addition, perisylvian, prefrontal, and cingulate cortices undergo a long developmental process and are sensitive to environmental influences and intrinsic physiological perturbations, as ED, throughout childhood and adolescence (57, 58). GRIN2A knocked out mice, a genetic model of epilepsy-aphasia spectrum (encompassing CECTS, Landau–Kleffner syndrome, and ESES), displayed impaired vocal communication as well as microstructural diffuse brain alteration in a specific development time window, corresponding to the human school-age/pre-adolescence (59, 60). In CECTS, morphometric analyses revealed diffuse increases in gray matter volumes that inversely correlated with age (49). In addition, the rate of physiological changes in cortical thickness during development was higher in CECTS than controls, and the time to reach normative values was delayed (49, 50, 61). This raise the possibility that the natural course of CECTS may reflect a deviation from the normal developmental trajectory in core regions during critical periods of life. However, such evidences did not consider specifically the effect of ED on causing these age-related disruptions.

In the current report, we shown that the BOLD effect of ED density is negatively correlated with age; on parallel, this effect increases over time given the linear positive correlation with the disease's duration. We can thus hypothesize that an elevated ED density more than the spike itself might alter specific cortical functionality during the critical period for language acquisition and consolidation (62). Persisting language problems following remission might also depend on the long-lasting disrupted effect of frequent epileptic activity on brain circuits during critical epochs of development and specialization. Unfortunately, selective language evaluation by specific subtests is lacking in the CECTS cohort examined, representing a limitation of the current study, and make our assumptions speculative. Nevertheless, the present findings are noteworthy, as they lay the groundwork for additional important future studies. We did not observe a correlation between the ED density (and even individual spike) BOLD changes and the IQ variables. The existence of a variable time lag between the cognitive evaluation and the fMRI experimental sessions across our CECTS patients might account for this negative finding. Nevertheless, such lack of correlation might corroborate the previous suggestion regard the IQ as low sensitive measures for the cognitive assessment in these patients (14). It is commonly reported that children with CECTS display normal-range IQ on a background of specific cognitive difficulties (34, 35). In addition, it raises the issue of the need for appropriate neuropsychological testing, individually tailored to specific deficits and interpreted in the light of the neurophysiology and functional neuroimaging data (63, 64).

Translated to the clinical practice, our findings suggest that CECTS patients with high-density EEG abnormalities during wakefulness need a comprehensive neuropsychological assessment including especially attentional skills and language abilities. In addition, these patients may be considered for specific neuropsychological or pharmacological treatment (if indicated based on several clinical and EEG parameters) early in their clinical history, and the disappearing of ED or a reduction in their frequency might be considered a prognostic factor for a better neuro-behavioral outcome.

Methodological Considerations

Previous EEG-fMRI studies in patients (adults and children) with focal epilepsies and frequent interictal spikes on EEG (range between number of spikes >100/35 min to >200/20 min) argued about the validity of GLM at such high spiking rate and suggested different statistical approaches that assume nonlinearity of the BOLD response (65, 66). To note, these studies were performed in patients with different epileptic conditions rather than CECTS. Previous EEG-fMRI evidence in CECTS patients, even in case with frequent ED, were performed assuming the validity of the GLM and demonstrated highly reproducible and stable findings (15, 20, 29, 67–69). Even in patients with continuous spike and wave during sleep (with more than 1,000 spikes/20 min for subject), and other self-limited focal epilepsies, the GLM was adopted (27, 28). **Supplementary Figure 2** shows a good correspondence between periods of increased spiking rate and BOLD amplitude. Based on these evidences and also the need to get comparable results with previous findings, we assumed the GLM to be valid despite the high number of spikes. To note, as for ESES spikes in CECTS do not occur with temporal regularity.

Study Limitations

We are aware that the present work is limited in several ways. First, it is limited by the small sample size, especially in relation to the subsample of patients with available cognitive assessment. Second, antiepileptic medications (AEDs) might have confounded BOLD findings, by altering the excitability and the neurovascular coupling. AED heterogeneity across the CECTS population prevented to test for their specific effect on the ED density-related BOLD maps. However, when we compared the CTS density BOLD maps in patients naive ($N = 13$) vs. patients on AED ($N = 10$), we did not observe any significant difference, even at low threshold. In addition, ED measures were not statistically different in patients naive compared to patients on AEDs (one sample t test, $p = 0.44$). Cognitive tests' results can be influenced by AEDs, especially in case of polypharmacy. Nevertheless, no patient was taking AEDs that are well-known to exert adverse effects on cognition, such as barbiturates, benzodiazepines, and topiramate.

Third, our cohort was not homogenous as patients were mostly at different stages of their disease at the moment of fMRI and intellectual testing, and, for those available, the time window between fMRI and neuropsychology was different across them. Finally, but probably more important, the neuropsychological assessment was limited to the IQ measures and our data lack of comparison with normal healthy peers (70).

CONCLUSION

There is mounting evidence that CECTS is a neurodevelopmental disorder with key neurocognitive impairments in speech, language, attention, and executive and motor functions (34).

It is generally accepted that neurobehavioral functioning in CECTS is multifactorially determined (71), with epileptiform activity "per se" being one of the main responsible for documented neuropsychological and behavioral problems (13,

15). In CECTS, more than other conditions like ESES is clear that the total amount of ED alone is not sufficient to predict the clinical course. Our work provides additional knowledge in this contest and highlights the importance of the ED frequency, even during wakefulness, as a prognostic factor to be taken into account during the diagnostic and therapeutic workup of CECTS patients. Of note, a timely evaluation of diurnal ED frequency is of importance, as it appears to increase its impact on normal brain functioning over time. The ED density parameter, together with the conventional clinical and neuropsychological assessment, might represent an additional feature useful to determine the severity of epilepsy and could help an early decision about whether to start AED treatment.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comitato Etico dell'Area Vasta Emilia Nord, Via Largo del Pozzo 71, 41124, Modena. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

AEV, PA, GC, and SM outlined the subject of the research theme and interpreted the literature and wrote the manuscript. AEV, and SM obtained ethical permission to perform the research and agreed to be accountable for all aspects of the work. AEV, GC, MF, EC, PB, AG, AV, MC, MS, PV, GGo, GGe, SM, BP, FP, and BD searched the patient files and collected the original data. AEV, PA, AR, and FT analyzed the data.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.01316/full#supplementary-material

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A Guide to Designing a Memory fMRI Paradigm for Pre-surgical Evaluation in Temporal Lobe Epilepsy

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There has been increasing interest in the clinical and experimental use of memory functional Magnetic Resonance Imaging (fMRI). The 2017 American Academy of Neurology practice guidelines on the use of pre-surgical cognitive fMRI suggests that verbal memory fMRI could be used to lateralize memory functions in people with Temporal Lobe Epilepsy (TLE) and should be used to predict post-operative verbal memory outcome. There are however technical and methodological considerations, to optimize both the sensitivity and specificity of this imaging modality. Below we discuss these constraints and suggest recommendations to consider when designing a memory fMRI paradigm.

Keywords: fMRI, memory, TLE, paradigm, guide, method, recall, recognition

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INTRODUCTION

The most important cognitive comorbidity of TLE is impairment in episodic memory. The hippocampus plays a major role in the generation and spread of temporal lobe seizures (1), and it is also a critical structure serving long-term memory, including episodic memory (2). It therefore follows that impairments in memory and learning are frequently seen in people with TLE, although more wide-spread cognitive deficits have also been reported (3). In up to 80% of TLE, epilepsy surgery can be curative (4), however, cognitive decline remains a significant complication of epilepsy surgery (5–10). Early onset seizures interfere with the normal process of hemispheric lateralization (11) and may result in the reorganization of memory functions (12–14). In unilateral TLE, both the function of the contra-lateral MTL (hippocampal adequacy theory), and functional reserve of the ipsilateral hippocampus have been posited in the maintenance of post-operative memory functions (15). It is therefore important to identify the lateralization and localization of memory functions prior to surgical intervention to evaluate the risk of significant post-operative memory deficits.

Memory functional magnetic resonance imaging (fMRI) has been used to study the localization and functional lateralization of critical structures involved in the specific memory task employed (16–22). Memory fMRI is also useful in the prediction of post-operative memory performance (20, 23, 24). Encouragingly, memory fMRI was shown to be the strongest independent predictor of post-operative memory decline compared to standard clinical outcome predictors such as age at onset of epilepsy, hippocampal volume, and pre-operative neuropsychometry (14, 20). Memory fMRI has also been used to investigate post-operative memory plasticity (25–28).

However, memory fMRI remains challenging due to several neuropsychological and technical considerations. Heterogeneous findings across memory fMRI studies may relate to methodological

differences, particularly with regards to the memory task itself. This is reflected in the failure to replicate results and paucity of MTL activations in some studies. The quality of fMRI data depends on several factors including paradigm design, task selection, data acquisition and analysis (29).

We aim to provide a guide for clinicians and researchers to design a memory fMRI protocol for pre-surgical evaluation of memory in TLE. This guide will help the readers with paradigm selection (section Paradigm selection), data analysis (section Analyses), and improvement of reliability of fMRI data (section Reliability of fMRI Data). The section on Paradigm Selection describes the different cognitive processes involved in memory. Understanding these processes will help the readers identify which process they wish to specifically study. Examples of paradigms are mentioned for each of those memory processes. Section Analyses discusses inter-subject variance in brain activation and its implication for interpretation of individual-subject data. In this section, event-related and block analyses are also discussed, as they should guide the design of the paradigm. Finally, the section on reliability of fMRI data discusses issues related to poor reliability of fMRI data and suggests ways to improve it. We hope that through this guide, the reader gains awareness in the parameters to consider when designing a memory fMRI paradigm. This guide is primarily for adults. Whilst similar principals apply in pediatrics, paradigm length and complexity may need to be adjusted according to the age of the participant.

PARADIGM SELECTION

Neuropsychology

Brain activation can vary depending on the nature of the memory task and other cognitive demands related to the task. For this reason, good understanding of the cognitive processes involved in memory is important when designing an fMRI protocol.

Associative Memory and the Hippocampus

Surgical intervention involves the resection of the temporal lobe lesion and the epileptogenic zone which usually encroaches on the hippocampus (30, 31). Pre-surgical investigation of a patient's functional anatomy surrounding the brain lesion is therefore critical for the surgical approach, and designing a memory fMRI task for which performance is supported by the hippocampus appears most relevant in this case.

It is well-recognized that the hippocampus is critical for the binding of information into a representation for later retrieval, as required in paired-associate learning tasks (7, 32–36). The hippocampus contributes to associative memory, whereas other non-hippocampal medial temporal regions contribute to single-item memory (32, 33, 37). Patient studies have demonstrated that the effects of lesion to the hippocampus are selective to specific forms of memory, and are apparent on tasks of arbitrary paired-associates (38), in which association between the items of a pair is necessary for successful performance. Given the role of the hippocampus in TLE, a paired-associate memory paradigm, such as word pairs (39) or face-name associations (40–42), may be most appropriate for the investigation of hippocampal-dependent memory.

Memory Formation

Memory formation is a complex dynamic process that is carried out by representational systems in the brain; distinguished by the nature of the information and task presented (43). Long-term memory is made up of explicit (declarative) and implicit (non-declarative) memory systems (44). Explicit memory allows conscious recall and is sub-divided into semantic memory; the conscious recall of factual knowledge, and episodic memory; recall of individual events in spatial and context order. Critical steps of episodic memory include the formation of distinct neural traces during memory encoding, memory storage and memory retrieval (45).

The first stage of memory is encoding, whereby the information is perceived and transformed into a mental representation. Retrieval is the process by which information that is stored in memory is re-accessed. Retrieving information from memory can occur through the processes of recollection and familiarity. Recollection refers to the reliving of vivid and detailed episodes, whereas familiarity is associated with a sense that information was previously encountered but without any contextual detail. These two processes are mediated by distinct sub-regions of the MTL. Recollection is supported by the hippocampus, and familiarity, the perirhinal cortex (46–48).

The frequently used "Old/New" paradigm compares brain activation associated with the retrieval of studied items ("Old") and new items ("New"). A potential drawback with these paradigms relates to the fact that brain activation associated with the retrieval of studied items could reflect either familiarity or recollection processes. This could lead to inaccurate conclusions regarding the differential role of sub-regions engaged within the MTL.

Paradigms that involve recollection processes are more likely to engage the hippocampus. This can be achieved using the "Remember/Know" paradigm (49–51) for which the responses are thought to reflect recollection and familiarity processes, respectively (52). However, familiarity and recollection may differ along a continuum depending on response confidence, and the imaging contrasts may not accurately reflect the underlying cognitive process (48). Brain activation during a so-called "recollection" contrast (i.e., "Remember>Know") may also include some activity related to familiarity; leading to variability in fMRI studies. In imaging studies, paradigms like the "Old/New" or "Remember/Know" can be adapted to either measure brain activity during the encoding phase or the retrieval phase of the memory process. These are described below.

Memory encoding

Memory fMRI studies often evaluate the encoding phase, with retrieval assessed after scanning (14, 17, 20, 22, 24, 53). Images are acquired during the presentation of information, when participants are encouraged to memorize items presented in the scanner, with retrieval of information occurring after the scanning session.

For example, in the "Old/New" paradigm first described by Powel et al. (54), used by Bonelli et al. (20), and adapted by Sidhu et al. (14, 22, 24), verbal and visual items are visually presented to the subjects during the scanning session. Subjects perform a deep encoding task which involves making a judgement on whether each presented stimuli is pleasant or unpleasant. After the scanning session, subjects perform a recognition test outside the scanner. During this test, the previously presented stimuli are randomly mixed with foils. For each item, subjects are instructed to indicate whether they remember seeing each stimulus during scanning, or whether it is new. The stimuli presented during scanning are then classified according to the responses made during the recognition test. A correct response indicates that the stimulus was subsequently remembered, whereas an incorrect response indicates that the stimulus was subsequently forgotten. Sidhu et al. later included a third response option ("Familiar") to distinguish between the processes of recollection ("Remember" response) and familiarity ("Familiar" response). This type of paradigm provides information about the neural network associated with the encoding phase of memory, but not the network that is involved in the retrieval of mnemonic information.

Memory retrieval

Paradigms that map the retrieval-related network can involve recognition- or recall-based retrieval, as described below.

Recognition

Recognition reflects the ability to identify presented items as familiar, and as such rely on familiarity processes and can be performed without involvement of the hippocampus. FMRI studies investigating retrieval-related activations often use a recognition task (for example "Old/New" or "Remember/Know" paradigms, as described above) (55), and examine MTL activity during successful recognition.

Smith et al. (51) used a "Remember/Know" paradigm which involved studying and making pleasant/unpleasant judgments to words prior to the scanning session. Twenty minutes after studying the words, subjects took a memory test inside the scanner which included the studied words along with foils. For each words presented inside the MRI scanner, subjects made an old/new judgment using a 20-point scale (1 = definitely new, 20 = definitely old). For words identified as "old," subjects were further asked to indicate whether the word was recollected, familiar, or a guess. Participants were instructed to use the "remember" response only if they could describe specific details about the experience of studying the word and to use the "familiar" response if the word was familiar but they could not retrieve contextual details. Subjects provided their responses inside the scanner by moving an MRI-compatible mouse to the relevant location on the screen. Whereas, recognition paradigms like the one described above are often used in memory fMRI studies, they lack in the ability to identify recall-related processes.

Recall

Recall refers to the ability to bring back to mind consolidated representations and relies on recollection processes. Based on evidence from patients with bilateral hippocampal damage of early onset, it is recognized that the hippocampus supports recall processes (56). Recall-based memory should be considered in memory fMRI studies to represent ecological scenarios of everyday memory process, and to optimize hippocampal activation.

During recall, a fragment of the pattern representing the event from the neocortical system triggers the retrieval of the whole representation via pattern completion supported by the hippocampal system (57). In order to recall an event (to bring back to mind a specific past episode), the different features of the event must be processed and bound together. Successful recall therefore requires the use of associative mechanisms, which depend on the hippocampus (58, 59).

Reas et al. (39) used a recall-based memory fMRI paradigm whereby subjects studied word pairs prior to the scanning session. After study, subjects were given a self-paced cued recall test where they were presented with one word of each pair and were asked to say out loud the word that was paired with it. Forgotten pairs were repeated until all pairs were successfully recalled. After a 20-min delay, subjects performed a recall and classify task inside the MRI scanner. They were presented with one word of each pair and were instructed to covertly recall the missing word and to classify it as living or non-living. A third response option ("unsure") was given if they did not remember the pair of the presented word. Subjects provided their responses inside the scanner using a four-button response box. Following the scan, subjects performed a self-paced cued recall test to evaluate the retrieval success of the in-scanner cued recall task.

To date, fMRI studies that use such recall paradigms usually involve covert responses, with additional verbal recall after the scanning session to measure performance (39, 60). A potential issue with this approach is that performance may differ between the two retrieval periods, and the fMRI data may therefore not fully represent activation related to successful performance. In this respect, in-scanner overt recall may be more valid (see section Overt Responses).

Combined encoding and retrieval paradigm

The specific memory process that is impaired in the patient group should guide the selection of the paradigm. People with TLE may have difficulty with both encoding and retrieval of information. As such, studying the mechanisms of both encoding and retrieval (41, 61) may be useful. An fMRI protocol that maps both the encoding and retrieval phases of the memory process could provide a more robust mapping of memory-related networks, as both phases are dependent on hippocampal involvement (62, 63). Obtaining robust hippocampal activation at the individual level has proven challenging across fMRI studies (63, 64), but a wider approach to memory mapping involving two memory phases (encoding and retrieval) may increase the sensitivity of this.

Aim of the Protocol

The clinical aim of the study is pertinent in paradigm selection. If the aim is to study re-organization of memory functions to the contralateral MTL, a material-specific paradigm would need to be employed. Verbal material activates the dominant hemisphere and visual, the non-dominant hemisphere (11, 65, 66), whereas

bilateral tasks such as picture or scene encoding incur bilateral MTL activations. "Failure of activation" using these bilateral tasks have been used to test the hippocampal adequacy vs. the functional reserve model in the prediction of post-operative memory outcome (17).

Irrespective of material type, test-retest reliability of a paradigm is an important consideration (see section Reliability of fMRI Data). In memory-fMRI, reproducible hippocampal magnitude was shown using "hometown walking," a paradigm which requires imagining a familiar route in the scanner (67). In the same study, test-retest of verbal memory recall most reliably identified hemispheric lateralization, which is clinically pertinent to guide surgical planning and predict memory outcome. The clinical aim of the study should therefore inform the design of the fMRI paradigm.

Overt Responses

Most fMRI studies involve covert verbal responses in order to avoid speech-related artifacts (21, 68). However, overt verbal responses may be advantageous for clinical studies, as they are useful to monitor in-scanner performance and conduct event-related analyses (see section Event vs. Block Analysis). Involving overt responses allows online measure of performance and this is beneficial as it makes it possible to explore specific brain activation associated with verbal output. This is particularly relevant for the interpretation of performance and the investigation of brain networks in people with cognitive impairment. The associated movement-related artifacts can be controlled for using image processing techniques (69). Studies have employed overt cued-recall paradigms and demonstrated significant activation in the MTL for successful recall (61, 70, 71). Overt responses should therefore be considered in memory fMRI paradigms.

Baseline Task

Baseline tasks are subtracted from the active memory conditions to generate "activation contrasts." In memory studies, there are two main considerations in selecting a baseline task. The first, is to model a pure memory process. For this, an active baseline task that removes attention, language and motor processes should be considered (72). Next, the baseline task should not activate the hippocampus as this would reduce the sensitivity of hippocampal activations associated with the active process, when contrasted. In a study comparing several baseline tasks, Stark and Squire (73) demonstrated higher activation in the hippocampal region associated with a memory task when the odd/even digit task was used as baseline, compared to when rest was used as baseline.

As in active tasks, baseline task activations vary. We examined hippocampal activation in three healthy participants during five baseline tasks, compared to rest. These included: an odd/even number task where participants were presented with double digits and were asked to decide whether the number was odd or even; an arithmetic subtraction task (for example 27–4); a non-word repetition task where participants were visually presented with two syllable non-words and were asked to read them out loud; a verbal noise detection task where participants were asked to indicate whether mixed letters were presented in pale green or blue and a visual noise detection task where participants were asked to indicate whether shapes, which were embedded in a visual white noise mask, were presented in pale green or blue. All the stimuli were presented every 2 s, apart for the subtraction task where stimuli were presented every 3 s. Compared to rest, there were significantly less bilateral hippocampal activations in all baseline tasks except for visual noise detection (**Figure 1**). These four baseline tasks are therefore ideal for maximizing hippocampal activations when subtracted from an active memory task. Careful piloting of both the active and baseline tasks is therefore recommended when designing a memory fMRI paradigm.

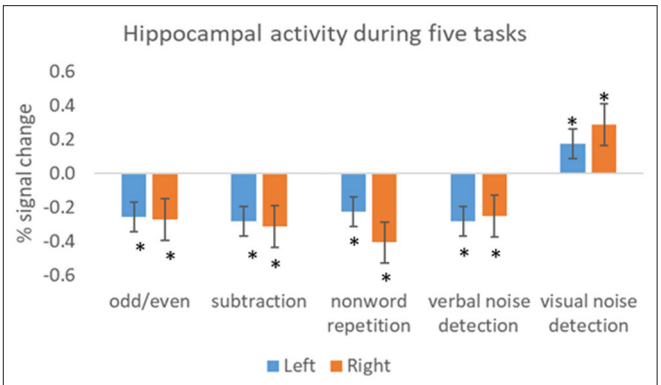

FIGURE 1 | Activity within the hippocampus (left and right) during five baseline tasks. The bars show the mean percent signal change during each task relative to the mean signal during rest. The results show significant less activation in all tasks, except visual noise detection, compared to rest. Error bars = SEM. Significant at $^*p < 0.05$.

ANALYSES

Single-Subject Level vs. Group-Level Analyses

Group analysis collapses data across subjects and examines the overlapping effects. Variability between subjects is considered as nuisance and is included as covariate in the model to make group inferences. One example of inter-subject variability is differences in cognitive strategy for the same task. Each strategy is associated with specific cognitive processes and leads to distinct activation pattern. However, group analyses assume that the task is performed using the same strategy across individuals, and inter-subject variability is ignored. Seghier and Price (74) argued that such between-subject variance should be treated as data rather than noise, particularly in the field of psychology [see (Seghier and Price) for a guide on how to model inter-subject variance]. Understanding normal inter-subject variance can help understand differences in cognitive outcomes between patients and optimize the full potential of neuroimaging applications. Moreover, inter-subject variance may be related to behavioral functions (75, 76) and could provide useful clinical information with regards to predicting outcome in a patient population. Whereas, group studies examine mean effects across subjects,

inter-subject variance may provide critical information, and should not be ignored.

With high variability in the pattern of brain activation, the question arises as to how a subject's memory activation can be interpreted in single-level analysis. Multivariate Pattern Analysis (MVPA) can be carried out on fMRI data to examine the distributed pattern of activation across voxels at the individual-subject level (77). MVPA exploits voxel-level variability within subjects and neutralizes the effects of subject variability, and is therefore more sensitive to neural differences at the individual level than univariate analyses.

A translational application of memory fMRI is to be able to use this to guide surgical planning in TLE. This is only possible if fMRI activations are valid at the single-subject level, and should be considered when examining validity of a novel fMRI tool. Further research is required to assist single-subject fMRI for clinical purposes.

Event vs. Block Analysis

Individual fMRI activations also vary depending on the choice of analysis (i.e., block- or event-related analysis). Block analyses allow examination of brain activity related to memory effort, irrespective of performance, whereas event-related analyses specifically examine successful memory formation. The latter is particularly relevant for predicting memory outcome in the clinical setting. In block analyses, memory and baseline conditions are separated into blocks of extended time intervals. Block analyses have a higher sensitivity (78), meaning that it has good ability to differentiate between different conditions. In event-related analyses, the Blood-Oxygenated Level Dependent response is modeled to each trial within a block (79). It allows the separation of trials based on the participant's performance, for example remembered vs. forgotten items. It provides a better representation of the latency of brain response by providing a better characterization of the shape and the onset of the hemodynamic response function than block analyses (80).

The type of analysis (block vs. event) should be considered prior to designing the fMRI paradigm as the design will depend on the analysis of interest. Maus et al. suggested an optimum block length of 15 s for block analysis (81), and a decrease in percent signal change was shown with longer blocks (82). By contrast, block length is less pertinent for event-related analyses. Block lengths should also take into consideration task-related cognitive demands. Too long or too "difficult" tasks could lead to reduced attention and performance, significantly impacting on the quality of data obtained.

Particularly in event-related analysis, the question of task difficulty is critical. For reliable fMRI activations, it is absolutely vital that participants are able to perform a task. In memory fMRI, the contrasts investigate brain activation for remembered vs. forgotten items, and as such enough trials are needed in each condition. Consider a task that is too difficult, most items will be forgotten, with very few "remembered" trials. In this case, the contrast "remembered vs. forgotten" will not accurately identify the successful memory network. The question of task difficulty is pertinent in pediatric and patient studies where ability levels vary considerably. The paradigm should be designed to reach levels of around 50% correct performance to allow inter-subject performance variability whilst avoiding floor/ceiling effect. Patient factors such as degree of cognitive impairment are therefore important considerations. A trade-off between optimal hippocampal activations, length of scan and paradigm complexity should be sought. With these considerations, the choice of block- or event-related analyses should be made prior to paradigm selection, as the design of the paradigm will depend on the analyses.

Other Analyses

Connectivity techniques investigate functionally connected brain regions involved in a task at a specific time [see (83) for a review]. This allows for the assessment of memory processes at the network level. Multivariate pattern analysis applied to fMRI data [see (84) for a review on the technique] focuses on the patterns of activity (rather than individual activations) across voxels in specific brain regions that are associated with individual memory traces (85–87). A detailed discussion of these techniques is out of the scope of this manuscript (88).

RELIABILITY OF fMRI DATA

Test-retest reliability of fMRI findings is rarely investigated, and studies that investigate it generally report poor reliability of brain activations [see (89), for a review]. This significantly impacts on the clinical utility of the paradigm. Despite advances in hardware and fMRI techniques, the sensitivity and therefore reliability of single-subject fMRI remains sub-optimal (90). Brandt and colleagues investigated reliability of memory fMRI activation using data from two sessions, 1 month apart. The authors measured Intra-Class Correlation (ICC) for the degree of activation at each voxel of the brain and reported that despite reliability of memory activation at the group-level, activation was not stable within individuals (91).

ICC is a measure generally used and represents the ratio of between-subject variance and between-tests variance. ICC can be easily computed using statistical analysis software such as SPSS, by running "Reliability Analysis" (under "analyse," then "scale") and checking "InterClass correlation coefficient." The value approaches 1 if the individual variability is low, and an ICC of 0.5 is considered largely concordant in fMRI studies (89).

Measures of reliability for the magnitude and extent of activation and for the lateralization of activations have been reported in several studies (61, 67, 91–94). Buck et al. measured reliability of memory retrieval lateralization across two separate sessions, 1.5 years apart, and demonstrated good inter-session reliability, suggesting its promising use in single-subject level analysis (61). In our current data, we looked at the ICC of 15 healthy controls scanned across three time-points. Although there was overlap in MTL activations across the three sessions, the spatial extent differed (**Figure 2A**). ICC for LIs across fMRI sessions were more stable for verbal (0.65) compared to visual (0.35) memory (**Figure 2B**). This is in keeping with previous reported ICC studies. Given the test-retest variability of fMRI activations, longitudinal studies in people with TLE should be contrasted with those of healthy controls scanned across the

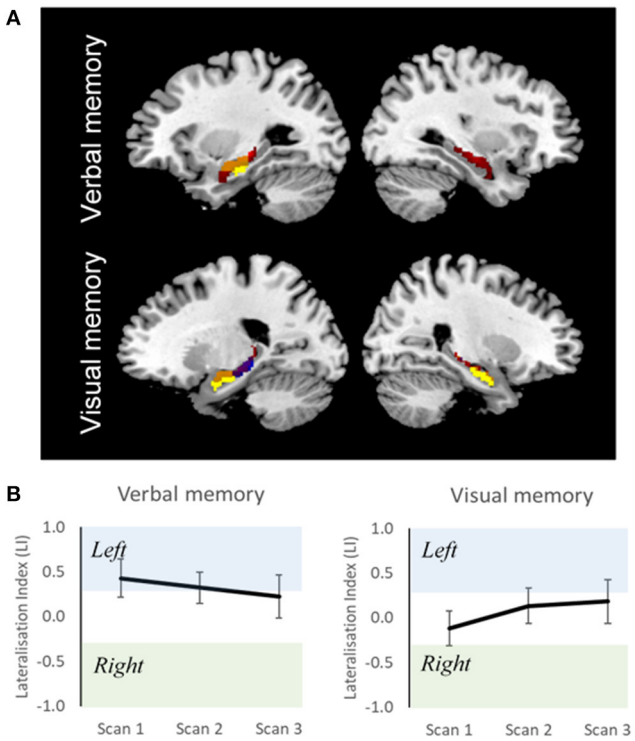

FIGURE 2 | Reliability of fMRI data in healthy individuals. **(A)** Overlap of group activation maps for three fMRI sessions, for verbal and visual memory separately ($p < 0.001$), masked around the hippocampi. Yellow, session 1 (time 0); blue, session 2 (time 0 + 5 months); red, session 3 (session 2 + 10 months); orange, overlap between session. **(B)** Group-Level Lateralisation Indices for verbal and visual memory across three fMRI sessions (95% CIs). Scan 1, time 0; scan 2, time 0 + 5 months; scan 3, scan 2 + 10 months. Despite overlap of brain activation between sessions, variation in functional lateralization is observed. This shows the importance of acquiring control scans at similar time points to patients in longitudinal studies.

same time-points. Performing a mixed ANOVA using a flexible factorial design (97) can be used to model changes in activation at the different time-points whilst controlling for between-subjects and between-group variance in a single model (27).

Regions within the MTL are particularly susceptible to poor reliability of brain activation (91), which has important implications with regards to interpreting fMRI results. Several factors can however improve reliability of fMRI results, including increasing the size of the regions of interests (95), having additional runs (96) and increasing the signal-to-noise ratio by having additional scans (89). Keeping physiologic functions as uniform as possible such as amount of sleep and time of day of scanning are also important considerations.

DIFFICULTIES WITH MEMORY fMRI

fMRI involving MTL structures is subject to distortions due to the inhomogeneous magnetic field. MTL susceptibility artifacts lead to image distortion and signal loss (98), making it difficult to obtain reliable signal thereby, hampering interpretation. For these reasons, methodological considerations need to be rigorously applied in fMRI studies that have a particular interest in the MTL. For example, a slice tilt can be applied to align the scans perpendicular to the long axis of the hippocampus and optimize the Blood Oxygenated Level Dependent sensitivity in medial temporal lobe regions (99).

Moreover, fMRI is susceptible to motion artifact as a result of long acquisition time. fMRI detects signal changes in an image over time (i.e., changes in neural activity), but head motion can be misinterpreted as relevant change. It has been shown that patients (100) and children (101) have particular difficulty remaining still inside the scanner, for whom motion artifacts are therefore particularly apparent. fMRI brain mapping is therefore limited by several factors which alter interpretation of fMRI findings. However, careful considerations related to paradigm selection (as described in the present guide), as well as data acquisition and data processing can be implemented to reduce or counteract these limitations [see (88) for a guide on pre-processing and analysis of fMRI data].

CONCLUSIONS

There has been accruing evidence for the clinical utility of memory fMRI in the pre-surgical assessment of people with TLE. The ultimate aim is to acquire reliable and sensitive data not just at the group level but also at the single-subject level for translational clinical application. There is no single "gold standard" memory fMRI protocol due to the variability in parameters to consider, such as specific memory process of interest and cognitive ability of patients. However, considering the involvement of the hippocampus in TLE, we recommend paradigms of associative memory (for the binding of information which is dependent on the hippocampus) or paradigms that involve encoding and recall (rather than recognition). We also discussed the advantages of overt responses, despite motion-related artifacts, for in-scanner monitoring of performance and for the application of event-related analysis. We hope this guide will be of assistance in identifying the specific paradigm and parameters to those who wish to design a memory fMRI paradigm for clinical or research purposes.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by National Hospital for Neurology and Neurosurgery and the Institute of Neurology Joint Research Ethics Committee, and London-Stanmore Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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METHODS
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A Functional MRI Paradigm Suitable for Language and Memory Mapping in Pediatric Temporal Lobe Epilepsy

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Functional Magnetic Resonance Imaging (fMRI) is a technique frequently used to determine the territories of eloquent tissue that serve critical functions, such as language. This can be particularly useful as part of the pre-surgical assessment for temporal lobe epilepsy (TLE) in order to predict cognitive outcome and guide surgical decision-making. Whereas language fMRI is widely used, memory fMRI is less frequently employed in adult TLE, and lacking in childhood TLE. We have developed a combined language/memory fMRI paradigm that is suitable for children, to provide clinically useful information for surgical planning in pediatric TLE. We evaluated this paradigm in 28 healthy children, aged 8 to 18 years. The advantages of this paradigm are: (a) it examines the functional mapping of language and memory networks within one scanning session, (b) provides assessment of both memory encoding- and retrieval-related neural networks, (c) examines recall-based retrieval to engage hippocampal involvement compared to recognition-based retrieval, and (d) provides overt verbal responses to monitor in-scanner memory performance. This novel fMRI paradigm was designed for language and memory mapping in pediatric TLE and could provide clinically useful information for surgical planning. Finally, parallel versions of the paradigm allow the comparison of brain activations pre- and post-surgical intervention.

Keywords: fMRI, memory, language, TLE, pediatric, recall, hippocampus

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INTRODUCTION

Surgical intervention for intractable epilepsy aims to halt or decrease the frequency of seizures (1). However, children with Temporal Lobe Epilepsy (TLE) are at risk of verbal learning and memory deficits after resection of the temporal lobe (2–5). There is a large variability in verbal memory outcome after surgery (6) highlighting the importance of identifying those patients who are at risk of severe memory impairment after temporal lobectomy. Moreover, it has been demonstrated that both short- and long-term verbal memory outcome after surgery in childhood is associated with the integrity of the left temporal lobe (6, 7), suggesting the need for tailored resection of the structures that are critical to memory. Identifying the pattern of language and memory organization prior to surgical intervention could therefore guide tailored resection and limit potential loss of function after surgery.

The self-generated expressive language network is often identified in both healthy children and patients with brain pathologies using a verb generation task, where participants are asked to generate a semantically-appropriate verb for each noun presented. Activated regions typically associated with such a task include Broca's area in the inferior frontal gyrus (IFG), Wernicke's area in the left superior temporal gyrus, the anterior cingulate gyrus, and the dorsolateral prefrontal cortex (8). As with adults, this task typically shows left lateralisation in frontal and temporal regions in children (8, 9). By contrast, the memory network in children has remained relatively unexplored compared to the same network in adults (10–13). Current reports suggest that the memory retrieval network in children is largely similar to that of adults (14, 15), although there is evidence of age-related changes (14). Moreover, despite the identification of task-dependent memory-related brain regions, the hippocampus remains as a central part of the memory network (16–18). Following the documentation of language and memory networks in children, there is a need for functional magnetic resonance imaging (fMRI) paradigms that allow examination of the *interaction* between these two systems. In the face of early brain injury, there is a heightened potential for reorganization, with neural circuits underlying the development of cognitive domains extending to cross circuit interactions to compensate for compromised functions (19).

Early onset seizures interfere with the normal pattern of circuit specialization and hemispheric lateralisation (20, 21). These processes are sacrificed to facilitate neural plasticity and, in turn, to rescue cognitive functions, especially high-priority functions such as speech and language, and verbal memory. Thus, early brain lesions alter the ontogenetic developmental trajectory with the pattern of functional specialization dependent on the age and extent of injury (21).

By virtue of enhanced neural plasticity across development, focal childhood-onset injury results in a pattern of circuit organization that is distinct from that of adult-onset injury. Early onset injury may result in reorganization of memory and language functions to a larger extent than in older patients (6, 22). In patients with TLE who have unilateral lesions, it is difficult to assess how much of their preserved memory is mediated by the unoperated side which can compensate for any failures of the operated side. There is therefore a growing interest in using functional imaging as a pre-operative tool with the aim of identifying the pattern of memory organization, and evaluating the risk of major post-operative memory deficits.

FMRI is a useful pre-surgical tool for language mapping to guide surgical decision making, and predicting cognitive outcome in both adults (23, 24) and children with TLE (25). In pediatric TLE, atypical language lateralisation is relatively frequent (26). It is possible that reorganization of memory function may also co-occur in such cases, as documented in adult TLE, and should be investigated alongside language lateralisation. Whereas memory fMRI is used in adult epilepsy studies (27–30), pediatric studies have not yet investigated memory organization, and have instead focused on identifying language lateralisation as a proxy for memory lateralisation.

Thus, information obtained from language fMRI is sometimes used to predict memory outcome in TLE, due to mesial temporal lobe (MTL) activation during language tasks (31). However, using language fMRI to predict memory outcome assumes co-lateralisation of these functions. Co-lateralisation of language and memory has previously been studied (32), but dissociating these domains of function can be difficult, partly due to reorganization, and to overlapping and/or interconnectivity of regions involved during cognitive processing. Moreover, Sepeta and colleagues demonstrated that whereas healthy adults show co-lateralisation of activation in Broca's area and the MTL during a language task, children do not demonstrate this pattern (31). This suggests that language fMRI may not be a viable substitute to predict memory outcome. There is therefore a need for developing suitable memory fMRI paradigms, as opposed to relying on language fMRI, for the prediction of memory outcome, particularly in pediatric patients. In addition, it is important to examine the relationship between language and memory lateralisation.

In adult studies, memory fMRI paradigms usually involve recognition- rather than recall-based responses (30, 33–35). Lesion studies have provided evidence of the distinction between recall and recognition processes. Patients with developmental amnesia (DA) who sustained selective early-onset bilateral hippocampal pathology (36) exhibit severe and selective impairment in recall memory, in the context of relatively well-preserved recognition memory (37–39). This suggests that fMRI paradigms that use recognition-based responses are more likely to be insensitive to recall-based (i.e., hippocampal) activation. Moreover, adult studies employing multiple levels of deep vs. shallow processes, such as the recognition tasks based on Remember/Know decisions, may be too complex for children. Given that children with TLE demonstrate difficulty in learning and recall of new information (35, 40), it is more informative to use a recall- rather than a recognition-based memory paradigm.

In an effort to meet the needs of the fMRI community, this study presents a novel fMRI paradigm for the functional mapping of language and memory, *within one scanning session*, to guide surgical decision-making and help with predictions of outcome. The paradigm was developed with the following goals:

a) Design a paradigm sensitive to MTL function because of its known involvement in episodic memory and its susceptibility to pathology in TLE.
b) Provide a combined language/verbal memory fMRI paradigm to examine the interaction of the two networks within one scanning session, thereby facilitating a cost- and time-effective investigation.
c) Examine hippocampal activity related to both memory encoding and retrieval.

Several variables related to the experimental fMRI paradigm will be specifically outlined in the results section to test paradigm validity and reproducibility.

MATERIALS AND METHODS

Participants

Thirty normally-developing, English-speaking children and adolescents were recruited through East London schools. Using the standard exclusion criteria (movement that exceeds 3 mm or 2°), two participants (one male and one female) were

excluded from further analyses due to high level of in-scanner movement (**Supplementary Figure S1**). The sample includes 11 males and 17 females, aged between 8 and 18 years ($M = 14$, $SD = 3$). Handedness was measured for each participant using the Edinburgh Handedness Inventory (41). The scores were representative of the sampling population: two participants were left-handed, one was ambidextrous. Socio-economic status (SES) was determined for each participant with deprivation deciles ranging from most deprived (score of 1) to least deprived (score of 10). SES deciles in the present cohort ranged from 2 to 10 ($M = 5$, $SD = 2$). **Table 1** illustrates the participants' demographics. Written informed consent was obtained from each participant prior to study start.

Neuropsychological Assessment

Intellectual status was assessed using the Wechsler Abbreviated Scale of Intelligence—Fourth Edition (WASI-IV). This test provides measures of full scale IQ ($M = 108$, $SD = 8$), verbal IQ ($M = 108$, $SD = 8$), and performance IQ ($M = 107$, $SD = 10$).

Verbal learning was assessed using the Word-Pair subtest of the Children's Memory Scale (CMS). This is a widely-used standardized diagnostic tool for memory in children. The Word-Pairs subtest of the CMS assesses the ability to learn a list of pairs of words over three consecutive trials, whereby the examinee is presented with the first word of each pair and is asked to recall the second word (cued recall). Following a 30 min delay, the participant is asked to retrieve as many word-pairs as possible, first through free recall, then through cued recall by presenting the first word of the pair, and finally through yes/no recognition judgments of each word pair to indicate whether they were part of the list that was learned earlier. Learning and memory scores are presented in **Supplementary Table S2**.

The Novel fMRI Paradigm

According to the levels of processing effect, deep processing of information (e.g., encoding the meaning of an item) leads to better subsequent retrieval than shallow processing (e.g., encoding the perceptual features of an item) (42). As such, a verb generation task, which involves generating a verb related to a noun heard, may be used as a deep encoding task. This paradigm comprises a noun-to-verb generation task for deep encoding (i.e., memory encoding), and a subsequent recall task of the nouns (i.e., memory retrieval). Therefore, this paradigm combines language and memory mapping within one scanning session.

TABLE 1 | Participants' demographics ($N = 28$).

	Mean	Min	Max
Age in years (M ± SD)	14 (3.0)	8	18
Gender (M/F)	11/17	N/A	N/A
Atypical handedness	3 (11%)	N/A	N/A
SES (M ± SD)	5 (2.0)	2	10
Full scale IQ (M ± SD)	108 (8)	90	126

Language Task: Verb Generation

Verb generation tasks produce strong and consistent lateralised activation in the left hemisphere language network and are the standard tasks used in the clinic (8, 43). During the verb generation task used here, participants were presented with nouns, one at a time, and were asked to overtly generate a verb for each noun (for example they heard "cake" and generated the verb "eating"). There were a total of 60 nouns, divided into 6 lists of 10 each.

Memory Task: Cued Recall

The memory task required the participants to overtly recall the nouns that were presented during the language task. Two-phoneme word stem cues were presented one at a time to the participants to guide recall of previously encoded words (for example "æn" as a cue for "animal"). Participants were asked to say the word it corresponded to, or say "pass" if they could not retrieve the word. Each stem was unique in the full list of study words (44).

Cued-recall using word-stems has multiple advantages. First, it allows event-related investigation of fMRI data, as retrieval-related activation is time-locked to each cue. This permits examination of brain activation specifically related to memory retrieval success (correctly recalled vs. forgotten). Second, the performance reflects declarative recall which is known to be dependent on the hippocampus (39). This approach has been successfully adopted in previous studies that reported activation in the hippocampus during successful recall (45, 46).

More details about the procedure (e.g., duration and timings) of the language and memory tasks is provided in the procedure section.

Accounting for priming effects

Priming is the facilitation in the processing and/or re-evoking of a stimulus due to a prior encounter with that stimulus, and is devoid of intentional and conscious recollection (47). In word-stem completion tasks, stems are more likely completed with previously presented words. In order to reduce the priming effect in our cued recall task, several control measures were adopted. First, stems for words that were not previously heard (foils) were inserted in the cued recall phase (15 words in each list: 5 foils and 10 target words), to which participants were expected to respond by saying "pass." The stems of these foils did not match any studied words. With this method, it is possible to have a measure of false alarms (i.e., stem completion with non-studied words). Second, each of these unique 90 stems (from 60 studied words and 30 foils) was shared with at least 4 other common words, thus requiring conscious recollection to retrieve the correct word. Using these methodological considerations, the risk of priming effects was minimized, and performance was expected to primarily reflect conscious recall.

Foils that were erroneously completed with a word, instead of a "pass" response, were categorized as "false alarms." Performance was calculated as percent correct recall, minus false alarms.

Baseline Task

The baseline task required making an odd/even decision to numbers; for example, the participant was presented with the number "3" and had to say "odd." The presentation rate of this number was similar to the rate of word and word-stem presentation (*viz,* every 4 s).

This baseline task was designed to meet three goals: First, it acted as a baseline to subtract from the active conditions (Language and Memory) and enable investigation of activation contrasts. The second purpose was to introduce a short delay between encoding and recall (50 s), and the third goal was to prevent subvocal rehearsal and maintenance of information in the short-term memory store during the delay. The selection of this baseline task therefore optimized investigation of brain activation during the language and memory tasks.

Stimulus Material

Stimuli were selected from the MRC Psycholinguistic Database. The stimuli matched the ones used for the clinical verb generation paradigm, currently the protocols of choice at Great Ormond Street Hospital, according to several features: word frequency (48), concreteness, familiarity, and imageability (**Supplementary Table S1**). In addition, all of the words were simple enough to have been acquired before the age of 8 (49) and were composed of 1 to 3 syllables, similar to the version used in the clinical setting.

Overt Response

The present paradigm required overt verbal responses (50) in order to monitor in-scanner performance and to conduct event-related analysis. Moreover, overt speech responses have the potential to reveal the interaction of memory and language networks as the memory item retrieved is translated into a verbal output.

Procedure

The scanning session consisted of 3 runs, each with two word-lists. Verbal responses were monitored via an MRI-compatible microphone. **Figure 1** illustrates the procedure of the fMRI paradigm. Before the beginning of each block, a visual prompt was displayed on the screen for 5,000 ms in order to prepare the participants for the upcoming task. These prompts were [ACTION WORDS] for the verb generation [ODD OR EVEN?], for the baseline block, and [REMEMBER OR "PASS"] for the cued recall block (**Figure 1**). The stimuli were presented at a rate of one every 4 s, which was purposely not locked to the TR (1.25 s) in order to improve effective sampling of the signal (51). Each block of verb generation and baseline lasted for 40 s (10 × 4 s), while the cued recall block lasted for 60 s (15 × 4 s), and the entire protocol lasted for 16 min. The presentation of stimuli followed the same order for each participant.

The standardized test of memory function, Children's Memory Scale (CMS) was administered outside the scanner, with a time delay of at least 1 h between the behavioral and the imaging sessions. The duration of the behavioral session (neuropsychological assessments) and the MRI session was approximately 1 h each, and occurred on the same day. The order of sessions depended upon scanner availability.

A subset of the sample ($N = 15$) were administered the same fMRI protocol, 1–2 years after the first session (mean elapsed time between sessions = 1.5 years, $SD = 0.6$), using another version of the paradigm (see Two Parallel Versions). This procedure allows the investigation of test-retest effects.

Two Parallel Versions

Two versions of this paradigm were developed using different words from the same database and with the same criteria (see Stimulus Material). The parallel versions allow administration to the same participants at two time points (e.g., before and after surgery). Participants in the current cohort were allocated randomly to one of the two versions (version A, $N = 13$; version B, $N = 15$). In-scanner memory performance is illustrated per fMRI version and per run in **Supplementary Table S3**.

Data Acquisition

Data were acquired on a 3T Siemens MRI system with a 20 channel head coil. Imaging parameters for multiband EPI images were the following: TR (repetition time) = 1,250 ms, TE (echo time) = 26 ms, slice thickness 2 mm, slice gap 1 mm. The 40 slices per volume were acquired with interleave. A slice tilt was applied to align the scans perpendicular to the long axis of the hippocampus and optimize the Blood Oxygenated Level Dependent (BOLD) sensitivity in medial temporal lobe regions (52). For each functional scanning run, 270 images were acquired, with a total of 810 images across the 3 runs. In addition to the functional images, a T1-weighted magnetization prepared rapid gradient-echo (MPRAGE) scan was acquired for anatomical localization, with a slice thickness of 1 mm, repetition time of 2,300 ms and echo time of 2.74 ms.

Data Pre-processing

Spatial realignment of the images was applied using Statistical Parametric Mapping software (SPM12, Wellcome Department of Cognitive Neurology, London, UK: www.fil.ion.ucl.ac.uk/spm/). The images were then unwarped to reduce spatial distortion using the TOPUP toolbox in FSL (53). Additional retrospective motion correction was applied using Functional Image Artifact Correction Heuristic (FIACH) (54). Finally, the images were co-registered, normalized to a standard MNI space for group analyses, and smoothed with a Gaussian kernel of 6 mm full width half maximum (52). We used the adult MNI template from SPM, due to the age variability in our cohort, and the inclusion of older children.

Image Analyses

Image analyses were conducted using SPM12. Movement parameters were included in the design matrix as covariates. For individual-subject analyses (1st level), the changes in BOLD signal over time were examined for each individual using fixed effect analysis across the three runs. For group analyses (2nd level), contrast estimates from each individual were entered into a GLM with individuals treated as a random factor. Extent and height thresholds were employed, and are specified where appropriate.

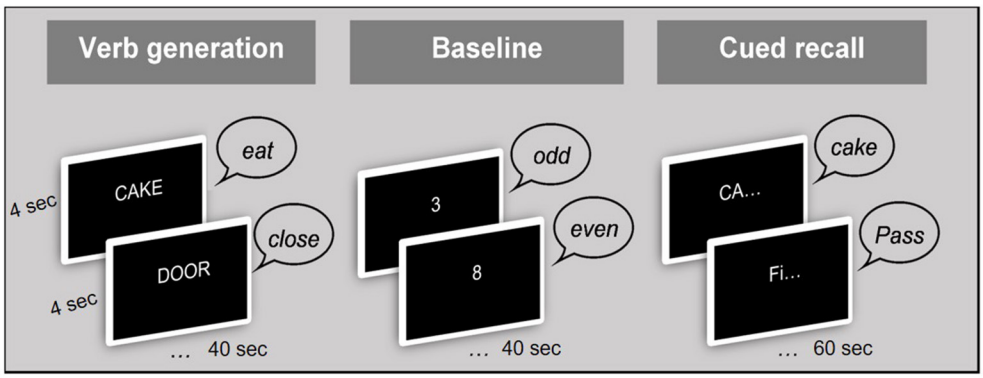

FIGURE 1 | Procedure of the fMRI paradigm.

Statistical Thresholds and ROI Analysis

For analyses without *a priori* hypotheses, whole-brain analysis at the group level is reported, corrected for multiple comparisons ($p < 0.05$ Family-Wise Error (FWE) corrected). For analysis of memory with prior anatomical hypotheses, analyses are reported at threshold $p < 0.001$, uncorrected, in keeping with a previous fMRI study of memory (55). We reduced the number of statistical tests by using a method that exploits anatomical information in the form, or region of interest (ROI) masks. In such masked analysis, only voxels within the mask are included in the analysis. The anatomical constraint in the block, and event-related analyses described below involved a gray matter ROI mask, reducing the number of voxels from 14,000 to 10,000. Moreover, as a result of the known involvement of the hippocampus in delayed-recall memory, this region was of *a priori* interest. As such, hippocampal activations were corrected for multiple comparisons, using a small volume correction (56) within the hippocampus ROI ($p < 0.05$, FWE corrected). To illustrate hippocampal activation after small volume correction, group analyses were repeated within a hippocampal mask ($p < 0.05$ FWE corrected) and are displayed in **Supplementary Figure S4**.

TABLE 2 | Description of each regressor of interest.

	Regressors	Description
Block analysis	Language	Verb generation task
	Baseline	Baseline task: odd/even decision to numbers
	Memory	Cued recall task, irrespective of performance
Event-related analysis	Subsequent Hits	Activation during the encoding of words that were later retrieved
	Subsequent Misses	Activation during the encoding of words that were later forgotten
	Baseline	Baseline task: odd/even decision to numbers
	Hits	Activation during the successful retrieval of words
	Misses	Activation during the unsuccessful retrieval of words
	Correct rejection	Activation during correct rejections of words at retrieval

Block Analysis

Three regressors of interest were created: Language, Baseline and Memory (**Table 2**). Language activations were investigated for the contrast "Language vs. Baseline." Whole-brain analysis at the group level is reported at a height threshold of $p < 0.05$, corrected for multiple comparisons (FWE correction).

Memory encoding activations were investigated for the contrast "Language vs. Baseline." Memory retrieval activations were investigated for the contrast "Memory vs. Baseline." Whole-brain analysis at the group level is reported at a height threshold of $p < 0.001$, uncorrected. Small volume corrections ($p < 0.05$ FWE corrected) within the hippocampus were subsequently applied (see section Statistical Thresholds and ROI Analysis).

Event-Related Analysis

Six regressors of interest were created (**Table 1**): Subsequent Hit, Subsequent Misses, Baseline, Hits, Misses, and Correct Rejections. *Memory encoding success* (also known as the subsequent memory effect) was examined by comparing activation for words that were subsequently remembered (Subsequent Hits) to activation for words that were subsequently forgotten (Subsequent Misses) (contrast Subsequent Hits vs. Subsequent Misses). *Memory retrieval success* was examined by comparing activation for words that were remembered (Hits) to activation for words that were forgotten (Misses) and for words that were correctly identified as "new" (Correct Rejections) (contrast Hits vs. Misses & Correct Rejections).

Whole-brain analysis at the group level is reported at a height threshold of $p < 0.001$, uncorrected. Small volume correction ($p < 0.05$ FWE corrected) within the hippocampus were subsequently applied (see section Statistical Thresholds and ROI Analysis).

Laterality Indices

Lateralisation indices (LI) assess hemispheric lateralisation for a specific cognitive function. This LI was calculated based on the

sum of voxel values in each hemisphere (57). Consistent with clinical studies, values above 0.2 are considered left lateralised, LIs below −0.2 are considered right lateralised, and values between −0.2 and 0.2 indicate bilateral representation.

For the present purpose, LIs were calculated in two ROIs; in Broca's area and in the hippocampus. Language lateralisation was determined based on LI values in Broca's area during the verb generation task, and memory lateralisation was determined in the hippocampus, based on group-level analysis that generated the strongest hippocampal activation (see Group-Level Activations), that is, memory encoding with block analysis and memory retrieval with event-related analysis. The distribution of language and memory LIs is illustrated in **Supplementary Figures S2C–E**.

Test Validity

Memory Performance Between the Two fMRI Versions

In-scanner memory performance was compared between the two fMRI versions, using an independent sample *t*-test, to examine (a) the feasibility of combining the two versions for subsequent analyses, and (b) the utility of these tools for comparable assessment across two time points.

In- and Out-of-Scanner Memory Performance

Performance on the task administered inside the scanner was compared to performance on a standardized test of memory administered outside the scanner, i.e., learning and delayed recall of Word-Pairs from the CMS. For the purpose of this correlation analysis, raw scores in percentages from the CMS, rather than the standardized scores, were used for better comparison with in-scanner memory performance.

Effect of In-scanner Movement on Data Quality

The impact of movement parameters (from the FIACH toolbox) on EPI mean image intensity was investigated. In-scanner motion can degrade image quality and reduce signal-to-noise ratio (SNR) (58). The effect of movement artifacts was therefore investigated in the hippocampus ROI due to its susceptibility to low SNR. Correlations were computed between signal intensity and FIACH temporal SNR (tSNR), which is a measure of deviation of the realigned images (54). The EPI mean signal intensity in the hippocampus was normally distributed (Shapiro-Wilk $p = 0.182$), and so was FIACH temporal SNR (Shapiro-Wilk $p = 0.184$); therefore, we proceeded with a Pearson correlation. Distribution of hippocampal signal intensity and FIACH tSNR are illustrated in **Supplementary Figures S2F,G**, respectively.

Age Effect on In-scanner Behavioral Performance

Due to the large age variability in the current sample, we tested the effect of age on in-scanner language scores (controlling for non-verbal IQ) and memory scores (controlling for full scale IQ), using partial Pearson Correlations. This verifies the usage of the fMRI paradigm across the age range of our sample. Distribution of in-scanner language and memory scores is illustrated in **Supplementary Figures S2A,B**, respectively.

Age Effect on Functional Lateralisation

We tested the effects of age on functional lateralisation for language and memory, using Pearson Correlations.

Reproducibility of the Paradigm

Memory Performance Across Runs

The reproducibility of the paradigm was determined based on the stability of the behavioral data across the three scanning runs, which were acquired a few minutes apart. For this section, each run was analyzed separately to investigate inter-run variability.

The consistency between performance across runs was measured using Intra Class Correlation (ICC), which is a measure of the ratio of between-subject variance and between-tests variance. In this respect, the value approaches 1 if the variability across individuals is larger than the variability within individuals across repeated runs. The ICC was based on a 2-way mixed-effects model.

Signal Intensity in the Hippocampus Across Runs

Signal intensity in the hippocampus was identified in each individual's EPI mean acquisition and compared across scanning runs. Signal intensity in a control region, the cingulate cortex, was also compared across scanning runs.

Laterality Indices (LIs) Across Runs

The consistency between LI values across runs was measured using ICC, based on a 2-way mixed-effects model.

Laterality Indices (LIs) Across Sessions

The consistency between LI values across two separate sessions (time 1 and time 2) was measured using ICC, based on a 2-way mixed-effects model.

RESULTS

Group-Level Activations

Language Activations

Activation was found in left Broca's area, the left STG, bilateral dorsolateral prefrontal cortex (DLPFC), pre-supplementary motor area (pre-SMA), right cerebellum, left thalamus, left anterior insula and bilateral middle cingulate cortex (MCC) (**Figure 2**).

Memory Activations

Block-level whole-brain activation associated with memory encoding (contrast Language vs. Baseline) is documented in the previous section (i.e., language activations), and is illustrated in **Figure 3A**, where left hippocampal activation is observed. The small volume correction resulted in significant activation within the left hippocampus in three separate peaks (1: peak coordinates −28 −28 −6, T = 4.30, corrected $p = 0.011$, 2: peak coordinates −20 −30 −4, T = 3.95, corrected $p = 0.030$, and 3: peak coordinates −14 −36 2, T = 3.82, corrected $p = 0.043$). Event-related activation associated with memory encoding success (contrast Subsequent Hits vs. Subsequent Misses) was shown in the left temporal pole and right posterior superior temporal lobe, shown in **Figure 3B**.

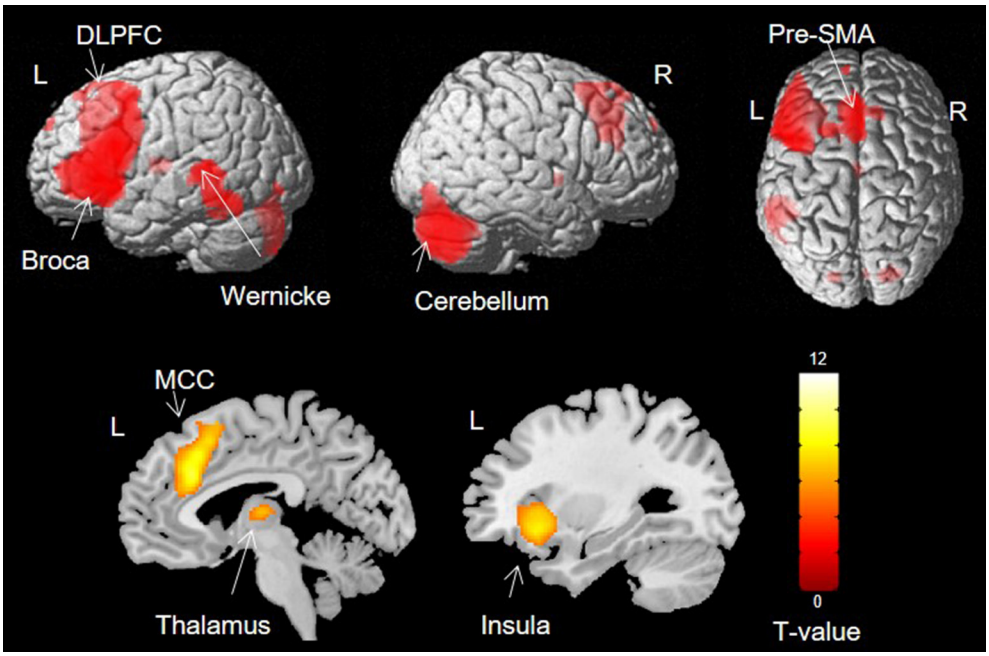

FIGURE 2 | Group activation during verb generation task ($p < 0.05$, FWE).

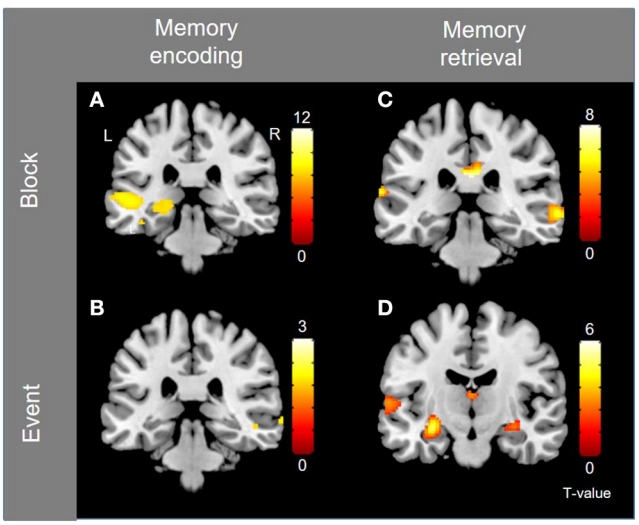

FIGURE 3 | Group-level activations for memory encoding and retrieval, for block- and event-related analyses, separately. **(A)** Block-activation for subsequent memory (i.e., memory encoding). **(B)** Event-related activation for subsequent memory (i.e., memory encoding). **(C)** Block-activation for memory retrieval (contrast Memory vs. Language). **(D)** Event-related activation for successful retrieval. Activations are shown with threshold of $p < 0.001$, uncorrected.

Block-level activations for memory retrieval (contrast Memory vs. Baseline) were found in left Broca's area, left dorsolateral PFC, bilateral cerebellum and bilateral posterior temporal lobes. Activations were also shown in bilateral anterior insula, bilateral pre-SMA, bilateral middle and posterior cingulate cortex (PCC & MCC), and bilateral caudate nuclei. Because many of these activations overlap with those reported for language, another contrast was investigated (contrast Memory vs. Language) to identify activations that are specific to the memory task. Activations were shown in right dorsolateral PFC, right orbitofrontal PFC, bilateral posterior temporal lobes (right posterior middle temporal gyrus and left posterior STG), right pre-SMA, and posterior cingulate cortex ($p < 0.001$, uncorrected), as shown in **Figure 3C**. Event-related activity associated with memory retrieval success (contrast Hits vs. Misses & Correct Rejections) was shown in bilateral hippocampi, left posterior STG and left caudate (**Figure 3D**). The small volume correction resulted in significant activation within the left hippocampus (peak coordinates −30 −14 −12, T = 4.38, corrected $p = 0.005$).

Left hippocampal activation is shown during encoding (block analysis) and retrieval (event-related analysis) after small volume correction and is illustrated in **Supplementary Figure S4**. Group-level analyses were repeated with age and gender as nuisance regressors, and yielded similar results (**Supplementary Figure S5**).

Test Validity

Memory Performance Between the Two fMRI Versions

Memory performance was not significantly different between versions A (54%) and B (60%) [$F_{(1, 26)} = 0.198$, $p = 0.504$]. Memory scores from the two versions were therefore collapsed for the subsequent analyses.

In- and Out-of-Scanner Memory Performance

For the purpose of this analysis, in-scanner memory performance was collapsed across fMRI versions (see Memory Performance Between the Two fMRI Versions) and runs (see Cued-Recall Performance Across Runs). Cued recall scores on the fMRI task were moderately correlated with CMS learning scores ($r = 0.45$, $p = 0.019$), but not with CMS delayed recall scores ($r = -0.025$, $p = 0.903$).

Effect of In-scanner Movement on Data Quality

No significant relation was found between in-scanner movement parameters and signal intensity in the hippocampus ($r = -0.104$, $p = 0.613$).

Age Effect on In-scanner Behavioral Performance

Partial correlations showed that age was significantly correlated with language scores ($r = 0.39$, $p = 0.048$), and memory scores ($r = 0.47$, $p = 0.019$) where older children performed better than younger children. However, the correlation between age and language scores was moderate and no floor/ceiling effect were shown in any of the measures.

Age-Effects on Functional Lateralisation

Age was not significantly related to functional lateralisation of language ($r = -0.18$ $p = 0.380$), memory encoding ($r = -0.18$ $p = 0.372$) or memory retrieval ($r = -0.04$ $p = 0.854$).

Reproducibility of the Paradigm

Cued-Recall Performance Across Runs

Performance accuracy was 56% ($SD = 35$) in the first run, 53% ($SD = 26$) in the second run, and 58% ($SD = 21$) in the third run (**Supplementary Figure S3A**). ICC was 0.92, indicating good stability of performance across runs. This implies that it is possible to collapse findings from across the runs and treat them as fixed effect in 1st level analyses.

EPI Mean Signal Intensity in the Hippocampus Across Runs

Signal intensity in the hippocampus was compared across scanning runs (**Supplementary Figure S3B**) and was found to be stable. ICC was 0.98, indicating high reliability of mean signal intensity in the hippocampus across runs. ICC for the signal intensity in the cingulate cortex was 0.99, indicating high reliability of mean intensity in the control region as well.

fMRI Laterality Indices (LIs) Across Runs

Group-level language and memory LIs were examined across the three runs (**Supplementary Figure S3C**). For language LIs, ICC was 0.44, indicating moderate stability of values across runs. For memory encoding, ICC was 0.37, indicating moderate stability of values across runs, however for memory retrieval ICC was −0.28 indicating low interclass correlation.

fMRI Laterality Indices (LIs) Across Sessions

Group-level language and memory LIs were examined across the two sessions in the subset of participants who were scanned twice. For language LIs, ICC was 0.71, indicating good stability of values across sessions. For memory encoding LIs, ICC was −0.71 indicating low interclass correlation. Finally, for memory retrieval LIs, ICC was 0.45, indicating moderate stability of values across sessions.

DISCUSSION

We designed a novel fMRI paradigm for the mapping of language and memory, and the examination of the interaction between those two systems, in children. Here we discuss the validity of this paradigm based on the performance of a group of healthy children and adolescents. Group-level activations were found in regions typically associated with expressive language. For memory, hippocampal activation was detectable during both memory encoding and retrieval, using block, and event-related analyses. The average memory performance across the runs (56% correct) provides enough trials in each condition (i.e., Hits and Misses) allowing event-related analyses. Validity of the paradigm was demonstrated through moderate correlations between in-, and out-of-scanner memory scores, suggesting that the novel fMRI paradigm relates to memory performance outside the scanner, but is also influenced by other factors inside the scanner, such as testing environment and nature of the test. In-scanner memory scores were correlated with out-of-scanner learning scores, but not with delayed recall scores possibly due to the longer delay interval (i.e., 20 min, as opposed to 50 s in the scanner). Importantly, in-scanner motion, often attributed to overt responses, did not significantly impede fMRI data quality. Notwithstanding a significant age effect on in-scanner language and memory scores, attributed to the trajectory of normal cognitive development, the correlations were moderate and children across the age range studied were capable of performing the tasks.

Reproducibility of the paradigm was tested by examining the stability of cued recall performance and EPI signal intensity in the hippocampus across three scanning runs, as well as the stability of fMRI LIs across three scanning runs and two scanning sessions separated by an average of 1.5 years. These variables showed intra-session stability of language and memory encoding, as well as inter-session stability of language and memory retrieval, providing evidence for the paradigm's reliability and reproducibility.

Effect of In-scanner Movement on Data Quality

Task-related motion, such as head movement related to speech, can cause signal changes which may hamper data quality and be misinterpreted as brain activation (59). Negative effects of in-scanner motion are especially pronounced in pediatric populations (60) and should be taken into consideration in fMRI studies involving overt speech. Image quality is specifically compromised in images with low SNR (61). Therefore, in the present study, the effect of movement artifact on image quality was specifically investigated in the hippocampus, but found not to have a significant impact on fMRI data quality. This provides evidence that overt speech should be considered in future fMRI

studies. FIACH is also very effective in reducing between- and within-volume motion-related effects (54).

Effect of Age on Functional LIs

In typically-developing children, language lateralisation is emergent by the age of 5 (44, 62), but changes with increasing age parallel the development of language skills (63). However, the present findings do not suggest a developmental trajectory in language and memory lateralisation. It is possible that tracking changes in degree of lateralisation as a function of age requires large cohorts separated by age bands to mirror the stages of cognitive development as compared to one group spanning a wide age range (8 to 18). Similar to language, it is possible that verbal memory lateralises early in life, and administering the memory paradigm in younger children (between the ages of 5 to 8) could potentially shed light on the developmental trajectory of memory lateralisation. Indeed, increasing left lateralisation for language in the MTL across childhood has been shown in a cohort of young children (6–13 years old) (31). To explore this further, age-related changes in memory-related MTL lateralisation should be further explored in children below the age of 8 years, particularly as different aspects of cognitive memory emerge at different stages of development.

Reproducibility and Reliability

The reproducibility of the fMRI paradigm was tested by investigating the stability of memory performance and EPI mean signal intensity in the hippocampus across the three scanning runs, as well as the stability of language and memory LIs over (a) three scanning runs and (b) two separate sessions. The consistency of performance across the runs indicates that the memory paradigm yields reproducible results.

Intra- and inter-session reliability of LIs was examined by measuring stability of language and memory LIs across three scanning runs, and across two scanning sessions (1.5 years apart on average), respectively. Bennett and Miller suggested a range of ICC values between 0.33 and 0.66 within which fMRI studies are typically reliable (64). As per this range, LI values (for both language and memory) were more stable across scanning sessions than across runs, possibly due to higher statistical power as a result of additional trials (20 trials per run vs. 60 for the whole session). This indicates the importance of having a considerable number of trials to provide a measurable and reliable response.

In the present study, language LIs were stable across runs and sessions, thereby reflecting reliable results. Memory encoding LIs were also stable across runs, but not across scanning sessions. This may be a result of noise in the data (e.g., physiological noise from the participants, and system noise in the scanner) or subject variability in arousal and use of strategy between sessions (64). Attention and arousal can modulate responses and influence brain activation (65), hence contributing to changes in the LI values in memory encoding. Other possible influences are differences in cognitive strategies used during the memory task to encode the words (66), or differences in performance (i.e., successful vs. unsuccessful memory), as a function of developmental change.

In contrast to memory encoding, memory retrieval LIs were not stable across runs, but showed good stability across sessions. There may not have been sufficient number of trials to capture stability of event-related LI values across runs, but the stability of retrieval LIs across sessions suggests good inter-session reliability, and is therefore promising. Stability of memory LIs should be confirmed in adults, who may show a more lateralised pattern of activation (31) and for whom ICC measurement might be appropriate. Overall, the stability of language and memory retrieval LI values across separate scanning sessions suggests reliability of these measures, and is a promising indicator of reproducibility of this paradigm.

Implications for Future Clinical Applications

This fMRI paradigm has multiple advantages over current neuroimaging tasks. First, the combined language/memory aspect of the paradigm offers pre-operative mapping of both networks in a time-, and cost-effective manner. Memory fMRI administered in conjunction with language fMRI could provide a better guide for tailored resections, particularly in the temporal lobe, and help predict outcome. This paradigm can be used to shed light on how the two systems interact in cases of early temporal lobe-related abnormality, and explore whether lateralisation for memory and language are interdependent. Whereas co-lateralisation of language and memory functions has been demonstrated in healthy adults, whereby those with language dominance in the left hemisphere also show left lateralisation for verbal memory (67), this is less clear in children. Moreover, patients with DA exhibit severe and selective impairment in recall memory but good preservation of language skills, especially vocabulary, and other aspects of semantic memory. This indicates that the hippocampus is not crucial for the development and maintenance of language functions and semantic memory [see Elward and Vargha-Khadem (68) for a review]. The relation between language and memory networks is therefore unclear at this stage, and may critically depend on long-term auditory verbal memory (69). Although this novel paradigm investigates language and memory processes separately, it does provide an indication of the interaction between these two networks, and, potentially, of the status of functional reorganization in the context of age at onset of brain damage.

Second, the paradigm enables examination of fMRI activation related to both memory encoding and retrieval, thus providing a more robust mapping of memory-related networks, as both phases are dependent on hippocampal involvement (70, 71). Moreover, obtaining robust activation in the hippocampus at the individual level has proven challenging across fMRI studies (71, 72), but a wider approach to memory mapping involving two memory phases (encoding and retrieval) may increase the chances of capturing such an effect.

Third, this paradigm investigates activity related to recall memory, as opposed to recognition, for a more fine-grained examination of the hippocampal-neocortical network (39, 73–75). Failure to show robust activation in hippocamal regions in

some fMRI studies may be due to the recognition nature of the tasks often employed, which may rely on other subregions of the MTL. Word-stem cued-recall tasks have been used by previous fMRI studies and show activation in healthy adults in several regions that are associated with successful recall, namely bilateral parietal cortex, bilateral medial temporal lobe, including the hippocampi, and left temporal cortex (45, 46, 76, 77). By contrast, adult patients with epilepsy show deficits in word-stem recall (78), making this task potentially sensitive to the identification of network abnormalities.

Fourth, the design of the paradigm permits investigation of fMRI data through both block and event-related analyses. Block analyses allow examination of brain activity related to memory effort, irrespective of performance, whereas event-related analyses examine memory success specifically, and are particularly relevant for predicting memory outcome in the clinical setting. Together, the features of this paradigm make it particularly useful for the investigation of pre-operative memory networks and for the prediction of memory outcome in TLE.

Lastly, the parallel versions of the paradigm allow systematic comparisons between performance across two time points. This paradigm can be administered before and after surgical intervention, and such clinical follow-up can provide indication of the impact of surgery on the functional organization of language and memory. Non-specific effects of test-retest can be controlled for by including a healthy controls group scanned across the same time-points as the patient group (79). A mixed ANOVA using a flexible factorial design (80) models the changes in brain activation at two time-points, whilst controlling for between-subjects and between-group variance (55). The inclusion of a control group at two time-points therefore allows adequate use of the parallel versions of the fMRI paradigm in patient groups.

Following the development of this protocol and its validation in a group of typically-developing children, confirmation of the findings is required by administering the protocol to a larger sample in order to confirm the feasibility of this tool for clinical purposes. Moreover, further work is required to validate the ability of the protocols to predict memory impairments after surgery by investigating post-surgical outcome in children with TLE. Overall, this paradigm has the potential to enhance clinical practice for pre-operative examination in TLE.

LIMITATIONS

Despite efforts to reduce the effect of priming, it is possible that the retrieval of words is still influenced by some level of automatic retrieval, or echoic memory. Another limitation relates to the short delay between encoding and retrieval phases (50 s). The attribution to long-term memory with such delay could be disputed, but methodological considerations were put in place to insure this. The baseline task involving active and overt response prevents subvocal rehearsal and maintenance of information in short-term memory. It is possible that a longer delay between encoding and recall phases of memory is more sensitive for the investigation of hippocampal-related brain activation, but this comes with the pitfall of longer scanning time, especially with children.

The current acquisition settings were selected on the basis of a prior pilot study aimed at optimizing the acquisition sequences for pre-surgical fMRI. However, we recognize that different fMRI acquisition settings could alter brain activity measurements, and careful piloting is necessary.

Low statistical thresholds ($p < 0.001$, uncorrected) were used for memory analyses to visualize brain activation in subregions of the MTL. Whereas components above such low threshold might be labeled as noise, the findings were consistent with hypotheses postulated on the basis of prior studies in adults. In addition, small volume corrections were subsequently applied to the hippocampal region to correct for multiple comparisons. In addition, LI calculation was carried out independent of an arbitrarily defined threshold. LI values for language and memory retrieval showed good inter-session reliability, providing their promising use in single-subject level analysis which has crucial implications in the clinical context.

Despite the above limitations, the present findings provide evidence of the utility of this new paradigm for the examination of memory network in TLE. We pursued hippocampal-driven analyses based on *a priori* hypotheses, and using anatomically-constrained masking. As a result of the precautionary measures taken for the analyses, we are confident that the present findings are robust and appear promising.

CONCLUSIONS

We present a novel fMRI paradigm to map language and verbal memory functions, as well as the interaction between them, *within one scanning session*. Other advantages of this fMRI protocol are (a) assessment of both encoding- and retrieval-related neural networks, (b) recall-based retrieval to increase hippocampal recruitment, and (c) overt responses allowing the investigation of neural networks that support successful memory specifically. This paradigm was developed to provide more precise information on neural networks subserving functions at risk, and to offer improved input to surgical decision-making in pediatric TLE. Finally, the parallel versions of the paradigm provide the means to compare language and memory activations pre- and post-surgical intervention.

DATA AVAILABILITY STATEMENT

The present script for the language/memory fMRI paradigm, as well as the scripts for pre-processing and data analyses are available upon request from the corresponding author.

ETHICS STATEMENT

This study was ethically approved by the UCL Research Ethics Committee (project number 7447/002), and was conducted in

accordance with the World Medical Association Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

SB acquired data at time 1 of the study. FB acquired data at time 2 of the study, for test-retest measurements. All authors contributed to manuscript revision, read, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.01384/full#supplementary-material

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Major Depressive Disorder Associated With Reduced Cortical Thickness in Women With Temporal Lobe Epilepsy

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Background: Major Depressive Disorder (MDD) is highly prevalent in patients with mesial temporal lobe epilepsy (MTLE), especially in women, carrying significant morbidity. This study aimed to investigate the cortical thickness (CT) abnormalities associated with MDD in women with MTLE and hippocampal atrophy (HA). Also, we investigated the impact of MDD upon the volumes of the hippocampus and amygdala in these patients.

Methods: We included 50 women with MTLE and HA (20 left, LMTLE; 30 right, RMTLE), 41 healthy women in the control group, and 15 women with MDD without epilepsy. MTLE patients were subdivided into three groups: *MTLE-without-MDD* (23 MTLE patients without MDD), *MTLE-mild-MDD* (nine MTLE patients with mild symptoms of MDD), and *MTLE-severe-MDD* (18 MTLE patients with moderate to severe symptoms of MDD). The five groups were balanced for age ($p = 0.56$). All participants had high-resolution 3D T1-weighted images in a 3T scanner. We used FreeSurfer 6.0 for volumetry and CT parcellation. All participants were submitted to a clinical psychological evaluation through the Structured Clinical Interview for DSM-IV (SCID-IV) and completed the Beck Depression Inventory (BDI-II).

Results: We identified a smaller ipsilateral amygdala volume ($p = 0.04$) in the *MTLE-severe-MDD* group when compared to the control group. Our results presented a reduced ipsilateral lateral orbitofrontal cortex ($p = 0.02$) in the *MTLE-severe-MDD* in comparison to the *MTLE-mild-MDD* group. We also identified a thinner ipsilateral fusiform gyrus ($p < 0.01$) in the *MTLE-severe-MDD* compared to both *MTLE-without-MDD* and control groups. A reduced CT of the contralateral superior frontal gyrus ($p = 0.02$) was observed in the *MTLE-severe-MDD* in comparison to the *MTLE-mild-MDD* group.

Conclusions: The identification of areas with reduced CT and atrophy of the ipsilateral amygdala in women with MTLE and MDD suggest that the cortical thinning in the network of the paralimbic system is related to the co-occurrence and intensity of depressive symptoms in this group.

Keywords: mesial temporal lobe epilepsy, major depressive disorder, women with epilepsy, cortical thickness abnormalities, surfaced-based methods

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INTRODUCTION

Major depressive disorder (MDD) has a high prevalence (20–55%) (1–6) in patients with mesial temporal lobe epilepsy (MTLE) (1, 7), in comparison to the general population (5–17%) (8). This psychiatric comorbidity brings significant concerns about the poor quality of life of these patients (2, 9). Also, the risk of suicide is a serious concern in patients with MTLE and MDD (13.5% of all suicides in people with epilepsy) (1, 10).

Although controversial, some studies have reported that women with or without epilepsy appear to be more affected by MDD than men (11). MDD has a female/male risk ratio of ∼2:1 in the general population and is one of the primary disease-disability impairments among women around the world (12). Some authors (12) suggest that the occurrence of this psychiatric disorder is not related to sexual hormones; however, more studies are needed to clarify the interplay between biological susceptibility and environmental influences, including the social aspects.

In the last decades, neuroimaging studies have been attempting to identify neuro-anatomical substrates of MDD (13). The surface-based methods (14) engender accurate maps of cortical thickness (CT) and have provided a large amount of information about automatic brain segmentation, allowing comparisons among groups of patients and controls (13). Taking into account the CT abnormalities in patients with MDD, some studies have reported alterations in the paralimbic circuitry, which includes the orbitofrontal cortex (13), cingulate cortex (13), insula, temporal (15), and prefrontal regions (13, 16, 17). Furthermore, volumetric alterations of the subcortical structures, including the amygdala (18) and hippocampus (19–21), have been consistently reported in patients with epilepsy and psychiatric disorders.

Although there are relatively few studies evaluating cortical abnormalities in patients with MDD, there are even less of such studies in MTLE patients with MDD (22). Authors suggest a bidirectional interaction between epilepsy and MDD, not as a causal relationship, but perhaps due to yet unclear common pathogenic mechanisms involving similar structures in both MTLE and MDD (6). Further investigations are needed to clarify the profile and pathogenesis effects of concurrent MDD in patients with MTLE, and whether these patients are neurobiologically different from people with MDD without epilepsy (22).

We aimed to investigate the CT abnormalities associated with MDD in women with MTLE and unilateral hippocampal sclerosis (HS) (23). Also, we investigated the impact of MDD upon the volumes of the hippocampus and amygdala.

MATERIALS AND METHODS

Subjects Selection

We evaluated 70 women with MTLE and a mean age of 45.7 [standard deviation (SD) ±8.9] years, currently followed at our outpatient epilepsy clinic (Tertiary Hospital—University of Campinas, UNICAMP, São Paulo, Brazil). During the analysis, we excluded four patients with bilateral HS, five patients with apparently non-lesional focal epilepsy, five patients with other brain lesions, two patients with MRI artifacts, and four patients due to errors in the automated cortex segmentation. The final sample included 50 women with MTLE [mean age of 43.9 (±8.8) years] with unilateral HS (left MTLE, $n = 20$; right MTLE, $n = 30$). All MTLE patients (age range from 26 to 64 years old) were diagnosed according to the International League Against Epilepsy (ILAE) criteria (24, 25) and had not been submitted to surgery. The definition of unilateral HS was made by an evaluation of an MRI epilepsy protocol by imaging experts as detailed previously (23, 26). We also included 15 women [38.8 (±9.7) years] with MDD without epilepsy (*MDD-without-epilepsy* group), and 41 healthy women without depressive symptoms as the control group [43.1 (±12.3) years].

Clinical and Sociodemographic Data

In addition to age and gender, we collected clinical data from medical charts, including the age of onset, duration of epilepsy, monthly frequency of seizures, pharmacoresistance status, side of HS, and current antiepileptic and antidepressants drugs. None of the patients were taking levetiracetam (27). All patients in this study had normal average IQ. All the subjects signed the consent form approved by the University Ethics Committee before their admission to our study.

Psychiatric Assessment

Participants were submitted to a clinical psychological interview with the Clinical Interview for DSM-IV (SCID-I) (28), focusing on possible current and past axis I psychiatric diagnoses. Additionally, we assessed depression symptoms by Beck Depression Inventory (BDI-II) (29). We followed recommended BDI-II cutoffs for the Brazilian population to determine MDD symptoms severity (0–13 as no depression, 14–19 as mild depression, 20–28 as moderate depression, and 29–63 as severe depression) (29). We only included patients with MDD diagnoses and excluded all subjects with other psychiatric comorbidities, as detailed in a previous study (3).

The 50 MTLE patients were subdivided into three groups according to the psychiatric assessment and BDI-II scores: *MTLE-without-MDD* (MTLE without depressive symptoms, $n = 23$), *MTLE-mild-MDD* (mild depressive symptoms, $n = 9$), and *MTLE-severe-MDD* (moderate to severe depressive symptoms, $n = 18$).

MRI Acquisition and Cortical Thickness Analysis

All participants underwent a high-resolution volumetric T1-weighted MRI in a 3T scanner with the following protocol (30):

- Volumetric (3D) images acquired in the sagittal plane: T1-weighted image: isotropic voxels of 1 mm, acquired in the sagittal plane (1-mm-thick, no gap, flip angle = 8°, TR = 7.0 ms, TE = 3.2 ms, matrix = 240 × 240, FOV = 240 × 240 mm).

All images were visually checked for abnormalities unrelated to MTLE and motion artifacts.

For the CT and the analyses of the subcortical structures, we used the fully automated software FreeSurfer 6.0 (31, 32) (https://surfer.nmr.mgh.harvard.edu), which performed cortical reconstruction and volumetric segmentation. In summary, FreeSurfer corrects images by inhomogeneity of the magnetic field, aligns the images to the atlas of Talairach-Tournoux, removes non-cerebral tissue, segments gray matter, white matter, cerebrospinal fluid, and identifies voxels by the intensity of each element and its adjacent regions. Algorithms and a smoothing process are applied to correct topological defects (31, 32). A second smoothing interaction was used to identify the pial surface, which is segmented into small neuroanatomic regions, according to an atlas proposed by Desikan et al. (33). This automated labeling system subdivides the human cerebral cortex into 34 cortical regions of interest (ROIs) in each cerebral hemisphere, totaling 68 areas (33).

We performed a visual inspection of every individual processed image to guarantee a high pattern of quality and accuracy in the automated segmentation process. Brain regions with segmentation failure were excluded from our analysis.

We defined the hippocampus and the amygdala as subcortical structures of interest, considering their roles in both MTLE and the limbic system (34). To determine the ipsilateral hippocampus of the *MDD-without-epilepsy* and in the control group, we randomly assigned the hippocampal volume to follow the same proportion of HS lateralization of the MTLE patients. Accordingly, we determined that in 40% of these participants, the ipsilateral cerebral hemisphere was the left side, and consequently, in the remaining 60%, the right side was set as ipsilateral.

Data Analysis

We performed the Kolmogorov-Smirnov test to evaluate data distribution and model fit and Pearson correlation tests to explore the relationship between continuous variables. To test group differences, we used the general linear model (GLM) with Sidak as *post-hoc* tests or Kruskal-Wallis test, when appropriate. Categorical variables were analyzed with the Pearson χ^2-test. All the analyses considered the following groups: *MTLE-without-MDD, MTLE-mild-MDD, MTLE-severe-MDD, MDD-without-epilepsy*, and control.

In details, the analyses were performed as follows:

1) Comparison of the clinical and sociodemographic data among the groups;
2) Comparison of the hippocampi and amygdala volumes among the groups, including age, supratentorial volumes, and antidepressant drug usage as covariates. The effects of the age of onset of epilepsy and seizure frequency on both hippocampi/amygdala values of MTLE patients were also controlled in a separate analysis using multiple linear regression residuals. In addition, we conducted a correlation analysis among the hippocampi and amygdala volumes with BDI-II scores.
3) Correlation analysis among the 68 CT regions (34 ipsilateral/34 contralateral) and the BDI-II scores in the *MDD-without-epilepsy* group; this initial investigation was performed to establish a baseline of the CT analysis with the areas most associated with symptoms of depression. Since our analyses were exploratory and intended to guide the next steps (see item 4), we did not correct for the number of ROIs evaluated.
4) Subsequently, we selected the CT regions with significant correlation from the previous step [$p < 0.05$ and the absolute r-value of at least 0.5 (starting at a moderate correlation)] to perform comparisons among the MTLE groups, including age and antidepressant drug usage as nuisance covariates. As step two, we also controlled the effects of the age of onset of epilepsy and seizure frequency on CT values of MTLE patients in a separate analysis using multiple linear regression residuals. Ipsilateral and contralateral ROIs were analyzed in separated GLMs to avoid multicollinearity.

We reported the results using mean ± SD for parametric data and median (range) for data with non-parametric distribution. We used the Statistical Package for the Social Sciences—SPSS22 (Armonk, NY, U.S.A) to perform statistical analysis with a significant level set at $p < 0.05$.

RESULTS

Clinical and Sociodemographic Information and BDI-II Scores

The *MTLE-without-epilepsy, MTLE-mild-MDD, MTLE-severe-MDD, MDD-without-MTLE,* and control groups were balanced for age ($p = 0.56$). Clinical and sociodemographic characteristics of the participants are presented in **Table 1**. We found a significant difference among the MTLE groups when we compared the frequency of seizures [Kruskal-Wallis test, χ^2 (2, $N = 50$) = 41.8, $p < 0.001$]. The group *MTLE-severe-MDD* presented a higher frequency of seizures ($p < 0.01$) when compared to the *MTLE-mild-MDD* and *MTLE-without-MDD* groups. The usage of antidepressant drugs was significantly higher [χ^2 (4, $N = 106$) = 66.5, $p < 0.01$] in the *MTLE-mild-MDD, MTLE-severe-MDD*, and *MDD-without-epilepsy* when compared to the *MTLE-without-MDD* and control groups. The groups *MTLE-mild-MDD, MTLE-severe-MDD*, and *MDD-without-epilepsy* did not present significant differences [χ^2 (3, $N = 42$) = 1.01, $p = 0.61$] related to the antidepressant drug usage. As expected, the *MTLE-mild-MDD, MTLE-severe-MDD*, and *MDD-without-epilepsy* groups had higher scores on BDI-II [Kruskal-Wallis test, χ^2 (4, $N = 106$) = 78.6, $p < 0.001$] when compared to the *MTLE-without-MDD* and control groups.

Subcortical Analysis

We compared both hippocampus and amygdala volumes among the groups. There was a significant multivariate group effect in the ipsilateral analyses [$F_{(8, 186)} = 5.26$, $p < 0.001$; Pillai's Trace = 0.37; $\eta^2 = 0.18$]. As expected, the *MTLE-without-MDD*, *MTLE-mild-MDD*, and *MTLE-severe-MDD* groups presented a smaller ipsilateral hippocampus [$F_{(4, 93)} = 8.56$, $p < 0.01$, partial $\eta^2 = 0.27$] when compared to the control group, however, they did not differ ($p > 0.05$) from the *MDD-without-epilepsy* group. No significant differences in the contralateral hippocampus were

TABLE 1 | Clinical and sociodemographic characteristics and BDI-II scores of the participants included in our study.

Groups	*MTLE-without-MDD* *N* = 23 mean (SD), or median (range), or *N* (%)	*MTLE-mild-MDD* *N* = 9 mean (SD), or median (range), or *N* (%)	*MTLE-severe-MDD* *N* = 18 mean (SD), or median (range), or *N* (%)	*MDD-without-epilepsy* *N* = 15 mean (SD), or median (range), or *N* (%)	*Control* *N* = 41 mean (SD), or median (range), or *N* (%)	*p*-value
Age (years)	44.9 (±8.1)	43.3 (±11.1)	43.1 (±9.2)	38.9 (±9.8)	43.1 (±12.3)	0.56
Duration of epilepsy	31.7 (±12.3)	31.3 (±13.9)	30.7 (14.4)	NA	NA	0.97
Age of onset	12 (1–37)	4 (1–32)	5 (1–48)	NA	NA	0.46
Side of hippocampal atrophy				NA	NA	0.86
Left	10 (43.5%)	3 (33.3%)	7 (38.9%)			
Right	13 (56.6%)	6 (66.7%)	11 (61.1%)			
Seizure frequency (monthly)	0.5 (0–12)	0.5 (0–4)	3.5 (0–12)	NA	NA	<0.001
Pharmacoresistance				NA	NA	0.41
Yes	12 (52.2%)	5 (55.6%)	13 (72.2%)			
No	11 (47.8%)	4 (44.4%)	5 (27.8%)			
Antiepileptic drugs				NA	NA	0.48
Monotherapy	6 (26.1%)	4 (44.4%)	4 (22.2%)			
Polytherapy	17 (73.9%)	5 (55.6%)	14 (77.8%)			
Antidepressant drugs						<0.01
Yes	2 (8.7%)	6 (66.7%)	15 (83.3%)	12 (80%)	0 (0%)	
No	21 (91.3%)	3 (33.3%)	3 (16.7%)	3 (20%)	41 (100%)	
BDI scores	3 (0–9)	15 (12–19)	26 (20–40)	30 (10–41)	4 (0–9)	<0.01

MTLE, mesial temporal lobe epilepsy; MDD, Major Depressive Disorder; MTLE-without-MDD, MTLE patients without psychiatric disorders; MTLE-mild-MDD, MTLE patients with mild depressive symptoms; MTLE-severe-MDD, MTLE patients with moderate to severe depressive symptoms; MDD-without-epilepsy, patients with Major Depressive Disorder without epilepsy; N, number of participants; SD, standard deviation; BDI, Beck Depression Inventory; NA, not applicable.

observed among all groups [$F_{(4, 95)} = 0.84$, $p = 0.5$, partial $\eta^2 = 0.03$], as presented in **Figure 1A**. Taking into account the amygdala, we only observed a significant reduction in the volume of the ipsilateral amygdala in the *MTLE-severe-MDD* group [$F_{(4, 93)} = 2.8$, $p = 0.04$, partial $\eta^2 = 0.11$] when compared to the control group, as shown in **Figure 1B**. No difference was observed in the contralateral amygdala volume among the groups [$F_{(4, 95)} = 1.31$, $p = 0.27$, partial $\eta^2 = 0.05$]. We did not observe significant differences in the correlation analysis ($r < -0.5$, $n = 106$, $p > 0.05$, one-tailed) among the hippocampus and amygdala volumes with the BDI-II scores in the five groups. We conducted further analysis considering only the MTLE groups and the subdivision of left and right atrophy sides. However, no significant differences were detected.

Cortical Thickness Correlations

In the first step, we investigated the significant correlations between CT and BDI-II scores in patients with depression without epilepsy (*MDD-without-epilepsy* group). We found 24 CT areas with significant negative correlations with BDI-II scores in the *MDD-without-epilepsy* group, as shown in **Table S1**.

Cortical Thickness Group Comparisons

As planned, we performed group comparisons with the 24 CT regions (16 CT ipsilateral and eight CT contralateral regions) significantly associated with symptoms of depression in our *MDD-without-epilepsy* group. The multivariate analysis of CT among the five groups (*MTLE-without-MDD, MTLE-mild-MDD, MTLE-severe-MDD, MDD-without-epilepsy*, and control) was significant for the ipsilateral [$F_{(64, 296)} = 1.46$, $p = 0.02$; Pillai's Trace = 0.96; $\eta^2 = 0.24$] and for the contralateral regions [$F_{(32, 340)} = 1.49$, $p = 0.047$; Pillai's Trace = 0.49; $\eta^2 = 0.12$]. We observed a reduced CT of the ipsilateral lateral orbitofrontal cortex [$F_{(4, 86)} = 0.52$, $p = 0.02$, partial $\eta^2 = 0.13$] in the *MTLE-severe-MDD* when compared to the *MTLE-mild-MDD* group. A thinner ipsilateral fusiform gyrus [$F_{(4, 86)} = 0.52$, $p < 0.01$; partial $\eta^2 = 0.16$] was found in the *MTLE-severe-MDD* when compared to the *MTLE-without-MDD* and control groups, as presented in **Figure 2**. We noticed a reduced CT of the contralateral superior frontal gyrus [$F_{(4, 88)} = 0.67$, $p = 0.02$, partial $\eta^2 = 0.15$] in the *MTLE-severe-MDD* when compared to the *MTLE-mild-MDD* group (**Figure 3**).

DISCUSSION

The application of a semi-structured psychological clinical interview (SCID-I) in patients with MTLE allowed us to diagnose those with and without depression. The analysis of CT atrophy in these groups revealed a differential pattern of CT abnormalities in the MTLE subgroups with and without depression. In addition, atrophy of the ipsilateral amygdala was detected exclusively in the *MTLE-severe-MDD* group. Differently

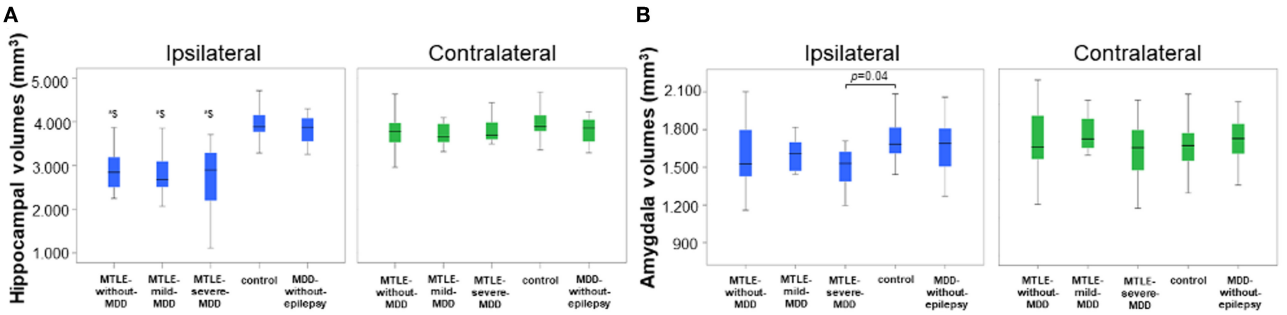

FIGURE 1 | Volumes of hippocampus and amygdala according to the groups. **(A)** Ipsilateral and contralateral hippocampus volumes. The *MTLE-without-MDD, MTLE-mild-MDD, and MTLE-severe-MDD groups* (*$) presented smaller ipsilateral hippocampus ($p < 0.01$) when compared to the *MDD-without-epilepsy* and control groups. **(B)** Ipsilateral and contralateral amygdala volumes according to the groups. The *MTLE-severe-MDD* group presented a smaller ipsilateral amygdala ($p = 0.04$) when compared to the control group. MTLE, mesial temporal lobe epilepsy; MDD, Major Depressive Disorder; *MTLE-without-MDD*, MTLE patients without depression; *MTLE-mild-MDD*, MTLE patients with mild symptoms of depression; *MTLE-severe-MDD*, MTLE patients with moderate to severe symptoms of depression; *MDD-without-epilepsy*, patients without epilepsy with MDD.

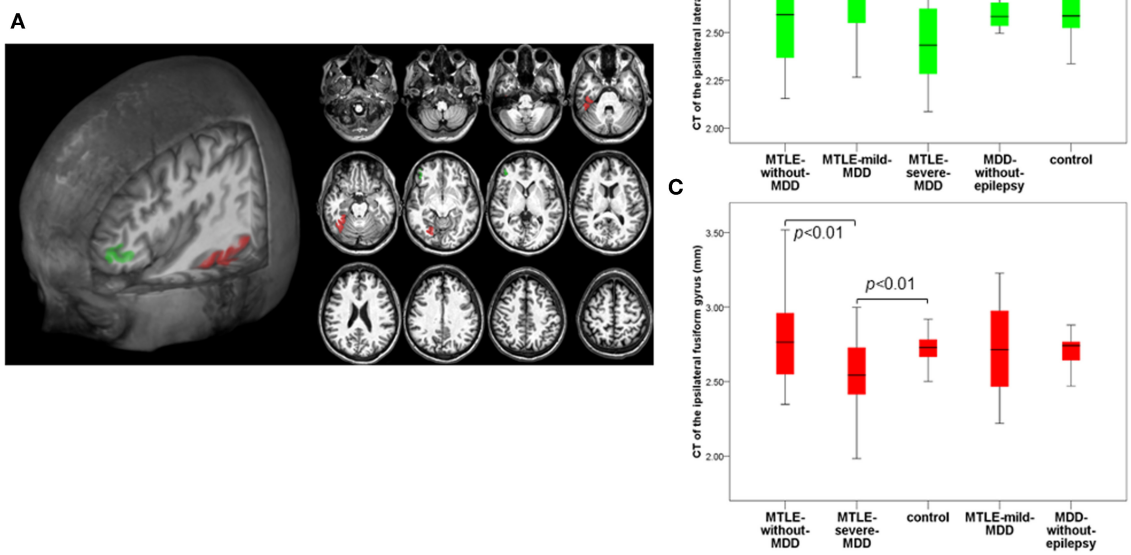

FIGURE 2 | Composition panel illustrating CT reduction in the ipsilateral lateral orbitofrontal cortex (green) and in the ipsilateral fusiform gyrus (red). **(A)** 3D and 2D automated FreeSurfer segmentation of the ipsilateral lateral orbitofrontal cortex and the ipsilateral fusiform gyrus. **(B)** Cortical thickness abnormalities in the ipsilateral lateral orbitofrontal cortex according to the groups. **(C)** Cortical thickness abnormalities in the ipsilateral fusiform gyrus according to the groups. CT, cortical thickness; MTLE, mesial temporal lobe epilepsy; MDD, Major Depressive Disorder; *MTLE-without-MDD*, MTLE patients without depression; *MTLE-mild-MDD*, MTLE patients with mild symptoms of depression; *MTLE-severe-MDD*, MTLE patients with moderate to severe symptoms of depression; *MDD-without-epilepsy*, patients without epilepsy with MDD.

from previous hypothesis-driven studies, we initially searched for brain regions associated with the degree of depressive symptoms in the *MDD-without-epilepsy* group. This procedure allowed us to reduce the number of variables appropriately and select a more specific subset of cortical areas for data-driven analysis. This approach allowed us to characterize a unique pattern of cortical alterations in the *MTLE-severe-MDD* group, including the lateral orbitofrontal cortex, fusiform, and superior frontal gyrus.

Psychiatric comorbidities, especially MDD, constitute a significant source of concerns in pharmacoresistant epilepsy, as previously reported (3, 35). The course of MTLE can be impacted

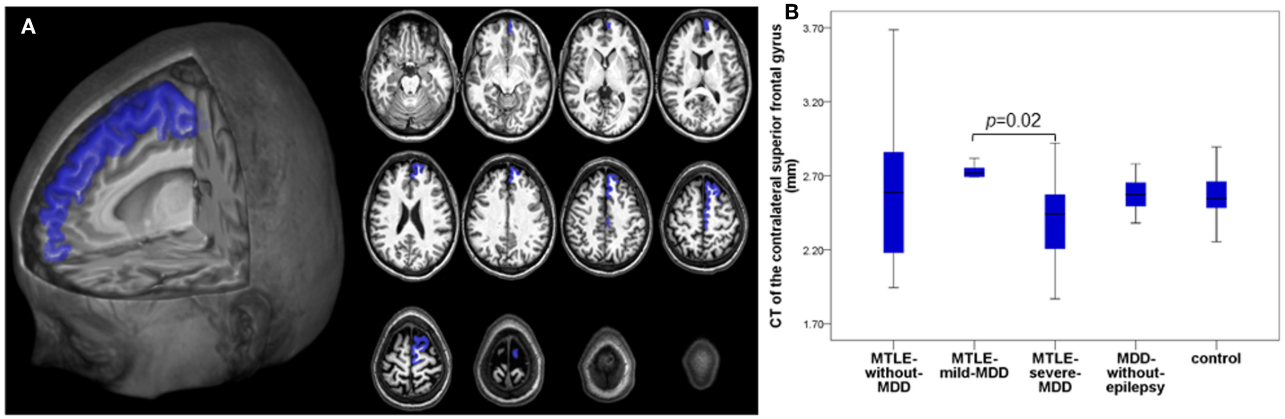

FIGURE 3 | Composition panel illustrating CT reduction in the contralateral superior frontal gyrus (blue). **(A)** 2D and 3D automated FreeSurfer segmentation of the contralateral superior frontal gyrus. **(B)** CT of the contralateral superior frontal gyrus among the groups. CT, cortical thickness; MTLE, mesial temporal lobe epilepsy; MDD, Major Depressive Disorder; *MTLE-without-MDD*, MTLE patients without depression; *MTLE-mild-MDD*, MTLE patients with mild symptoms of depression; *MTLE-severe-MDD*, MTLE patients with moderate to severe symptoms of depression; *MDD-without-epilepsy*, patients without epilepsy with MDD.

by psychiatric aspects, including the predisposition to seizure worsening (3, 36), unsatisfactory response to pharmacologic treatment (37), AEDs tolerance, and the surgical outcome (35, 36). One study (38) included 780 consecutive patients with recently diagnosed epilepsy and identified significant psychiatric comorbidities preceding onset. MDD history had twice the risk of pharmacoresistance. Another study (39) evaluating 100 TLE patients who underwent anterior temporal lobectomy reported a lifetime history of MDD in 12% of seizure-free patients (after 2 years of the surgical procedure) in comparison to MDD history in 79% of patients who persisted with disabling seizures. These studies emphasize the negative interaction between MTLE and MDD, highlighting the possible involvement of common pathogenic mechanisms in both disorders (6).

Patients with psychiatric diagnoses have a higher risk of presenting refractory seizures (3, 40). In our study, the *MTLE-severe-MDD* group showed a higher frequency of seizures when compared to the *MTLE-without-MDD* and *MTLE-mild-MDD* groups. A recent study (27) evaluated 933 patients with epilepsy to identify the prevalence of depression, taking into account some factors as AEDs, seizure frequency, and other clinical and sociodemographic data. They found a significant association between the seizure frequency and the number of AEDs prescribed, with the occurrence of depression in patients with epilepsy. Patients with pharmacoresistant-epilepsy presented more severe symptoms of depression when compared to seizure-free patients.

Our results demonstrated a significant volume reduction in the ipsilateral amygdala in the *MTLE-severe-MDD* compared to the control group. Although symptoms of depression have been related to changes in both the amygdala and hippocampus (41), the MTLE groups were undistinguished in terms of HS. Both regions are associated with the modulation of emotional behavior and motivation, and they have connections to the orbitofrontal cortex, medial prefrontal cortex, and hypothalamic areas (41).

The amygdala has a crucial role in emotional memory and perception (42), as well as being highly associated with the genesis and spreading of epileptiform activity in MTLE. It also plays an essential role in psychiatric symptoms in pharmacoresistant epilepsy (41). Taking into account the connections between the amygdala and the brainstem regions, some studies (43) have reported abnormalities in emotion recognition related to amygdala dysfunction in MTLE patients. Very few studies analyzed CT in adult patients with epilepsy and MDD. One study (44) evaluated subcortical and cortical differences in 88 children with epilepsy, and 25 of these children had a current anxiety disorder. They showed a larger left amygdala in the group of children with anxiety disorder, as well as thinning in the left medial orbitofrontal cortex, right lateral orbitofrontal, and in the right frontal pole in this group. Given the importance of the amygdala in both epilepsy and psychiatric symptoms, further research (especially in MTLE patients) should assess the impact of antidepressants and AEDs usage, mainly focusing on mood stabilizers concerning the dynamic changes processes of the amygdala.

Although fewer studies have previously shown a correlation between hippocampal volumes and the BDI-II scores, we did not observe such association in our analyses. One study (20) evaluated the relationship between depression and hippocampal volume loss in 55 patients with TLE, showing that patients with right TLE and depression presented a reduced left hippocampal volume. They concluded that the observed contralateral hippocampal atrophy could not be exclusively attributed to epilepsy, suggesting a significant impact of the depression on the hippocampal volume loss. A previous study of our group (21) used voxel-based morphometry to investigate the differences in gray matter volume in 48 MTLE patients with and without depression (compared to 96 healthy controls). There was widespread gray matter atrophy in MTLE patients with MDD, but no correlation between BDI scores and regional gray

matter atrophy. More studies are necessary to better clarify this relationship between subcortical structures and the intensity of depression symptoms in patients with MTLE.

Our results revealed CT abnormalities in the ipsilateral orbitofrontal cortex, ipsilateral fusiform gyrus, and in the contralateral superior frontal gyrus in the group of patients with concurrent MTLE and moderate to severe symptoms of MDD. Some studies have focused on depression-associated abnormalities in frontal regions related to emotional regulation (45), including the dorsolateral prefrontal cortex, anterior cingulate areas (46), and the orbitofrontal cortex (22, 47). Unfortunately, while several studies have examined structural alterations (with both gray and white matter) in TLE, fewer have accurately analyzed the structural changes in MTLE patients with concurrent MDD. Further investigation is still required to achieve a better understanding of the relationship between alterations of extratemporal and frontal regions in MTLE patients with MDD (22).

A considerable number of functions have been attributed to the orbitofrontal cortex, such as driving social behavior, inhibiting responses, emotional and reward of decision-making, among others (48, 49). The orbitofrontal cortex connects bidirectionally with the sensory association cortices and temporal lobe areas, having a robust connection with the amygdala (46) and being associated with the modulation of the aggressive behavior (50). Hypometabolism in the orbitofrontal cortex was identified in patients with TLE and MDD, suggesting anomalies in the functioning of glia and neurons of this region (22, 51). In line with previous studies on depression, we observed a negative association between the intensity of MDD and CT of the lateral orbitofrontal cortex in patients with MTLE. The most extensive worldwide study (13) (ENIGMA-MDD) evaluated the cortical structural alterations in depression in 2,148 patients with MDD compared to 7,957 healthy controls. A reduced bilateral CT in the orbitofrontal cortex, insula, temporal poles, and cingulate (anterior and posterior) regions was associated with MDD in adults. In another study, the correlation between the orbitofrontal cortex CT and depressive symptoms scores in 38 patients with TLE and 45 controls (22) demonstrated a negative correlation in controls and a positive correlation in TLE patients. They also detected a positive correlation between the BDI-II scores and the right fusiform gyrus, and a negative correlation with a small region in the right parietal cortex. One limitation of that study was the small number of TLE patients, added to the absence of a structured diagnostic interview for MDD. In the present study, we applied a structured diagnostic interview and used different methodological approaches for neuroimaging analysis, taking into account the lateralization of ipsilateral and contralateral structures, in contrast to the left and right side of the brain regions.

Atrophy of the fusiform gyrus was present in the *MTLE-severe-MDD* group, compared to the *MTLE-without-MDD* and control groups. The fusiform gyrus, or lateral occipitotemporal gyrus, is associated with the processing of color information, face and body recognition, word recognition, and within-category identification (52). Donix et al. (53) evaluated 27 young individuals with MDD and 23 older participants without MDD and demonstrated an association between the fusiform cortices and subjective memory impairments in the young group with MDD. Another study (54) investigated whether the CT abnormalities indicate initial adverse properties of environmental and genetic risk factors predisposing MDD or appear with the mood disorders onset. They evaluated MRI data from 111 young adults without MDD but with a high familial risk to develop this psychiatric disorder and 93 healthy controls. Reduction in the fusiform thickness and the right parahippocampal gyrus was associated with a familial vulnerability to mood disorders. Although these studies enrolled patients without epilepsy, their results support our findings as they indicate a significant role of the atrophic fusiform gyrus in MDD. The ENIGMA-Epilepsy consortium (55) analyzed CT from 754 MTLE patients, regardless of the presence of depressive symptoms and confirmed reduced CT of the ipsilateral fusiform and the superior frontal gyrus (among other regions) in patients with left MTLE. The similarity between those findings (in isolated MDD and epilepsy) and ours (concurrent MTLE and MDD) reinforce the hypothesis of shared physiopathology for depression and MTLE.

In agreement with the comprehensive examination of CT performed in the ENIGMA-MDD study (13), we also observed superior frontal gyrus atrophy in the *MTLE-severe-MDD* compared to the *MTLE-mild-MDD* group. However, while the ENIGMA-MDD study (13) demonstrated reduced surface area exclusively in adolescents with depression (without alterations in CT), we identified reduced CT in the same region in our subgroup of adult patients. Conversely, another study (56) with 32 MDD patients (16 untreated and 16 first episode) examined the cortical maps of thickness, gyrification, and surface area, and reported increased surface area in the superior frontal regions without CT abnormalities. Since the function of the superior frontal gyrus is related both to the self-awareness in association with the sensory system (57) and to the "laughter brain region" (58), its involvement in the manifestation of depression is expected. This novel finding in our study and the controversies from the previous research related to superior frontal gyrus and depression highlights the need for further neuroimaging studies, including functional MRI, to investigate the impact of MDD on dysfunctions of the frontal lobe in epilepsy.

LIMITATIONS

A reduced number of individuals and cross-sectional design was a limitation with possible impact in our statistical models; however, we applied corrections for our multiple comparisons to avoid false-positive results. Another relevant point was the selective inclusion of women in our study. This composition was determined because we only had women in our group with depression without epilepsy. The most likely explanation for this bias is that in our cultural scenario, men have been remarkably resistant to seek health care, especially mental health care. Moreover, our outpatient clinic is part of a neurological tertiary center, specialized in epilepsy care. The individuals with only depression were volunteers and recruited for transversal research,

without implications or personal gain to their treatments. The participants who were not receiving any MDD treatment were referred to an adequate treatment service. Our results are preliminary, and further studies with a larger number of patients, including men, and validation in independent cohorts are necessary for confirming our findings.

CONCLUSIONS

Our findings suggest a specific pattern of CT atrophy in women with MTLE and depression, implicating a dysfunction in networks composed of some structures related to both epilepsy and MDD. These observations contribute to the existing theory about the bidirectional interaction between epilepsy and depression. However, additional studies with a higher number of subjects (mixing men and women) are necessary to explore these abnormalities in epilepsy, with an investigation of other structural characteristics as well as a combination with functional analyses. The identification of specific alterations in patients with concurrent epilepsy and depression may provide future targets for personalized treatment of the two comorbidities.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/**Supplementary Material**. Any additional information can be available upon reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the State University of Campinas (CEP/FCM 1191/2011). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MN designed the study, recruited and evaluated patients, visually checked and analyzed the MRI images, performed statistical analysis, and wrote the paper. LP recruited patients, contributed to the discussion session, performed statistical analysis, and wrote the paper. JV performed the processing of the MRI and implemented the FreeSurfer scripts. TR contributed to the knowledge and discussion about the FreeSurfer methodology in addition to the creation of the FreeSurfer segmentation images to illustrate our results. TZ recruited and evaluated patients. BC created the FreeSurfer segmentation images to illustrate our results and contributed to the discussion session. CY and FC designed the study, performed statistical analysis, wrote the paper, and provided mentorship and funding for the study.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/article/10.3389/fneur.2019.01398/full#supplementary-material.

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REVIEW
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Cognitive Function in Genetic Generalized Epilepsies: Insights From Neuropsychology and Neuroimaging

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Genetic generalized epilepsies (GGE), previously called idiopathic generalized epilepsies, constitute about 20% of all epilepsies, and include childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, and epilepsy with generalized tonic-clonic seizures alone (CAE, JAE, JME, and GGE-GTCS, respectively). GGE are characterized by high heritability, likely underlain by polygenetic mechanisms, which may relate to atypical neurodevelopmental trajectories. Age of onset ranges from pre-school years, for CAE, to early adulthood for GGE-GTCS. Traditionally, GGE have been considered benign, a belief contrary to evidence from neuropsychology studies conducted over the last two decades. In JME, deficits in executive and social functioning are common findings and relate to impaired frontal lobe function. Studies using neuropsychological measures and cognitive imaging paradigms provide evidence for hyperconnectivity between prefrontal and motor cortices, aberrant fronto-thalamo-cortical connectivity, and reduced fronto-cortical and subcortical gray matter volumes, which are associated with altered cognitive performance. Recent research has also identified associations between abnormal hippocampal morphometry and fronto-temporal activation during episodic memory. Longitudinal studies on individuals with newly diagnosed JME have observed cortical dysmaturation, which is paralleled by delayed cognitive development compared to the patients' peers. Comorbidities and cognitive deficits observed in other GGE subtypes, such as visuo-spatial and language deficits in both CAE and JAE, have also been correlated with atypical neurodevelopment. Although it remains unclear whether cognitive impairment profiles differ amongst GGE subtypes, effects may become more pronounced with disease duration, particularly in absence epilepsies. Finally, there is substantial evidence that patients with JME and their unaffected siblings share patterns of cognitive deficits, which is indicative of an underlying genetic etiology (endophenotype), independent of seizures and anti-epileptic medication.

Keywords: genetic generalized epilepsies, cognition, neuropsychology, neuroimaging, endophenotype

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INTRODUCTION

Genetic generalized epilepsies (GGE) are a group of generalized epilepsy syndromes underpinned by high heritability and complex polygenetic inheritance (1, 2). Though GGE have traditionally been regarded as benign, recent research indicates specific profiles of cognitive impairment (3–5), particularly encompassing functions reliant on frontal lobe processing. Potential underlying mechanisms of cognitive dysfunction have been elucidated via advanced neuroimaging techniques, which allow quantifying morphological and functional brain changes as well as their relation to neuropsychological test scores.

The etiology of cognitive impairment in GGE is often regarded as neurodevelopmental (6, 7). Recent research has focused on profiling first-order relatives alongside index patients, in an effort to characterize the cognitive phenotypes of GGE subgroups while identifying familial traits with likely genetic underpinnings. General linear models, on the other hand, have been used to assess the relationship between cognitive impairment and disease-associated variables, including age at onset, duration of epilepsy, or the influence of specific anti-epileptic medication.

Relatively recent reviews have detailed the cognitive profiles of mixed GGE samples (4) or individual GGE syndromes, particularly JME (3), providing evidence of frontal lobe dysfunction. However, there is a scarcity of work focusing on potential syndrome-specific patterns of impairment, attempting to characterize the neural correlates of dyscognitive traits, or identifying potential determinants of such abnormalities. An updated view on these topics is therefore timely and compelling. Improved knowledge may aid clinical practice, by highlighting the extent of interventional needs, informing patient counseling, and identifying targets for cognitive rehabilitation and novel therapeutic approaches.

In this review, we will first summarize evidence on the overarching cognitive profile of GGE. We will then detail subsyndrome-specific investigations, which suggest slightly distinct patterns of dysfunction in juvenile myoclonic epilepsy and absence epilepsies. We will also elucidate recent structural and functional imaging research, which shed light on the putative abnormalities underlying cognitive dysfunction. Finally, we will discuss investigations assessing patients and their first-order relatives, which indicate genetic underpinnings as relevant determinants of cognitive profiles in GGE.

SEARCH STRATEGY AND SELECTION CRITERIA

For this review, we conducted a literature search on PubMed ranging from January 1, 1985 to June 30, 2019, querying the following terms and related synonyms: "genetic generalized epilepsy," "idiopathic generalized epilepsy," "childhood absence epilepsy," "juvenile absence epilepsy," "absence epilepsy," "juvenile myoclonic epilepsy", in combination with the following individual key terms: "neuropsychology," "neuropsychological," "cognition," "cognitive test," "MRI," "functional MRI/fMRI," "family study," "relatives," "siblings," "intermediate phenotype," "endophenotype". Searches were also repeated using common abbreviations of disease names (i.e., "IGE," "GGE," "CAE," "JAE," "JME"). We restricted our initial search to articles published in English. In addition, we carried out manual searches on reference lists of the identified articles and selected review papers published in the last 5 years, and complemented the former with extraction of relevant manuscripts from our records. Final inclusion was based on originality and direct relevance to the topics discussed in this Review.

COGNITIVE DOMAINS AND ASSOCIATED NEUROPSYCHOLOGICAL TESTS

The investigations reviewed in this manuscript implemented a variety of neuropsychological tests addressing different cognitive functions. Here, we briefly detail the most commonly assessed cognitive abilities and associated neuropsychological tests, to aid the interpretation of findings across studies. A more in-depth description of frequently used tests, parsed by cognitive domain, is provided in **Table 1**.

General cognitive ability, often denoted by *g* or intelligence quotient (IQ), broadly refers to the ability of an individual to solve problems across multiple domains, independent of educational level (38). Full-scale IQ scores are formally derived after completion of a set of tests included in the Wechsler Intelligence Scale, currently in its fourth edition [WAIS-IV; (11)]. Abbreviated assessments, such as the National Adult Reading Test for British English speakers (8), are also available. The latter tests provide IQ estimates based on an individual's ability of reading words with irregular spelling, thus probing vocabulary, and produce scores that are highly correlated with IQ measures obtained via the Wechsler Scale.

Processing speed, defined as the maximum speed at which elementary cognitive operations can be executed (39, 40), involves efficient allocation of processing resources and tracking of ongoing tasks, and relies on intact attention and visuo-spatial skills. Frequently employed processing speed tasks include the Trail Making Test-A (10), requiring an individual to connect numbers in ascending order with a continuous line, or the Grooved Pegboard test (9), assessing an individual's ability to match pegs to unique holes. Attention, defined as the cognitive process enabling selective focus on specific stimuli while ignoring other perceivable information, is assessed via standardized test batteries (13, 14) quantifying levels of alertness, vigilance, visual scanning, cueing and ability to simultaneously concentrate on different tasks. While also relying on visuo-spatial abilities, intact attention represents a prerequisite for optimal executive control (41).

Other frequently administered tests, such as the Rey-Osterrieth Complex Figure test [ROCF; (17, 18)], include an initial "Copy" condition that entails an accurate reproduction of a visually presented complex line drawing, and thus assesses visuo-spatial constructional abilities. More generally, visuo-spatial processing is common to a multiplicity of cognitive domains, including perceptual reasoning, probed via WAIS subtests involving recognition of spatial relationships

TABLE 1 | Cognitive tests employed in GGE studies.

Domain	Test (References)	Test description
General intellectual ability	NART (8)	Requires the reading of 50 British English words with irregular spelling and unpredictable pronunciation
Processing Speed	Grooved Pegboard (9)	The participant is asked to place 25 pegs into 25 unique holes as quickly as possible (maximum time allowed: 3 min)
	Trail Making Test: Time—part A (10)	A series of numbers have to be connected in ascending order, using a continuous line, as quickly as possible
	(Digit–Symbol) Coding (WAIS) (11)	Visual symbols have to be assigned to an appropriate number, according to a given code pairing, as quickly as possible
	Stroop: Color–Word (12)	The maximum reading speed for color words and the naming speed of ink colors is recorded
Attention	Alertness tasks (13, 14)	The subject is asked to press a button instantaneously after viewing a stimulus, with and without a warning cue
	Vigilance task (13, 14)	The subject is asked to respond, as quickly as possible, to the omission of an expected switch of pattern between two squares. Testing lasts for 15 min
	Visual scanning task (13, 14)	The subject is asked to locate and react to a "critical stimulus" in a matrix of stimuli. The critical stimulus is not dissimilar enough from the other objects in the matrix so as to be obvious
	Posner Cueing task (15)	The subject is asked to respond to a stimulus, located to one side of a fixation point. A cue, which can either be congruent or incongruent, is used to "set" the directional attention of the participants, requiring an attentional shift in a proportion of the trials
Dexterity	Finger Tapping (16)	The participant is asked to tap the index finger on a lever as quickly as possible within a 10 s interval
Semantic knowledge	Vocabulary (WAIS) (11)	The participant is required to provide definitions for 33 unique words of increasing difficulty
	Similarities (WAIS) (11)	The subject is given 19 sets of word pairs and is asked to provide the common link (i.e., describe their relationship)
	Information (WAIS) (11)	The subject is asked a series of general knowledge questions of increasing difficulty
Visuo–spatial Abilities and Perceptual Reasoning	Block Design (WAIS) (11)	The participant is presented with a series of spatial problem-solving tasks of increasing difficulty, involving red and white cubes
	Matrix Reasoning (WAIS) (11)	The subject is required to complete a matrix of abstract patterns with one image missing
	ROCF—Copy (17, 18)	The participant is required to copy freehand a visually presented complex line drawing
Verbal generativity [Fluency can be considered an executive function reliant process, and is often included in executive function test batteries (21)]	Phonemic fluency—COWAT, "FAS Test" (10, 19, 20)	The subject is asked to generate as many words as possible starting with a given letter (F/A/S) in 1 min
	Semantic fluency—COWAT, "Animals, Fruit, and Vegetable Test" (10, 19, 20)	The subject is asked to generate as many category-specific words as possible (e.g., animals, fruits, vegetables) in 1 min
Expressive language (Naming)	McKenna Graded Naming test (22)	The participant is asked to name 30 items presented as black and white line drawings of graded difficulty.
	Boston Naming Test (23)	The participant is asked to name 60 items presented as black and white line drawings of graded difficulty.
	Auditory Naming (24)	The participant is asked to name 60 items based on verbal descriptions provided auditorily
Working memory	Digit Span (WAIS) (11)	The subject is required to repeat a set of numbers of increasing length in the correct order immediately upon presentation; this is followed by a second set in reverse order
	Spatial Span (WMS—III) (25) and Corsi Block Tapping test (26)	The participant is asked to copy block-tapping sequences of increasing length. Each trial, the number of taps required to complete a sequence increases by one
Verbal learning and memory	AMIPB: List learning (27)	The participant is required to learn a 15-item word list, presented auditorily over five trials, and recall that after a 15-item distracting list
	CVLT (28)	The participant is required to learn a 16-item word list over five trials and recall that after a 16-item distracting list, a long delay, and via a recognition task

(Continued)

TABLE 1 | Continued

Domain	Test (References)	Test description
	Logical memory I and II (WMS) (29)	The participant is required to recall an orally presented prose passage immediately (Condition I) and after a long delay (Condition II). A recognition task is incorporated in the delayed recall subtest
Non–verbal Learning and Memory	AMIPB: Design learning (27)	The subject is asked to reproduce a 9-element design on a 4 × 4 grid over five consecutive trials, and again following a distracting design
	ROCF—Recall (17, 18)	The subject is asked to copy a complex figure and then reproduce it from memory, shortly after presentation and after a 30 min delay' interval
	Designs I and II (WMS) (29)	The participant is presented with a series of unfamiliar designs. Short and long-term recall are measured by conditions I and II, respectively. The latter also probes visual recognition
Executive Functions	Stroop: Interference (12)	The subject is asked to name the ink color of color words written in incongruent color. Used as a measure of response inhibition.
	Trail Making Test: Task–switching (10)	The subject is asked to connect numbers and letters of the alphabet in sequence, alternating between letters and numbers, as quickly as possible. Used as a measure of cognitive flexibility.
	Five Points (30)	The subject is asked to create as many unique shapes as possible in 5 min, by connecting five symmetrical dots with straight lines. Used as a measure of strategy formation
	Tower of London (31)	The subject is asked to move colored shapes between three pegs in the minimum number of moves to achieve the required solution. Used as a measure of planning ability
	Wisconsin Card Sorting test (32)	Participants are asked to match cards in a stimulus set, but are not explicitly provided with rules. They are, however, told whether a match is correct. Cards are then sorted based on the implicit rules defined by the participant. The rules are then changed, and the participant is required to reformulate rules. Used as a measure of cognitive flexibility
	Hayling sentence completion (33)	The subject is asked to complete 15 sentences, each missing the last word, with an appropriate word. Subsequently, there are 15 sentences and the subject is required to provide a word that renders the sentence meaningless. Provides measures of response initiation and suppression, respectively
	Porteus Maze test (34)	The participant is asked to complete a set of variably complex mazes under time constraints. Used as a measure of planning ability
	Visual/Verbal test (35)	The subject is shown 42 cards, each depicting four objects, and asked to create a rule unifying three of the images on the card. They are then asked to create another one. Used as a measure of concept formation and cognitive flexibility
	Iowa Gambling task (36)	The participant is asked to win as much money as possible, by choosing from four decks of cards associated with variable gains and losses. Performance is dependent on reinforcement learning and identification of decks associated with advantageous choices. Used as a measure of decision making
	Ruff Figural Fluency Test (37)	The subject is asked to connect dots to create as many unique patterns as possible in 60 s. Used to measure strategy formation and non-verbal fluency

AMIPB, Adult Memory and Information Processing Battery; COWAT, Controlled Oral Word Association Test; CVLT, California Verbal Learning Test; NART, National Adult Reading Test; ROCF, Rey–Osterrieth Complex Figure; WAIS, Wechsler Adult Intelligence Scale; WMS, Wechsler Memory Scale.

among items with increasing complexity (Block Design, Matrix Reasoning), and motor dexterity, which refers to fine motor skills and coordination. Tests addressing the latter rely on the correct execution of controlled sequential motor responses, such as those assessed via the Finger Tapping test (16).

With regards to language abilities, manipulation of acquired verbal information is often subsumed under the term of semantic knowledge, and is assessed via WAIS subtests including "Vocabulary," "Similarities" and "Information," which collectively probe general verbal knowledge attained through education and environmental exposure. Tests assessing auditory and visual confrontation naming, on the other hand, require naming items from their auditory description or from related black and white line drawings, respectively (22–24, 42). Verbal fluency, often categorized into phonemic and semantic fluency, refers to verbal generativity, and is probed via tests such as the Controlled Oral Word Association or "FAS" test, for the phonemic component, and animal naming for the semantic one (19, 20). These tasks require an individual to generate the largest possible number of words starting with a given letter, or to name as many items as possible belonging to a given category (i.e., animals, in most cases) in a specified time frame.

Working memory refers to the cognitive system responsible for the short-term storage of recently acquired information for

manipulation and immediate use (43, 44), and is generally parsed into a verbal and a visuo-spatial component. Common working memory tests are represented by the Digit Span and Arithmetic tasks for verbal cues, included in the WAIS, and the Corsi Block-Tapping test (26), addressing visuo-spatial abilities. Tests such as the California Verbal Learning Test [CLVT; (28)], and the List Learning subtests of the Adult Memory and Information Processing Battery [AMIPB; (27)], assess the ability to encode and retain verbal cues, referred to as verbal learning and memory. Similar batteries are available for testing visuo-spatial learning and memory, such as the Design Learning subtest of the AMIPB or the recall phases of the ROCF, which require an individual to reproduce complex line drawings from memory. Similarly, measures of immediate and delayed verbal and visual learning and memory are also provided by the Wechsler Memory Scale [WMS; (29)].

A cognitive domain frequently included in the assessments of GGE, and closely related to information manipulation (45), is represented by executive functions, which encompass the high-order, top-down mental processes required to pay attention, concentrate, evaluate the efficacy of automatic responses and suppress "default," stereotyped output when appropriate (41, 46). Response inhibition, concept formation, cognitive flexibility, goal selection, strategy usage, planning and monitoring are all examples of executive functions, and overall enable purposeful, self-serving and adaptive behavior. While language-based, verbal fluency tasks also require executive control, and are frequently included in test batteries addressing executive function (21). Traditionally, successful executive cognition relies on the integrity of the frontal lobes, particularly the prefrontal cortex, whose dorsolateral, ventrolateral and rostral subdivisions may exhibit some degree of functional specialization (47–50). There is a large variety of cognitive tests assessing dysexecutive traits, and the neuropsychological test batteries implemented by Wandschneider et al. (51), Moschetta and Valente (52), Jackson et al. (53), or Wandschneider et al. (54) may provide helpful examples.

GENETIC GENERALIZED EPILEPSIES

GGE constitute about 20% of all epilepsies and are composed of four main subsyndromes: childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, and epilepsy with generalized tonic-clonic seizures alone (CAE, JAE, JME, and GGE-GTCS respectively). Whilst varying with regard to age of onset, combination of different seizure types, EEG traits and disease courses, all GGE share a genetically determined multi-factorial etiology.

CAE, which presents with frequent typical absence seizures, has an age of onset which peaks at 6 to 8 years, an incidence of 0.7/100,000/year, and is twice as common in females as in males (55, 56). Age of onset for JAE peaks between 9 and 13. The syndrome is characterized by typical, though less frequent, absence seizures, often accompanied by generalized tonic clonic seizures (GTCS), and a similar distribution between males and females (57). Whilst CAE and JAE are two independent clinical entities, it is commonly surmised that these two disorders have highly overlapping etiology and pathological mechanisms. Consequently, the majority of investigations into their cognitive profiles have collapsed both diseases into the unitary category of absence epilepsy (AE). The hallmark of the most common GGE subsyndrome, JME, is represented by myoclonic jerks occurring in the morning. Most patients also suffer from GTCS and, more rarely, absence seizures. Disease onset peaks during adolescence and early adulthood, between 12 and 18 years of age (range: 5–25). JME likely represents 15–20% of all GGE cases, and is slightly more common in females (ratio of 3:2) (56, 58). Finally, GGE-GTCS has the most variable age of onset, generally ranging from the second to the fourth decade of life, and is believed to account for up to 15% of GGE, though prevalence estimates are often inconsistent (59).

COGNITIVE PROFILES OF GGE: NEUROPSYCHOLOGICAL EVIDENCE

Although GGE have traditionally been regarded as benign, studies have consistently shown that executive functioning in GGE may be impaired. This has been complemented by research documenting a higher prevalence of impulsive personality traits (60, 61), cluster B personality disorders (62, 63), impaired emotion recognition and social cognition (64–66), suboptimal academic performance (53), and poor long-term social outcome (67, 68), particularly in JME. Moreover, meta-analytical syntheses of neuropsychological investigations conducted over the last three decades suggest that profiles of cognitive impairment may exhibit some degree of syndrome specificity (4). Here, we will discuss investigations of cognitive function in mixed groups of GGE patients, followed by studies detailing cognitive profiles in the most common GGE subsyndromes, juvenile myoclonic epilepsy and absence epilepsy.

Cognition in Mixed GGE Samples

In mixed GGE samples, general cognitive ability is often reported as affected, with meta-analyses (4, 69) documenting IQ scores ranging from 0.5 to 1 standard deviation lower than controls, indicative of moderate to large effect sizes. However, whilst most investigations described lower general intelligence in GGE compared to controls, the IQ measures reported for GGE groups generally fall within the normal range, clustering around average values at the population level, i.e., between 90 and 110 (53, 70–73). Hence, it remains unclear whether general intellectual abilities in GGE may be lower than normative values, or whether differences between patient and control samples may arise, for instance, from the recruitment of high-performing, non-representative control cohorts across investigations.

Patients with GGE also exhibit reduced ability to manipulate acquired information, i.e., semantic knowledge. The recent meta-analysis by Loughman et al. (4) points to significantly lower scores in GGE compared to controls on tests such as the Vocabulary and Information items of the WAIS. In parallel, the latter meta-analytical synthesis also indicated impaired problem solving and reasoning abilities, elsewhere referred to as fluid

intelligence. Two reports also documented poorer performance on standardized arithmetic tests, assessing both knowledge of mathematical operations and problem-solving skills, with scores of GGE patients up to one standard deviation lower than control subjects (53). Rathouz et al. (72) found that scores of arithmetic subtests were lower in GGE than in patients with focal epilepsy, and that both groups performed worse than healthy controls.

Across studies, there is homogenous reporting of worse dexterity, attention and processing speed in GGE, with all studies documenting moderate to substantial impairment in patients (53, 73–77). While evidence for disrupted motor and cognitive processing speed is consistent, and may point to altered visuo-motor integration, more research is required to address its potential determinants, particularly in regard to the detrimental influence of anti-epileptic medication. As several of these have been associated with cognitive slowing (78–80), the extent to which abnormal processing speed may thus represent an intrinsic feature of GGE, rather than a medication-associated effect, remains unestablished.

A smaller number of investigations indicate that phonological processing may also be impaired in GGE, with scores for letter and category fluency falling about one standard deviation below population-level normative ranges (60, 71, 74, 77). Jackson et al. (53) found that reading and measures of vocabulary did not differ between controls and patients with GGE, but reported a selective phonemic fluency deficit in the latter. More abundant evidence of abnormal verbal generativity, however, has been conveyed by investigations separately assessing individual GGE syndromes.

Evidence for working memory impairment is conflicting. Whilst some studies found significant deficits in mixed GGE groups compared to controls (60, 71, 74), other studies did not (53, 73, 81, 82). One investigation (74) detected differences between patients and controls for non-verbal attention performance, but no specific working memory dysfunction. Deficits in working memory are reported more often for the verbal (74) than for the non-verbal domain, suggesting greater compromise of the phonological loop than the visuo-spatial sketchpad, which refers to the subsidiary working memory construct accounting for visuo-spatial processing (44). Similarly, there is less concordant evidence for learning and memory impairment in GGE. While some authors suggest moderate to large effect sizes (74, 76, 82, 83), particularly for long-term memory in pediatric cohorts, other studies did not detect significant differences (81, 84), and confidence intervals of effect estimates appear fairly wide across all investigations (4). While these findings may point to syndromic heterogeneity, and warrant further consideration in the context of individual GGE syndromes, it overall appears that memory deficits may not be a specific GGE trait.

Finally, widely-documented impairment of both verbal and non-verbal fluency, strategy formation (73, 77), attention (53, 71), response inhibition (72), concept formation and mental flexibility (4) indicates moderate to pronounced executive dysfunction in GGE, pointing to abnormal frontal lobe function.

In summary, the available evidence in GGE conveys a cognitive profile characterized by average general intelligence along with consistent impairment of processing speed, dexterity, verbal generativity, and executive function. Literature supporting weak semantic knowledge, problem-solving and visuo-spatial reasoning is also available, though less abundant, whilst findings pertaining to working memory, learning and long-term memory performance are conflicting.

Cognition in Patients With Juvenile Myoclonic Epilepsy

An overview of the studies assessing the cognitive profile of JME is provided in **Table 2**. General intellectual abilities are consistently found to be within the average range, though slightly lower than in controls (53, 73, 88–90, 94, 99). As discussed in section Cognition in Mixed GGE Samples, it is possible that differences in general intelligence between JME and controls may be partially ascribed to the investigation of high-performing control cohorts.

Across studies summarized in the meta-analysis by Loughman et al. (4), there is evidence for consistent impairment of semantic knowledge and problem-solving skills, which recapitulates findings in mixed GGE samples. With regards to visuo-spatial abilities, visual attention has also been reported as impaired in JME (89, 90, 100, 104). While a meta-analytical synthesis (4) and more recent evidence (73, 104) suggested, on the other hand, that visuo-spatial thinking may be relatively intact, other findings (88) implicated minor visuo-spatial dysfunction, as assessed via clock drawing and cube copying tests. In line with evidence in mixed GGE samples, a number of studies documented impaired dexterity and processing speed (53, 73, 87, 90, 99, 100, 104, 105), with patients often performing more than one standard deviation below controls.

In relation to phonological processing, impairment of phonemic and semantic fluency was detailed in early investigations (88, 90) and confirmed by a large number of subsequent studies. Performance levels ranging between 0.5 and 1 standard deviation lower than controls have been reported by most investigations, indicative of moderate to consistent dysfunction (51, 91–95, 99, 100, 104). Medication-related effects might be involved, but have not yet been specifically addressed. Moschetta and Valente (52), for instance, highlighted an association between sodium valproate usage and worse performance on several cognitive tasks, including those assessing verbal fluency. As patients taking higher doses of valproate had a higher seizure frequency, however, it remains unclear whether worse executive performance may relate to epilepsy severity, anti-epileptic medication, or both the former. Information regarding treatment with topiramate, a drug commonly associated with adverse cognitive effects (107), was also lacking in several of the above investigations.

Most studies into working memory in JME reported some degree of impairment (90, 95, 99, 101). Other groups have examined dimension-specific performance, with some finding evidence for visuospatial impairment (51, 85, 86, 94, 101), and others documenting deficits in verbal working memory

TABLE 2 | Studies investigating cognitive function in JME.

References	Design	Patients/ Controls (n)	Patient Age (sd)	Age of Epilepsy Onset (sd)	Disease Duration (sd)	AED Regimen	Impaired Cognitive Domains	Unimpaired Cognitive Domains	Imaging
Swartz et al. (85, 86)	C	9/15	28.0 (4.0)	9–20	N/A	Mixed	1. Working memory	1. Attention	FDG-PET
Devinsky et al. (87)	C	15/15	34.3 (N/A)	14.6 (N/A)	19.8 (N/A)	Mixed	1. Processing Speed[#] 2. Abstract Reasoning* 3. Executive Functions (Concept Formation*, Cognitive Flexibility*, Perseverative Tendencies[#], Planning[#])	1. Dexterity[#]	N/A
Sonmez et al. (88)	C	35/35	21.7 (4.5)	<25	7.2 (4.7)	Polytherapy	1. Visuo-spatial Perception (Cube Copying, Clock Drawing 2. Abstract Reasoning 3. Semantic Fluency 4. Verbal Learning and Memory 5. Non-verbal Learning and Memory 6. Executive Functions (Response Inhibition)	1. IQ 2. Visuo-spatial Perception (Facial recognition) 3. Expressive Language (Naming) 4. Working Memory	N/A
Kim et al. (89)	C	27/27	16–29	12–23	0.4–9	Drug-naïve	1. Processing Speed 2. Semantic Fluency 3. Working Memory 4. Verbal Learning 5. Executive Functions (Cognitive Flexibility)	1. General Cognitive Abilities 2. Verbal Memory 3. Non-verbal Memory	N/A
Pascalicchio et al. (90)	C	50/50	26.2 (7.4)	N/A	13.8 (8.5)	Monotherapy (VPA)	1. General Cognitive Abilities (IQ, VIQ, PIQ) 2. Processing Speed 3. Phonemic Fluency 4. Expressive Language (Naming) 5. Working Memory 6. Verbal Learning 7. Non-verbal Learning 8. Executive Functions (Cognitive Flexibility, Response Inhibition)	1. Semantic Knowledge (Information, Similarities) 2. Visuo-spatial Perception 3. Abstract Reasoning (Block Design)	N/A
Piazzini et al. (91)	C	50/40	37.3 (10.5)	19.0 (13.3)	18.3 (9.9)	Mixed	1. Phonemic Fluency 2. Executive Functions (Cognitive Flexibility)	1. General Cognitive Abilities (IQ)	N/A
Iqbal et al. (92)	C	8/16	28.1 (6.7)	N/A	N/A	Mixed	1. Phonemic Fluency 2. Semantic Fluency 3. Executive Functions (self-reported, questionnaire-based)	1. Processing Speed 2. Dexterity 3. Visuo-spatial Perception 4. Abstract Reasoning 5. Semantic Knowledge (Vocabulary) 6. Working Memory 7. Verbal Learning and Memory 8. Non-verbal Learning and Memory	N/A[$]

(Continued)

TABLE 2 | Continued

References	Design	Patients/ Controls (n)	Patient Age (sd)	Age of Epilepsy Onset (sd)	Disease Duration (sd)	AED Regimen	Impaired Cognitive Domains	Unimpaired Cognitive Domains	Imaging
Roebling et al. (93)	C	19/20	24.2 (9.9)	N/A	N/A	Mixed	1. Phonemic Fluency 2. Semantic Fluency	1. Processing Speed 2. Attention 3. Semantic Knowledge (Vocabulary) 4. Working Memory 5. Verbal Learning and Memory 6. Non-verbal Learning 7. Executive Functions (Response Inhibition, Figural Fluency)	VBM and Working Memory fMRI
Wandschneider et al. (51)	C	19/42	25.5 (9.6)	N/A	11.1 (10.8)	Mixed	1. Attention 2. Semantic Knowledge (Vocabulary) 3. Semantic Fluency 4. Working Memory (Non-verbal) 5. Prospective Memory 6. Executive Functions (Response Inhibition)	1. Working Memory (Verbal) 2. Executive Functions (Cognitive Flexibility, Planning)	N/A
O'Muircheartaigh et al. (94)	C	28/55	33.6 (10.1)	14.4 (3.4)	20.2 (10.3)	Mixed	1. Semantic Knowledge (Similarities) 2. Phonemic Fluency 3. Expressive Language (Naming) 4. Non-verbal Learning 5. Cognitive Flexibility	1. General Cognitive Abilities 2. Semantic Knowledge (Vocabulary) 3. Semantic Fluency 4. Working Memory 5. Verbal Memory and Learning 6. Non-verbal Memory	VBM
Kim et al. (95)	C	25/30	25.3 (7.6)	14.7 (3.1)	10.6 (7.7)	Mixed	1. Processing Speed 2. Phonemic Fluency 3. Working Memory 4. Executive Functions (Cognitive Flexibility, Response Inhibition)	1. General Cognitive Abilities	Diffusion MRI
Moschetta and Valente (52)	C	42/42	26.6 (8.4)	14.0 (4.4)	17.8 (N/A)	Monotherapy (VPA)	1. Processing Speed 2. Phonemic Fluency 3. Working Memory 4. Executive Functions (Cognitive Flexibility, Response Inhibition)	N/A	N/A
Jackson et al. (53)	C	26/72	14.6 (3.1)	13.2 (4.1)	8.5 (3.5) (months)	96% Monotherapy	1. Processing Speed 2. Attention 3. Dexterity 4. Working Memory 5. Executive Functions (Problem Solving, Response Inhibition)	1. General Cognitive Abilities (VIQ, PIQ) 2. Semantic Knowledge (Vocabulary) 3. Phonemic Fluency 4. Expressive Language (Naming) 5. Verbal Learning and Memory 6. Executive Functions (Task-switching)	N/A
Lin et al. (96)	C	56/42	26.5 (9.0)	12.5 (4.6)	14.3 (10.0)	Mixed	N/A	1. General Cognitive Abilities 2. Vocabulary	MRI

(Continued)

TABLE 2 | Continued

References	Design	Patients/ Controls (n)	Patient Age (sd)	Age of Epilepsy Onset (sd)	Disease Duration (sd)	AED Regimen	Impaired Cognitive Domains	Unimpaired Cognitive Domains	Imaging
								3. Phonemic Fluency 4. Expressive Language (Naming) 5. Verbal Memory and Learning 6. Non-verbal Memory and Learning	
Wandschneider et al. (97)	C	21/11	33.5 (22–64)**	N/A	N/A	Mixed	N/A	1. Processing Speed 2. Phonemic Fluency 3. Semantic Fluency 4. Working Memory 5. Executive Functions (Cognitive Flexibility, Decision Making*)	Working Memory fMRI
Zamarian et al. (98)	C	22/33	26.0 (18–50)**	14.0 (1–20)**	11.5 (3–45)**	Mixed	1. Processing Speed 1. Abstract Reasoning 2. Semantic Fluency 3. Executive Functions (Cognitive Flexibility, Planning, Decision Making)	1. Attention 2. Phonemic Fluency 3. Working Memory	N/A
Thomas et al. (99)	C	60#	31.0 (19–67)**	12.0 (8–15)##	21.0 (10–31)##	Mixed (Refractory to VPA)	1. General Cognitive Abilities (FSIQ, VIQ, PIQ) 2. Processing Speed 3. Semantic Knowledge (Vocabulary) 4. Abstract Reasoning (Block Design) 5. Phonemic Fluency 6. Semantic Fluency 7. Expressive Language (Naming) 8. Working Memory 9. Verbal Memory 10. Non-verbal Learning and Memory 11. Executive Functions (Response Inhibition)	1. Abstract Reasoning (Matrix Reasoning) 2. Verbal Learning 3. Executive Functions (Cognitive Flexibility)	N/A
Iqbal et al. (100)	C	22/44	26.7 (7.3)	N/A	N/A	Mixed	1. Dexterity (dominant hand) 2. Phonemic Fluency 3. Semantic Fluency	1. General Cognitive Abilities 2. Processing Speed 3. Dexterity (non-dominant hand) 4. Visuo-spatial Perception 5. Abstract Reasoning 6. Semantic Knowledge 7. Working Memory 8. Verbal Learning and Memory 9. Non-verbal Learning and Memory	N/A$
Giorgi et al. (101)	C	20/20	26.7 (6.6)	14.0 (3.8)	12.7 (8.4)	Mixed	1. Processing Speed 2. Semantic Fluency 3. Working Memory 4. Verbal Learning 5. Non-verbal Learning and Memory	1. Phonemic Fluency 2. Verbal Memory 3. Executive Functions (Cognitive Flexibility, Response Inhibition)	N/A

(Continued)

TABLE 2 | Continued

References	Design	Patients/ Controls (n)	Patient Age (sd)	Age of Epilepsy Onset (sd)	Disease Duration (sd)	AED Regimen	Impaired Cognitive Domains	Unimpaired Cognitive Domains	Imaging
Valente et al. (102)	C	57/44	27.4 (8.2)	N/A	N/A	Monotherapy (VPA)	1. Processing Speed 2. Phonemic Fluency 3. Working Memory 4. Verbal Memory and Learning 5. Non-verbal Memory and Learning 6. Executive Functions (Cognitive Flexibility, Response Inhibition)	N/A	N/A
Abarrategui et al. (73)	C	19/21	33.0 (8.1)	14.0 (12–16)**	18.0 (14–25)**	Mixed	1. Processing Speed	1. General Cognitive Abilities 2. Semantic Knowledge (Information) 3. Visuo-spatial Perception/ Orientation 4. Abstract Reasoning 5. Phonemic Fluency 6. Expressive Language (Naming) 7. Working Memory 8. Verbal Memory 9. Non-verbal Memory 10. Executive Functions (Cognitive Flexibility, Response Inhibition, Planning)	N/A[$]
Rzezak et al. (103)	C	79/69	27.3 (8.4)	N/A	N/A	Mixed	1. Processing Speed 2. Phonemic Fluency 3. Semantic Fluency 4. Working Memory 5. Executive Functions (Cognitive Flexibility, Response Inhibition)	N/A	
Sezikli et al. (104)	C	45/15	22.9 (6.8)	15.6 (4.1)	7.2 (5.6)	Monotherapy (VPA)	1. Processing Speed (Trail Making A) 2. Semantic Fluency 3. Working Memory 4. Non-verbal Memory 5. Executive Functions (Cognitive Flexibility, Figural Fluency)	1. Processing Speed (Stroop CW) 2. Attention 3. Verbal Memory 4. Executive Functions (Response Inhibition)	N/A
Unterberger et al. (105)	C	36/38	25.3 (5.3)	14.3 (3.4)	N/A	Mixed	1. Processing Speed 2. Attention 3. Executive Functions (Risk taking)	1. General Cognitive Abilities (VIQ) 2. Phonemic Fluency 3. Semantic Fluency 4. Executive Functions (Cognitive Flexibility, Response Inhibition)	N/A
Paiva et al. (106)	C	35/39	29.0 (9.1)	15.7 (5.2)	13.7 (9.4)	Mixed	1. Executive Functions (Risk taking)	1. Executive Functions (Decision Making under ambiguity)	N/A

*Studies are listed in chronological order. Unless specified otherwise, age, age of epilepsy onset and disease duration are reported as mean values in years, or as ranges, if provided in such format by the original reference. **Median (range). [##]Median (interquartile range). [$]Studies employing video-EEG during neuropsychological testing. C, Cross-sectional design; CW, Color-Word (Stroop test); IQ, Intelligence Quotient; PIQ, Performance Intelligence Quotient; VBM, Voxel-Based Morphometry; VIQ, Verbal Intelligence Quotient; VPA, Sodium Valproate. In Devinsky et al. (87): *, reduced function in JME compared to TLE; [#], comparisons against healthy controls. In Wandschneider et al. (97): *, shift toward more advantageous choices (i.e., task-associated learning) was impaired in JME patients with ongoing seizures, but not in those who were seizure-free. In the "AED Status" column, "Mixed" is given for studies where AED use was not restricted to a single regimen (i.e., monotherapy, polytherapy, or drug-naïve).*

(52, 89, 101). While only few reports documented normal functioning (93, 100), whether working memory weaknesses may be more prominent in the verbal than non-verbal domain remains unclear.

Dysexecutive traits are very commonly described for JME, and may represent its hallmark. The typical profile encompasses impairment of response inhibition (51, 53, 90, 95, 99, 102), attention, goal maintenance, concept building, problem solving, task-switching, and cognitive flexibility (52, 53, 87, 89, 91, 94, 104). Two studies attempted within-groups stratification of effects, documenting moderate to severe deficits in executive functions in 83% and 68% of the respective samples (52, 99). Of note, however, Thomas et al. (99) explicitly focused on difficult-to-treat patients with JME, who had not experienced seizure freedom with sodium valproate. It is also reported that JME patients may experience more "everyday life problems" as a result of dysexecutive traits (92, 100). Decision-making, another high-level executive function, also appears affected. Patients with JME may exhibit difficulties in making advantageous decisions under ambiguity (98), and commit to more risky choices than controls (105, 106). Interestingly, Wandschneider et al. (97) suggested that risky decision making may be particularly relevant in the patient subgroup with poorly controlled seizures, pointing toward an interplay between epilepsy severity and cognitive outcome.

Prospective memory, a system of creating, retaining, and implementing prior intentions and plans, is heavily reliant on executive functions, and has been evaluated via a complex multi-step task (51). At the intention formation stage, patients with JME developed more rudimentary plans than controls, suggesting impaired planning and cognitive flexibility. Furthermore, patients also completed significantly fewer tasks, suggestive of deficits in the executive component underlying prospective memory.

The involvement of cognitive functions reliant on temporal and hippocampal processes in the JME profile is uncertain. Several studies reported normal levels of functioning on tests of learning and memory (51, 53, 73, 93, 96, 100, 108), whereas others detailed deficits in short and long-term recall when compared to controls (4, 90, 99, 101). Impaired memory has been considered a consequence of impoverished visual and verbal learning (88, 89, 104). Conflicting evidence may be partially due to syndromic heterogeneity.

Some reports have suggested that heterogeneity of cognitive performance in JME may relate to compensatory strategies, dependent on general intelligence level (103). While it can be argued that higher IQ in a proportion of JME cases may relate to more effective strategy formation, enabling successful compensation and thus normative executive performance, the hypothesis of IQ as a protective factor for cognitive dysfunction in JME lacks strong empirical support. Moschetta et al. (52) previously reported that cognitive performance in most domains was lower in JME than controls even after co-varying for IQ, thus suggesting independence of effects.

On balance, studies investigating cognition in JME documented average general intelligence, which is however paralleled by impairment of verbal generativity, working memory and a wide range of executive functions, with moderate to large effect sizes. Semantic knowledge, reasoning, processing speed and dexterity also appear affected, while evidence regarding learning and memory deficits is conflicting. Finally, the literature is overall not supportive of impairment of visuo-spatial abilities.

Cognition in Patients With Absence Epilepsies

Table 3 summarizes findings of the investigations assessing cognitive function in CAE and JAE, often subsumed under the unitary category of AE, as specified earlier. Seminal research from Pavone et al. (109) found that AE may present with a subtle lowering of IQ compared to controls, which is corroborated by a recent review and several investigations (5, 73, 113, 114). As for mixed GGE samples and JME, however, IQ values are generally reported as within average ranges for the majority of AE patients. It is suggested that general cognitive ability may negatively correlate with disease duration (110, 111).

Phonological processing represents one of the most frequently described domains of cognitive impairment in AE (5), and relates to reduced linguistic abilities, semantic knowledge, verbal intelligence quotient [VIQ; (53)] and spoken language quotient [SLQ; (110)]. Decline in several aspects of linguistic functioning may be associated with disease duration (111). Alongside expressive naming (53, 74, 116), both semantic and phonemic fluency have been found as weak in AE, with performances falling one standard deviation below those of normative controls (112, 115).

Early reports also documented impoverished performance on tests of visuo-spatial skills in AE, as measured by the Performance IQ (PIQ) component of the WISC-R (53, 109). This was associated with relatively poor scores on tests of dexterity (53, 74, 112) and processing speed (112, 115). Abstract visuo-spatial reasoning and line orientation may also be poorer in AE patients than controls (73). Most research has not found evidence for working memory deficits in AE, though a recent study suggest impairment of its visuo-spatial component (73). It is possible that this finding may be a consequence of more general disruptions in visuo-spatial processing.

As a distinguishing feature of AE, several studies reported impairment of attentional control, affecting both verbal and non-verbal modalities (73, 74, 112, 115–118, 120). In the largest investigation to date, involving over 400 individuals with newly diagnosed, drug-naïve CAE, attentional deficits were reported in more than a third of probands despite average intelligence, and persisted 16–20 weeks after treatment initiation, even when successful seizure control was attained (117). Moreover, causal modeling indicated downstream sequential effects of attentional deficits on memory, executive function and academic achievement (117), corroborating early reports that proposed impaired attention as the underlying mechanism for poor memory performance (109). Reduced attentional skills were elsewhere found associated with higher levels of distractibility and forgetfulness (113) and lower arithmetic proficiency (119).

Though impaired attention is the predominant finding in AE, dysexecutive traits are also reported in AE samples, in accord

TABLE 3 | Studies investigating cognitive function in AE.

References	Design	Patients/ Controls (n)	Patient Age (sd)	Age of Epilepsy Onset (sd)	Disease Duration (sd)	AED Regimen	Impaired Cognitive Domains	Unimpaired Cognitive Domains	Imaging
Pavone et al. (109)	C	16/16	9.2 (3.0)	5.3 (3–8)**	N/A	Mixed	1. General Cognitive Abilities (IQ) 2. Visuo-spatial Skills 3. Non-verbal Learning and Memory	1. Semantic Knowledge 2. Verbal Memory	N/A
Henkin et al. (74)	C	12/20	14.4 (1.83)	7.2 (4–11)*	N/A	Monotherapy (VPA)	1. Attention 2. Semantic Fluency 3. Verbal Learning and Memory	1. Dexterity 2. Phonemic Fluency 3. Non-verbal Learning and Memory	N/A
Caplan et al. (110)	C	69/103	9.6 (2.5)	6.2 (2.5)	3.5 (2.8)	Mixed	1. General Cognitive Abilities (FSIQ, PIQ, VIQ) 2. Spoken Language Quotient	N/A	N/A
Caplan et al. (111)	C	78/102	N/A	N/A	N/A	Mixed	Same as above	Same as above	N/A
Conant et al. (112)	C	16/29	8.0 (1.3)	4–8	13.8 (8.5)	Mixed	1. Dexterity 2. Attention 3. Phonemic Fluency 4. Executive Functions (Cognitive Flexibility, Planning and Integration)	1. Processing Speed 2. Semantic Fluency 3. Verbal Memory 4. Non-verbal Memory 5. Executive Functions (Response Inhibition)	N/A
Vega et al. (113)	C	38/46	10.5 (2.3)	6.9 (2.8)	3.4 (2.7)	Mixed	1. Attention	N/A	N/A
Tosun et al. (114)	C	24/28	9.2 (2.2)	7.0 (2.0)	2.3 (2.2)	Mixed	1. General Cognitive Abilities (FSIQ, VIQ)	1. General Cognitive Abilities (PIQ)	SBM
D'Agati et al. (115)	C	15/15	11.4 (2.2)	8.8 (1.7)	2.7 (1.3)	Monotherapy (VPA)	1. Processing Speed 2. Phonemic Fluency 3. Semantic Fluency 4. Executive Functions (Task-switching)	1. Working Memory 2. Verbal Memory 3. Non-verbal Memory 4. Executive Functions (Planning)	N/A
Kernan et al. (116)	C	31/51	9.0 (2.0)	6.0 (2.0)	3.0 (2.0)	Mixed	1. Verbal Learning and Memory (CLVT and Stories) 2. Executive Functions (Cognitive Flexibility)	1. General Cognitive Abilities 2. Processing Speed 3. Working Memory 4. Verbal Memory and Learning (Doors and People) 5. Non-verbal Learning and Memory 6. Executive Functions (Response Inhibition)	N/A
Jackson et al. (53)	C	11/72	12.2 (3.5)	11.2 (3.5)	9.7 (3.2) (months)	Mixed	1. General Cognitive Abilities (VIQ, PIQ, Spelling) 2. Attention 3. Dexterity 4. Phonemic Fluency 5. Expressive Language (Naming) 6. Working Memory 7. Executive Functions (Problem Solving, Response Inhibition)	1. Processing Speed 2. Semantic Knowledge (Vocabulary and Reading) 3. Verbal Learning and Memory 4. Executive Functions (Task-switching)	N/A

(Continued)

TABLE 3 | Continued

References	Design	Patients/ Controls (n)	Patient Age (sd)	Age of Epilepsy Onset (sd)	Disease Duration (sd)	AED Regimen	Impaired Cognitive Domains	Unimpaired Cognitive Domains	Imaging
Masur et al. (117)	L	446/N/A	N/A	N/A	N/A	Mixed	1. Attention	1. General Cognitive Abilities 2. Processing Speed 3. Semantic Knowledge (Vocabulary) 4. Working Memory 5. Verbal Memory 6. Non-verbal Memory 7. Executive Functions (Cognitive Flexibility)	N/A
Cheng et al. (118)	C	37/37	8.0 (2.3)	6.2 (1.5)	N/A	Mixed	1. General Cognitive Abilities 2. Attention 3. Processing Speed 4. Executive Functions (Cognitive Flexibility)	1. Visuo-spatial Perception 2. Working Memory 3. Verbal Learning and Memory 4. Non-verbal Learning and Memory	N/A
Cheng et al. (119)	C	35/33	7.3 (1.3)	6.7 (1.3)	7.0 (7.0) (months)	Drug-naïve	1. General Cognitive Abilities 2. Attention 3. Executive Functions (Cognitive Flexibility, Problem Solving)	1. Processing Speed 2. Visuo-spatial Perception 3. Semantic Knowledge 4. Working Memory	N/A

*Studies are listed in chronological order. Unless specified otherwise, age, age of epilepsy onset and disease duration are reported as mean values in years, or as ranges, if provided in such format by the original reference. *Mean (Range); **Median (Range). C, Cross-sectional design; CVLT, California Verbal Learning Test; FSIQ, Full-Scale Intelligence Quotient; IQ, Intelligence Quotient; L, Longitudinal design; PIQ, Performance Intelligence Quotient; SBM, Surface-Based Morphometry; VIQ, Verbal Intelligence Quotient; VPA, Sodium Valproate. In the "AED Status" column, "Mixed" is given for studies where AED use was not restricted to a single regimen (i.e., monotherapy, polytherapy, or drug-naïve). Kadish et al. (120) outlined a validation of a screening tool for attention and executive function, but did not provide individual subtest scores, hence could not be included in the table.*

with typical findings in GGE, and include reduced scores for measures of problem-solving, response inhibition, processing speed, planning and mental flexibility (53, 112, 115, 118). Jackson et al. (53) indicated that impairment of attention and executive skills is clinically relevant, with performance of more than one standard deviation below normative levels in patients. We did not identify any investigation exploring decision-making or prospective memory in AE patients.

As in JME, evidence for impaired functions relying on mesiotemporal involvement in AE is controversial (5). Pavone et al. (109) reported abnormal non-verbal learning and memory, along with impaired delayed recall. Impoverished performance on standardized spelling tests has also been suggested as a potential indicator of altered long-term memory (53, 74, 116). Other studies, however, have found comparable performance on tests of learning and memory in patients and controls (73, 112, 115, 121). It is possible that learning and memory deficits may not be specific, and arise as a consequence of impaired phonological processing.

Lower IQ and impaired phonological ability in AE may be associated with anti-epileptic medication usage and disease duration. In the largest randomized controlled trial to date, sodium valproate appeared associated with significantly more frequent attentional deficits than ethosuximide and lamotrigine, independent of treatment response (117). Reduced FSIQ and PIQ appeared more prominent at a younger age and/or earlier age at disease onset than linguistic deficits, indicating a possible neurodevelopmental mechanism and differential modulatory effects of disease-related-variables (111). In a study considering cognitive dysfunction independently across GGE subsyndromes, Abarrategui et al. (73) posited that AE may present with the most severe cognitive impairment of all GGE, based on the assessment of a medicated cohort with a long disease duration (mean = 24.5 years). Other studies, however, report smaller effect sizes. On balance, it is maintained that inadequate seizure management relates to poor cognitive prognosis (68).

On balance, neuropsychological investigations in absence epilepsies also indicate average general intelligence, but principally substantiate impairment in two domains: phonological processing, which relates to most stages of language production and semantic knowledge, and attention, which represents the most commonly affected skill, and may in turn detrimentally affect executive function. Contrary to evidence in JME, however, there is a relative paucity of reports addressing high-level dysexecutive traits, and no evidence of altered decision making or risk-taking behavior. It remains to be established whether the latter traits may be specific to JME. Finally, while evidence for impaired verbal generativity is also widely documented for JME, its presence is mostly emphasized within the broader context of dysexecutive traits, rather than globally dysfunctional linguistic abilities. Future analyses directly comparing JME and AE across a test battery addressing language performance may shed further light on potential syndrome-specific cognitive features.

NEURAL CORRELATES OF COGNITIVE IMPAIRMENT IN GGE

By ILAE definition, patients with GGE present with normal clinical MRI. Advanced post-processing methods such as voxel-based morphometry (122), surface-based MRI analysis (123), diffusion tensor imaging [DTI; (124)], and functional MRI have identified widespread structural and functional abnormalities in GGE, mostly implicating fronto-cortico-thalamic regions and their connections (125–133).

During the generalized spike-wave paroxysms typical of GGE, combined EEG-fMRI studies have documented the involvement of the thalamus and fronto-parietal cortices, mostly overlapping with default-mode network (DMN) areas (134–137). Overall, these findings have led to the conceptualization of GGE as disorders of thalamo-cortical connectivity. The diffuse abnormalities of cortical and subcortical structure, function, and connectivity in GGE may also relate to altered cognitive functioning, and most studies have investigated the neural correlates of cognitive function in separate GGE subsyndromes. Findings are summarized in **Table 4**.

Neural Correlates of Cognitive Impairment in JME

In JME, early functional imaging studies aimed to identify the neural correlates of working memory and executive dysfunction. The first positron emission tomography (PET) investigation documented an association between impaired working memory performance in JME and reduced 18-fluorodeoxyglucose uptake within premotor, anterior frontal cortices and caudate nucleus (86). Subsequently, McDonald and collaborators detected an association between frontal PET hypometabolism and lower mental flexibility scores (139). In an MR-spectroscopy study, Savic and colleagues reported reduced frontal lobe N-Acetyl Aspartate (NAA) concentrations, a marker of neuronal damage or dysfunction, in JME patients (148). Low frontal NAA was more prominent in those with poorer performance on an abbreviated cognitive assessment addressing frontal lobe function (138). Collectively, these early investigations provided complementary evidence linking dysexecutive traits to markers of impaired frontal lobe function across imaging modalities.

Subsequent investigations assessed the neural underpinnings of cognitive function in JME using task-based fMRI. Initial reports did not detect activation differences between JME patients and controls during a working memory fMRI task, which included verbal and visuo-spatial modified versions of the Sternberg Item Recognition Test (93). More recently, however, Vollmar and collaborators identified abnormal motor co-activation and increased functional connectivity between motor system and prefrontal cognitive networks during a visuo-spatial working memory task, which entailed joystick usage (141). While not substantiating the pattern of "hypofrontality" suggested by early imaging work, these findings point instead to an altered interplay between functionally segregated brain networks, modulated by task complexity, and implicate a potential disruption of whole-brain functional network hierarchy. In keeping with evidence of enhanced structural connectivity between the cognitive pre-SMA and motor cortex (149), these results may also provide a mechanistic explanation of cognition-triggered myoclonus in JME, i.e., *praxis induction* (141, 150). During the same working memory fMRI task, increased activation of the left dorso-lateral frontal cortex, on the other hand, was detected in JME patients with poorer decision-making performance (97). The latter may be interpreted as a compensatory mechanism to adequately engage working memory networks, required to carry out a complex decision-making task, and is reminiscent of findings in other neuropsychiatric disorders, such as schizophrenia (151, 152).

Other investigations in JME attempted to link the putative substrates of ictogenesis, likely represented by fronto-thalamo-cortical circuitry (150), with the associated cognitive comorbidities. O'Muircheartaigh and collaborators (129) demonstrated aberrant fronto-cortico-thalamic connectivity in JME during a verbal fluency fMRI task, which was associated with impoverished fluency performance. Complementary evidence was provided by a structural imaging analysis in recent-onset JME, which detected an association between performance on executive function tests and both thalamic and frontal volumes (140). On balance, this work suggests that the same circuitry accounting for seizure generation in JME may also mediate impairment of executive skills.

Other analyses sought to identify the neural correlates of cognitive traits in JME via structural imaging methods. Altered microstructural integrity of the supplementary motor area was associated with reduced performance on an expressive language task, while both gray matter volume and microstructural integrity of the posterior cingulate cortex related to mental flexibility (94). In a diffusion MRI tractography analysis, connectivity between post-central gyrus and precuneus was positively associated with verbal IQ, expressive language as well as verbal memory scores (143). Other studies, however, reported no correlations between white matter markers and a wide range of neuropsychological test scores, most of which relating to frontal lobe functions (95). While implicating midline frontal, primary sensory and parietal regions, structural imaging findings provide a less cohesive picture, as opposed to the more concordant evidence garnered via functional imaging studies.

Longitudinal investigations in new-onset JME may offer a window into the developmental trajectories of cognitive comorbidities. Lin et al. (142) documented lower response inhibition and psychomotor speed in patients with JME compared to controls at baseline, accompanied by persistence of intergroup differences after a 2 year follow-up, and more limited increase of general intelligence scores in the JME group. The latter cognitive traits were paralleled by structural abnormalities of high-order fronto-temporo-parietal association cortices, as demonstrated by an attenuation of the expected cortical thinning and contraction of surface areas. These findings overall implicate disrupted cortical maturation, and point to a post-migrational neurodevelopmental mechanism (142). Interestingly, further support to the neurodevelopmental hypothesis comes from recent analyses, indicating increased cortical folding complexity and inefficient cortico-cortical connectivity of orbitofrontal, ventrolateral frontal, premotor and temporo-polar areas. The

TABLE 4 | Studies investigating imaging correlates of cognitive function in JME and AE.

Reference	Design	Patients/ Controls (n)	Patient Age (sd)	Age of epilepsy onset (sd)	Disease duration (sd)	AED regimen	Summary
JME							
Swartz et al. (86)	C	9/14	28.0 (4.0)	9–20	N/A	Polytherapy	FDG-PET– 1) Rest: ventral premotor, dorsolateral frontal, temporal, limbic and caudate hypometabolism in JME 2) Working Memory: dorsolateral frontal, premotor and basal frontal hypometabolism, fusiform and temporo-polar hypermetabolism
Savic et al. (138)	C	26/10	30.6 (7.7)	13.6 (3.0)	17.2 (8.2)	Mixed	MR Spectroscopy—Reduced processing speed and cognitive flexibility scores in JME patients with lower frontal lobe N-Acetyl Aspartate concentration
McDonald et al. (139)	C	10/14	27.9 (4.7)	N/A	N/A	N/A	FDG-PET—No frontal hypometabolism in JME. Bilateral orbito-frontal and premotor metabolism related to non-verbal fluency, bilateral frontal hypometabolism associated with mental flexibility
Pulsipher et al. (140)	C	20/51	15.5 (2.8)	14.5 (3.0)	8.9 (3.7) (months)	Mixed	Structural MRI—Smaller thalamic volumes and increased frontal cerebrospinal fluid in JME. Thalamic volumes related to cognitive flexibility in the JME and control groups, frontal gray matter associated with cognitive flexibility and response inhibition in the JME group only
Roebling et al. (93)	C	19/20	24.2 (9.9)	N/A	N/A	Mixed	Structural MRI and working memory fMRI—No gray matter volume differences between patients with JME and controls, and no intergroup activation differences during a verbal and a visuo-spatial working memory task
O'Muircheartaigh et al. (94)	C	28/55	33.6 (10.1)	14.4 (3.4)	20.2 (10.3)	Mixed	Structural MRI—in JME, fractional anisotropy of anterior SMA positively correlated with naming performance, fractional anisotropy and gray matter volume of the posterior cingulate cortex negatively correlated with processing speed
Vollmar et al. (141)	C	30/26	32.8 (9.9)	N/A	N/A	Mixed	Working memory fMRI—1) abnormal co-activation of motor cortex and SMA with high cognitive load, and 2) impaired deactivation of the default-mode network in JME
Kim et al. (95)	C	25/30	25.3 (7.6)	14.7 (3.1)	10.6 (7.7)	Mixed	DTI—Impairment of processing speed, phonemic fluency, working memory, cognitive flexibility, and response inhibition in JME not correlated with fractional anisotropy or mean diffusivity abnormalities
O'Muircheartaigh et al. (129)	C	28/27	34.1 (9.9)	14.8 (2.7)	8.7 (11.5)	Mixed	Language fMRI—Phonemic fluency scores associated with attenuation of thalamocortical connectivity during verbal fluency paradigm, which was defective in JME
Lin et al. (96)	C	56/42	26.5 (9.0)	12.5 (4.6)	14.3 (10.0)	Mixed	Structural MRI—In JME, hippocampal volumes associated with performance on tests of semantic knowledge, phonemic fluency, verbal memory and learning
Wandschneider et al. (97)	C	21/11	33.5 (22–64)**	N/A	N/A	Mixed	fMRI—Poor decision-making associated with bilateral dorsolateral frontal activation in JME, and with reduced DMN deactivation in controls. Performance in JME patients with ongoing seizures negatively correlated with dorsolateral frontal activation. Non-learners had stronger activation of pre-SMA, left dorsolateral frontal cortex, and right superior frontal gyrus than learners

(Continued)

TABLE 4 | Continued

References	Design	Patients/ Controls (n)	Patient Age (sd)	Age of epilepsy onset (sd)	Disease duration (sd)	AED regimen	Summary
Lin et al. (142)	L[#]	19/57	14.9 (0.7)	14.0 (0.7)	8.4 (0.9)	Mixed	MRI—Lower longitudinal improvement in IQ, processing speed, and response inhibition scores in JME related to attenuation of the expected cortical thinning and surface area reduction in fronto-temporo-parietal association areas
Caeyenberghs et al. (143)	C	35/35	26.8 (7.8)	15.0 (3.5)	15.2 (8.8)	Mixed	Structural MRI—Tractography-based connectivity between right precuneus and left postcentral gyrus positively correlated with VIQ, naming, abstract reasoning, and verbal memory. Connectivity between right hippocampus and right postcentral gyrus also associated with abstract reasoning.
Caciagli et al. (108)	C	37/36	32.0 (14.0)***	15.0 (4.0)***	19.0 (16.0)***	Mixed	Structural MRI—IQ and memory scores not associated with hippocampal malrotation in JME. Memory fMRI—Abnormal mesiotemporal and dorsolateral frontal activation in all JME patients during verbal memory, reorganized mesiotemporal activation for visual memory in JME with hippocampal malrotation only
AE							
Caplan et al. (144)	C	26/37	9.7 (2.1)	6.9 (2.1)	2.2 (2.3)	Mixed	Structural MRI—Gray matter volume loss in left orbital frontal gyrus and bilateral temporal lobes in CAE. Volume of these areas related to IQ in controls, not in patients.
Killory et al. (145)	C	26/22	12.0 (4.0)	N/A	N/A	Mixed	EEG-fMRI—Decreased medial frontal fMRI activation associated with poorer continuous performance test results in CAE. Concomitant impaired connectivity within attentional networks in CAE compared to controls
Tosun et al. (114)	C	24/28	9.2 (2.2)	7.0 (2.0)	2.3 (2.2)	Mixed	Structural MRI (SBM) 1) *Sulcal depth:* PIQ and VIQ less associated with medial/superior frontal, superior temporal, and occipito-parietal sulcal depth in CAE than controls, and more associated with middle frontal sulcal depth in CAE than controls 2) *Cortical thickness:* frontal and temporal thickness less associated with PIQ and VIQ in CAE than controls, while orbito-frontal thickness is more associated with PIQ and VIQ in CAE
Lin et al. (146)	C	21/27	9.6 (2.1)	7.0 (2.1)	2.6 (2.5)	Mixed	Structural MRI—in CAE, no association between thalamic volumes and cognitive measures (IQ, SLQ), but negative correlation detected between left thalamic volume and scores on a social problem assessment scale.
Guo et al. (147)	C	39/ no controls	9.9 (3.1)	N/A	3.0 (2.5)	Medication withheld 48h prior to scanning	EEG-fMRI during tasks—Absence seizures with behavioral impairment during finger tapping and attention tasks associated with more marked fMRI signal increases in default-mode, fronto-parietal and thalamic-/sensory-motor network than seizures with no impairment in task performance.

*Studies are listed in chronological order. Unless specified otherwise, age, age of epilepsy onset and disease duration are reported as mean values in years, or as ranges, if provided in such format by the original reference. **Median (range). ***Median (interquartile range). [#]Demographics are provided for the sample at baseline. C, Cross-sectional design; CAE, Childhood Absence Epilepsy; DMN, Default Mode Network; DTI, Diffusion Tensor Imaging; (f)MRI, (Functional) Magnetic Resonance Imaging; IQ, Intelligence Quotient; JME, Juvenile Myoclonic Epilepsy; L, Longitudinal Design; PIQ, Performance Intelligence Quotient; SBM, Surface Based Morphometry; SLQ, Spoken Language Quotient; SMA, Supplementary Motor Area; VIQ, Verbal Intelligence Quotient. Mixed AED status is given for studies where AED use was not restricted to a single regimen (i.e., monotherapy, polytherapy, or drug-naïve).*

latter regions also displayed abnormal cognitive network embedding, with fronto-parietal, dorsal attention and limbic cognitive systems being most affected (132).

Finally, a recent multi-modal imaging investigation in JME focused on the mesiotemporal lobe. Structural morphometric analyses indicated anomalies of hippocampal

shape and positioning, pointing to altered mesiotemporal neurodevelopment during the prenatal stages, which related to reduced memory-related activation of both hippocampus and dorsolateral frontal areas (108). This work thus substantiates morphometric and functional abnormalities in JME extending beyond the classically involved fronto-cortico-thalamic or fronto-parietal systems, and supports functional relevance of mesiotemporal structural alterations, which reverberate on a fronto-temporal network subserving episodic memory.

Neural Correlates of Cognitive Impairment in AE

As opposed to evidence in JME, direct assessments of the imaging correlates of cognitive function in AE are less numerous. Orbitofrontal and temporal lobe gray matter volumes were described as diminished in CAE (144), though formal correlations between the latter imaging measures and IQ scores were statistically significant in controls only. An investigation relating cortical thickness and sulcal depth to verbal and performance IQ found differential patterns of association between cognitive and structural measures in CAE compared to controls. Effects were particularly prominent for thickness and sulcal depth of medial/superior frontal and superior temporal areas, and implicated a negative relation between the latter and verbal IQ, which was instead positive in typically developing controls (114). In CAE, however, the authors identified positive associations between intelligence measures and thickness of the orbitofrontal cortex as well as sulcal depth of the middle frontal gyrus. Overall, these findings indicate distinct patterns of morphological signatures associated with general cognitive abilities, which may result from disease-related plasticity and reorganization.

Subsequent investigations assessed subcortical structures, in light of increasing evidence suggesting thalamic involvement in the generation of seizures and interictal discharges (137, 153, 154). While one study identified smaller thalamic volumes in CAE compared to controls, it did not detect a significant association between the latter and IQ measures (146). In JAE, reductions of gray matter volume and surface area were detected in the frontal, cingulate, and mesiotemporal locations, but formal correlations with cognitive measures were not available (155).

Functional imaging investigations in AE principally addressed the neural correlates of attention. During a sustained attention paradigm, an association was detected between lower activation of the medial frontal cortex and impaired task performance in CAE, which co-existed with reduced resting-state connectivity within an attentional network encompassing anterior insula and medial frontal cortex (145). More recently, combined behavioral and EEG-fMRI investigations detailed an association between (a) entity of functional activity changes within default-mode, fronto-parietal task-positive and sensorimotor-thalamic networks, and (b) intensity of absence seizures and related behavioral impairment. These findings thus provide direct evidence of a relationship between seizure-related cognitive compromise and levels of activity within large-scale brain networks (147).

DETERMINANTS OF COGNITIVE DYSFUNCTION: FOCUS ON HERITABILITY

GGE are characterized by multi-factorial etiology and likely polygenetic underpinnings (156–158). A commonly held view regards GGE as heritable disorders of abnormal neurodevelopment, which may provide a unifying framework to understand vulnerability to seizure activity, distributed anomalies of functional and structural connectivity, as well as the associated cognitive and psychopathological comorbidities. Factors exerting additional modulation of the cognitive phenotype in GGE include disease-related variables, such as the combination of seizure types, seizure frequency and their responsiveness to treatment, disease duration, frequency of interictal epileptiform discharges, and specific effects of anti-epileptic medication (68, 107, 110).

Here, we will predominantly summarize research addressing genetic factors as determinants of cognitive impairment in GGE via family studies. Investigating neurobehavioral traits in first-order relatives of index cases provides the opportunity to account for potential effects of medication and seizures, whilst investigating individuals with comparable upbringing and socio-economic determinants. Common findings in patients and their relatives can be interpreted as intermediate phenotypes, or endophenotypes (159, 160) i.e., heritable traits co-segregating in affected families, underlying predisposition to disease and shedding light on its pathological mechanisms. Thus far, a few investigations have tested whether patterns of cognitive impairment in GGE may be heritable, and the majority of endophenotype research has focused on JME probands. While Levav et al. (121) detailed familial impairment in both JME and CAE samples, we are not aware of further subsyndrome-specific research in absence epilepsies or GGE-GTCS.

Levav et al. (121) demonstrated comparable deficits in attentional functioning for patients with GGE and their siblings relative to controls. More recently, Chowdhury et al. (71) showed that patients with GGE and first-degree relatives exhibited similar levels of impairment on tests of working memory, non-verbal reasoning, verbal fluency, and attention. In first-degree relatives, performances in the aforementioned domains mostly fell between patients and controls, suggesting a heritable component for cognitive impairment in GGE whilst implicating additional detrimental effects in patients, which may relate to a combination of seizures, anti-epileptic medication and/or greater genetic burden. In JME, two investigations described concomitant impairment of motor dexterity and phonemic fluency in probands and their siblings (92, 100). Semantic fluency and psychomotor speed also followed a similar trend, with relatives underperforming compared to controls. Interestingly, the familial similarities in cognitive performance were observed independent of abnormal interictal EEG in both studies. Furthermore, evidence suggests that JME probands and siblings both performed worse than controls during the memory formation and intention execution stages of a prospective memory task (51), which indicates heritability in relation to a complex cognitive skill, with tangible "everyday life" implications. Collectively, these investigations

highlighted common neurobehavioural traits in patients and their unaffected siblings, mostly affecting executive function. Dyscognitive traits are thus implicated as a feature underpinned by genetic contribution, likely part of an extended disease-related phenotype, rather than mere consequence of seizure activity or anti-epileptic drug effects.

In parallel, recent imaging research complemented evidence on cognitive intermediate phenotypes. In patients with JME and their siblings, Wandschneider et al. (54) detected concomitant motor co-activation and abnormal connectivity between motor and prefrontal cognitive systems during a working-memory task, suggesting that altered interplay between functionally distinct macroscale networks may also be genetically driven. The previously detailed surface-based morphometry study, which investigated cortical folding complexity and cortico-cortical connectivity via a geodesic distance metric, identified concomitant abnormalities within high-order fronto-temporal cortices both in patients with JME and siblings. Similarly, abnormal embedding of the latter areas within large-scale cognitive networks, mostly affecting fronto-parietal, dorsal attention and limbic systems, was detected in both groups (132). Finally, recent work demonstrated co-segregation of abnormalities of hippocampal volume, shape and positioning both in patients with JME and their siblings, and showed their association with reorganization of both hippocampal and lateral frontal recruitment during a memory encoding functional MRI paradigm (108).

Collectively, these findings strongly indicate concomitant cognitive network abnormalities in patients with JME and their relatives, suggest involvement of cognitive domains beyond executive functions, and implicate high heritability.

CONCLUSIONS

There is substantial evidence that GGE present with widespread cognitive impairment, predominantly involving executive functions. Cognitive profiles may slightly diverge across GGE subsyndromes, with absence epilepsies mostly affected in regard to phonological processing and attention, while high-level dysexecutive and risk-taking traits may be more prominent in JME. Studies assessing the neural correlates of cognitive dysfunction are more abundant in JME, and have frequently implicated thalamo-fronto-cortical and motor to prefrontal connections. In AE, on the other hand, there is evidence for a relationship between abnormal fronto-cortical morphometry and IQ, and impaired attention is paralleled by altered activation and connectivity within fronto-insular attentional networks. Whilst the etiology of cognitive impairment in GGE is likely multi-factorial, assessments of first-degree relatives, mostly of JME index patients, support heritability of cognitive profiles and the associated neural underpinnings, which qualify as suitable intermediate phenotypes (endophenotypes). Further research is awaited to (1) characterize profiles of cognitive impairment in homogeneous JAE samples, instead of assessing those along with CAE cases, irrespective of syndromic distinction; (2) elucidate patterns of dysfunction in GGE-GTCS; and (3) advance our insights into the pathological mechanisms of cognitive abnormalities, which may entail longitudinal investigation of cognitive trajectories in patients and their relatives, and, ultimately, require analyses of multi-source datasets encompassing neuropsychology, neuroimaging, genetics and neurophysiology.

AUTHOR CONTRIBUTIONS

CR, BW, MK, and LC planned the manuscript. CR and LC wrote the manuscript and carried out the subsequent revisions. CR and LC prepared the supporting material. PT and SB assisted in the interpretation of cognitive test results. All the co-authors provided substantial contributions to the first manuscript draft and subsequent revised versions.

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