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Enlarged hippocampal fissure in psychosis of epilepsy

James Allebone [a,c,*], Richard A. Kanaan [c,h], Jerome J. Maller [f,g], Terrence O'Brien [d], Saul Mullen [b], Mark Cook [e], Sophie Adams [d], Simon Vogrin [e], David Vaughan [b,c], Alan Connelly [b,c], Patrick Kwan [d], Samuel F. Berkovic [b], Wendyl D'Souza [e], Graeme Jackson [b,c], Dennis Velakoulis [d], Sarah J. Wilson [a,b,c]

[a] Melbourne School of Psychological Sciences, The University of Melbourne, Australia
[b] Comprehensive Epilepsy Program, Austin Health, Melbourne, Australia
[c] The Florey Institute of Neuroscience and Mental Health, Australia
[d] The Royal Melbourne Hospital, Australia
[e] St Vincent's Hospital Melbourne, Australia
[f] Monash Alfred Psychiatry Research Centre, The Alfred and Monash University, Melbourne, Australia
[g] Centre for Research on Ageing, Health and Wellbeing, ANU College of Health and Medicine, Australian National University, Canberra, Australia
[h] Department of Psychiatry, Austin Health, University of Melbourne, Australia

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ABSTRACT

Psychosis of epilepsy (POE) can be a devastating condition, and its neurobiological basis remains unclear. In a previous study, we identified reduced posterior hippocampal volumes in patients with POE. The hippocampus can be further subdivided into anatomically and functionally distinct subfields that, along with the hippocampal fissure, have been shown to be selectively affected in other psychotic disorders and are not captured by gross measures of hippocampal volume. Therefore, in this study, we compared the volume of selected hippocampal subfields and the hippocampal fissure in 31 patients with POE with 31 patients with epilepsy without psychosis. Cortical reconstruction, volumetric segmentation, and calculation of hippocampal subfields and the hippocampal fissure were performed using FreeSurfer. The group with POE had larger hippocampal fissures bilaterally compared with controls with epilepsy, which was significant on the right. There were no significant differences in the volumes of the hippocampal subfields between the two groups. Our findings suggest abnormal development of the hippocampus in POE. They support and expand the neurodevelopmental model of psychosis, which holds that early life stressors lead to abnormal neurodevelopmental processes, which underpin the onset of psychosis in later life. In line with this model, the findings of the present study suggest that enlarged hippocampal fissures may be a biomarker of abnormal neurodevelopment and risk for psychosis in patients with epilepsy.

1. Introduction

Despite over a century of investigation into the relationship between epilepsy and psychosis [1], the neuropathology of psychosis of epilepsy (POE) remains unclear. Following early reports of increased rates of POE in temporal lobe epilepsy (TLE) [2–4], researchers focused on structural changes in the hippocampus — a key limbic structure located in the mesial temporal lobe [5–10]. Some studies [5,9], but not others [6–8,10], identified reduced hippocampal volume in POE relative to controls with epilepsy. These mixed results likely reflect small sample sizes and segmentation protocols, which either include nonhippocampal tissue [5,11], or exclude posterior hippocampal regions [8,9]. In a recent study that addressed these limitations [12], we systematically measured the hippocampal head, body, and tail (i.e., gross anatomical subregions of the hippocampus) in a large cohort of patients with POE and patients with epilepsy without psychosis (controls with epilepsy). The results showed reduced volume in posterior hippocampal subregions (body and tail) in patients with POE, pointing to the role of the posterior hippocampus in its neuropathogenesis. The same cohort was examined in the present study where the hippocampus was further subdivided into anatomically and functionally distinct subfields, which have distinctive histological characteristics [13] (Fig. 1). Importantly, atrophy at the subfield level is not captured by measures of total or subregional hippocampal volumes.

Volume loss in hippocampal subfields has been identified in psychotic disorders, including schizophrenia and bipolar disorder [14–17]. In schizophrenia, volume reductions have been identified in CA1 [14,17], CA2/3 [15,16], CA4 [15], and the subiculum [14,15] relative to healthy controls, with changes in specific subfields linked to the emergence of psychotic symptoms. For example, research suggests that changes in glutamate transmission in the dentate gyrus (DG) can cause faulty encoding of memories, giving rise to delusional mind states

* Corresponding author at: Melbourne School of Psychological Sciences, The University of Melbourne, Victoria 3010, Australia.
E-mail address: jallebone@unimelb.edu.au (J. Allebone).

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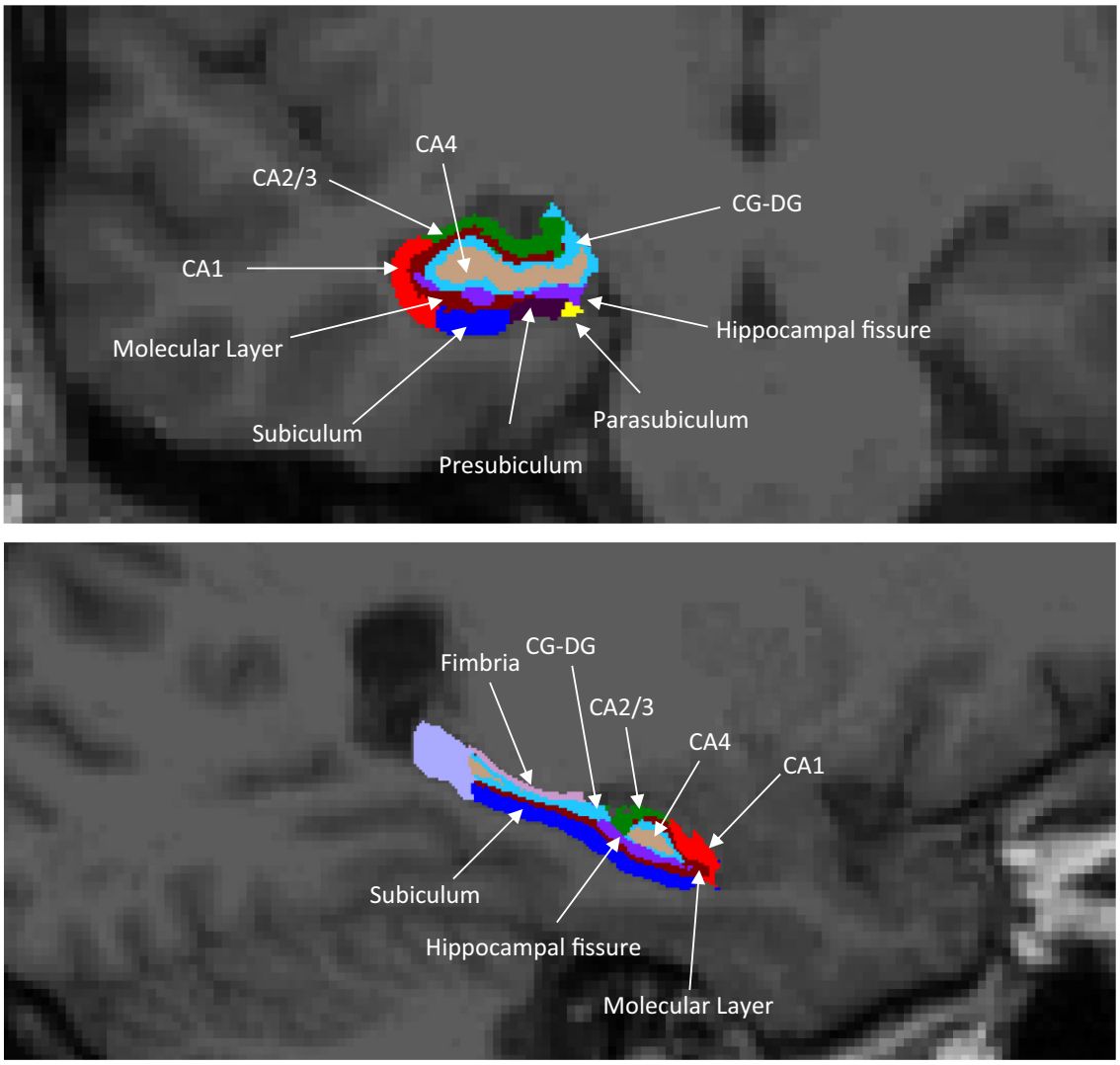

Fig. 1. Coronal (top) and sagittal (bottom) views of hippocampal subfields segmented using FreeSurfer. CA = cornu amonis, CG-DG = granule cell layer of the dentate gyrus.

[18]. Volume loss in hippocampal subfields has also been identified in epilepsy [19,20]. In mesial TLE, significant volume loss has been identified in CA1, CA2–3, CA4, DG, the subiculum, and fimbria relative to healthy controls [20] with reductions in specific subfields, particularly the DG, associated with hyperexcitability [19]. The hippocampal fissure is a vestigial space that sits between the DG and the presubiculum and parasubiculum [21]. Enlarged hippocampal fissures, which reflect a failure of the two sides of the fissure to fuse, have been identified in both epilepsy [22] and schizophrenia [23], and are thought to reflect abnormal neurodevelopment [21]. According to current research, the primary mechanism for enlarged hippocampal fissures is exposure of the developing brain to prenatal [24] and postnatal stressors [25]. Exposure to stressors in early neurodevelopment is a known risk factor for epileptogenesis in the hippocampus [26], and for psychosis [27]. As such, abnormal development of the hippocampus, reflected in enlarged hippocampal fissures and/or volume loss in hippocampal subfields, may in part explain why some patients with epilepsy develop psychosis.

Despite the links between hippocampal fissure and subfield abnormalities on the one hand, and both epilepsy and psychosis on the other, no study to date has examined the volume of hippocampal subfields or the hippocampal fissure in POE. Importantly, volume reductions in specific subfields may be obscured when hippocampal volume is calculated for the whole hippocampus, or at the gross anatomical subregional level (i.e., at the level of the head, body, and tail). Therefore, we employed an automated analysis procedure to segment hippocampal subfields in T1-weighted magnetic resonance images (MRIs) of the group with POE and control group with epilepsy and compared the volume of individual hippocampal subfields and the hippocampal fissure of the two groups. Because of uncertainty around the boundaries of hippocampal subfields in the hippocampal tail, subfield volumes were only measured in the head and body of the hippocampus. Based on past research in schizophrenia and bipolar disorder, which has shown reduced volume in CA1 [14,17], CA2/3 [15,16], CA4 [15], and the subiculum [14,15] relative to healthy controls, and studies showing enlarged hippocampal fissures in both epilepsy [22] and schizophrenia [23], we hypothesized that patients with POE would show (i) smaller volumes in CA1, CA2/3, CA4, and the subiculum and (ii) larger hippocampal fissure volumes relative to controls with epilepsy.

2. Material and methods

2.1. Participants

The details of our recruitment procedure, inclusion and exclusion criteria, and classification of seizures and psychoses have been detailed elsewhere [12]. In brief, the study comprised retrospective and prospective arms that were approved by the relevant Human Research Ethics Committees at The Royal Melbourne Hospital, Austin Health, and St

Vincent's Hospital, Melbourne, Australia. For the retrospective arm, a neuropsychiatrist and epileptologist from each site reviewed the files of all patients who had been admitted to the Comprehensive Epilepsy Programs (CEPs) of the three hospitals between January 1993 and September 2014 in order to identify patients with POE. Fifty-one T1-weighted MRI scans of patients with POE who met inclusion criteria were then obtained. For the prospective arm, 12 patients with POE were identified on admission to the three CEPs between January 2015 and February 2017. A 3T T1-weighted magnetization-prepared rapid gradient echo image was acquired for each prospective participant at the Melbourne Brain Center, Australia (TR: 1900 ms, inversion time 900 ms, TE: 2.6 ms, acquisition matrix = 256 × 256, flip angle: 9, 0.9 mm isotropic voxels). All participants were classified as TLE or extratemporal lobe epilepsy (ETLE) based on the location of the seizure focus, determined by scalp video-electroencephalography (EEG) and MRI, or as genetic generalized epilepsy (GGE) if EEG showed characteristic generalized (bilateral) spike–wave discharges, no clear site of seizure onset, and consistent semiology.

Controls with epilepsy were identified via the same file review process, and matched as closely as possible to a participant with POE scanned on the same machine according to the following variables: age (±5 years), gender, epilepsy syndrome, laterality, and lesion status on MRI (positive or negative). Following automated segmentation of hippocampal subfields and the hippocampal fissure, scans were visually inspected in order to ensure that the gross boundaries of the hippocampus were accurate. Three scans were excluded because of segmentation errors in FreeSurfer. A further 14 scans of participants who had undergone anterior temporal lobectomy were excluded, as FreeSurfer was unable to accurately calculate hippocampal subfield volumes. The final sample comprised 31 patients with POE and 31 controls with epilepsy. Characteristics of each scan selected from the retrospective cohort for the present study are presented in Supplementary Table 1. A flow diagram of the recruitment, screening, and matching process, as well as the scanner type is presented in Fig. 2.

2.2. MRI analyses

Cortical reconstruction, volumetric segmentation, and subsequent hippocampal subfield estimations were performed on the same workstation using the FreeSurfer 6.0 software package (http://surfer.nmr.mgh.harvard.edu/). In brief, this process involves motion correction and averaging of volumetric T1-weighted images [28], removal of nonbrain tissue, automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures including the hippocampus [29,30], intensity normalization, tessellation of the gray–white matter boundary, automated topology correction, and surface deformation [31,32]. These procedures have

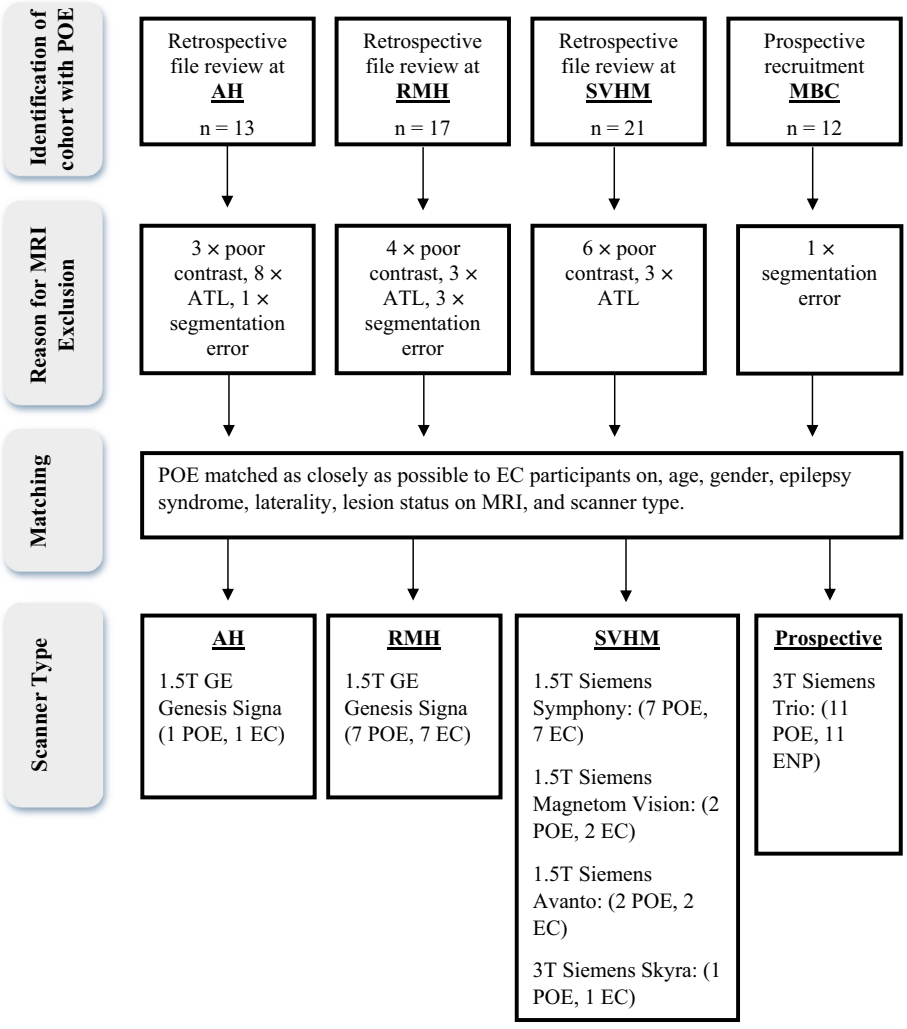

Fig. 2. Flow diagram depicting the recruitment, exclusion, and matching process, and scanner characteristics. EC = controls with epilepsy, AH = Austin Health, RMH = Royal Melbourne Hospital, SVHM = St Vincent's Hospital Melbourne, MBC = Melbourne Brain Centre; ATL = anterior temporal lobectomy.

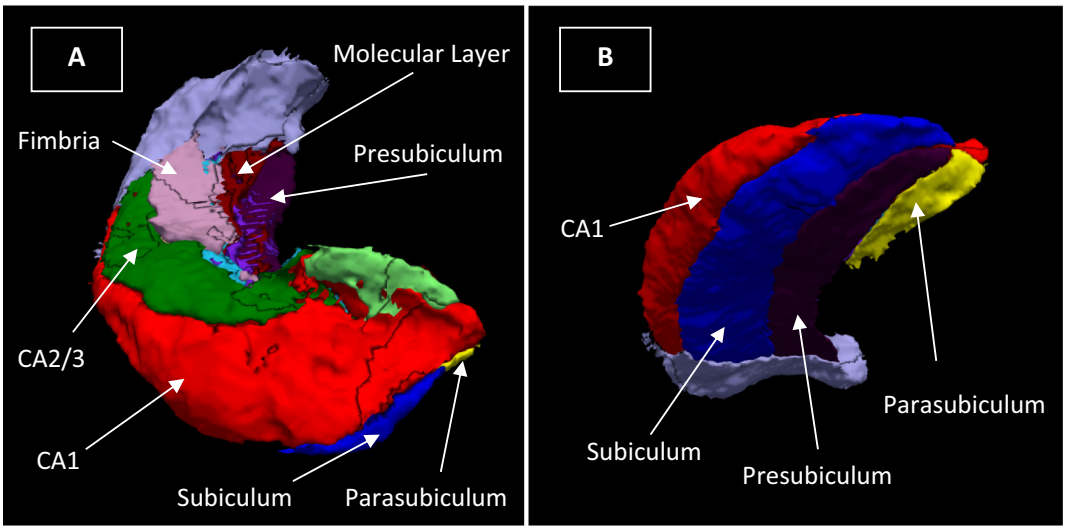

Fig. 3. 3D render of automated segmentation of the hippocampus a participant with POE. A = anterior view, B = inferior view. CA = Cornu amonis.

been validated against histological analysis [33] and manual measurements [34,35]. FreeSurfer morphometric procedures also have good test–retest reliability across scanner manufacturers and field strengths [36,37].

Hippocampal subfields were labeled using an algorithm, which models the spatial distribution of the subfields, learned from labeled training data [38]. Prior to the release of FreeSurfer version 6.0, hippocampal subfield segmentation was based on in vivo MRI data. Because of image resolution, some subfields were not able to be distinguished accurately and did not correspond well to histological studies [20]. The algorithm in version 6.0 utilizes ex vivo MRI data from postmortem medial–temporal lobe tissue, which was imaged on a 7T scanner with long acquisition times, yielding images with very high resolution and signal-to-noise ratio. The volumes obtained using this new technique have been shown to closely approximate subfield estimations obtained through histological analysis [38]. A 3D render of the output of the subfield segmentation process is presented in Fig. 3.

The "segment" module in SPM12 (Wellcome Department of Cognitive Neurology, UK) was utilized to calculate intracranial volume (ICV; gray matter plus white matter plus cerebrospinal fluid) and total brain volume (TBV; gray plus white matter) for each participant. This method was employed because SPM12 shows less systematic bias in calculating ICV than Freesurfer in adults with neurological disease, and correlates very strongly with manually traced ICV [39,40]. Segmentations were visually inspected to ensure that the data were valid. In six scans (3 with POE, 3 controls with epilepsy) the whole skull was not included in the field of view, and since ICV and TVB could not be calculated in these participants, they were excluded from these analyses.

2.3. Statistical analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 23.0 and JASP (https://jasp-stats.org) [41]. Data were checked for extreme outliers, normality, and homogeneity of variance, with nonparametric statistics used where necessary. Two-tailed t-tests and Mann–Whitney U Tests were employed to test the hypotheses that patients with POE would show (i) smaller hippocampal subfield volumes in CA1, CA2/3, CA4, and the subiculum and (ii) larger hippocampal fissure volumes relative to controls with epilepsy. All subfields measured by FreeSurfer were compared between groups. The alpha level was set at 0.05, with effect sizes reported as per Cohen [42]. In order to control the familywise Type 1 error rate for each theoretical prediction, correction for multiple comparisons was separately performed for each hypothesis using the Holm–Bonferroni sequential correction method [43]. Bayesian statistics were also calculated for each hypothesis test because, unlike frequentist statistics, they convey the likelihood of the result under the null hypothesis and the alternative hypothesis, and are more intuitive to interpret. Bayesian independent samples t-tests were employed to determine the extent to which the data were supported by hypotheses (i) and (ii), with the prior width left at its default value of 0.707.

3. Results

There was no significant difference in the mean ICV between the 2 groups ($p = 0.2243$); hence, volumetrics were not normalized by ICV nor was there any significant difference in TBV or on any of the demographic or epileptological variables ($p > 0.05$ for all comparisons, Table 1).

As shown in Table 2, the volume of the right hippocampal fissure was significantly larger in the group with POE compared with the control group with epilepsy $t(60) = -2.39$, $p = 0.020$, $d = 0.60$ (medium effect). A Bayesian independent samples t-test revealed that the data were 5.373 times more likely to be observed under the hypothesis that participants with POE would have a larger right hippocampal fissure than under the

Table 1
Total brain volume (TBV), intracranial volume (ICV), demographic, and epileptological characteristics of the patient groups.

	POE (n = 31)	EC (n = 31)	*p*
TBV (liters)	1.11 (0.11)	1.09 (0.14)	0.53
ICV (liters)	1.42 (0.17)	1.37 (0.15)	0.22
Age in years (±SD)	40.87 (11.38)	39.58 (11.43)	0.65
	Range: 18–63	Range: 19–65	
Gender, male, *n* (%)	19 (61.3%)	19 (61.3%)	1.00
Epilepsy syndrome, *n* (%)			0.98
Temporal	21 (67.7%)	22 (71%)	
Extratemporal	5 (16.1%)	4 (12.9%)	
Generalized	4 (12.9%)	4 (12.9%)	
Unclear	1 (3.2%)	1 (3.2%)	
Side of epilepsy focus, *n* (%)			
Right	12 (38.7%)	13 (41.9%)	0.82
Left	9 (29.0%)	11 (35.5%)	
Bilateral	5 (16.1%)	2 (6.5%)	
GGE	4 (12.9%)	4 (12.9%)	
Unclear	1 (3.2%)	1 (3.2%)	
Lesion detected on MRI, *n* (%)	15 (48.4%)	12 (38.7%)	0.44

Note: SD = standard deviation, POE = psychosis of epilepsy; EC = controls with epilepsy; GGE = genetic generalized epilepsy.

Table 2
Mean hippocampal subfield and fissure volumes (mm^3) of the patient groups, and Bayes factors for each comparison.

	POE (n = 31)	EC (n = 31)	*p*	Adjusted *p*	Bayes factor
Left (±SD)					
Subiculum	406.49 (70.64)	406.35 (77.51)	0.99	1.00	0.257
CA1	615.42 (96.56)	622.64 (112.36)	0.78	1.00	0.319
CA2/3	195.76 (32.78)	196.53 (36.62)	0.93	1.00	0.276
CA4	244.76 (39.64)	243.80 (47.66)	0.93	1.00	0.243
Hippocampal fissure	147.12 (26.98)	136.18 (21.01)	0.09	0.09	1.590
Right (±SD)					
Subiculum	398.97 (78.62)	369.02 (84.41)	0.88	1.00	0.234
CA1	625.15 (131.11)	600.69 (136.96)	0.47	1.00	0.165
CA2/3	212.01 (48.58)	205.30 (48.67)	0.58	1.00	0.182
CA4	250.26 (56.04)	241.18 (57.61)	0.53	1.00	0.173
Hippocampal fissure	158.57 (26.18)*	142.24 (27.56)	**0.02**	**0.04**	**5.373**

Note: POE = psychosis of epilepsy; EC = controls with epilepsy. For tests of the right and left hippocampal fissures, the hypothesis specifies that EC volumes are less than the group with POE. For all other tests, the hypothesis specifies that POE volumes are less than the EC group. Volumes are expressed in mm^3.
* $p < 0.05$.

null hypothesis (moderate evidence) [44]. A Bayes factor robustness check indicated that the analysis was robust to alternative prior widths. The left hippocampal fissure was also larger in the group with POE compared with the control group with epilepsy but did not reach statistical significance $t\ (60) = -1.68$, $p = 0.097$, with a small effect size, $d = 0.45$, and a Bayes factor of 1.59. There was no significant difference between the groups on any other variable ($p > 0.05$, Bayes factor < 1 for all comparisons; Table 2). In order to investigate the relationship between duration of epilepsy and hippocampal fissure volume, and between age at seizure onset and hippocampal fissure volume in the group with POE, two-tailed Pearson product–moment correlation coefficients were calculated. Two patients with POE were excluded from these analyses because of missing data. There was no significant correlation between duration of epilepsy and the volume of the left $r = -0.13$, $p = 0.50$, or right hippocampal fissure $r = -0.13$, $p = 0.48$, or between age at habitual seizure onset and volume of the left $r = 0.32$, $p = 0.08$, or right hippocampal fissure $r = 0.33$, $p = 0.07$.

4. Discussion

This is the first study to examine the volume of hippocampal subfields and the hippocampal fissure using an automated methodology in a large cohort of patients with POE. The results showed that, on average, the group with POE had larger hippocampal fissures compared with the control group with epilepsy, which was significant on the right.

4.1. Larger hippocampal fissure volumes in POE may reflect abnormal neurodevelopment

One interpretation of this finding is that an enlarged hippocampal fissure reflects atrophy of the whole brain, or hippocampal structures, possibly due to chronic seizures, which are known to cause damage to the hippocampus [45]. However, the volumes of the subiculum, and CA regions, and the whole brain were almost identical in the group with POE and control group with epilepsy (Table 2). Furthermore, there was no statistical relationship between duration of epilepsy or age at habitual seizure onset and hippocampal fissure volumes in the group with POE, suggesting that hippocampal fissure enlargement is not explained by chronicity of seizures. An alternative explanation is that an enlarged hippocampal fissure is underpinned by abnormal neurodevelopment. The hippocampal fissure – a vestigial space that begins medially and extends laterally, sitting between the DG and the presubiculum, parasubiculum, and subiculum – appears as a small indentation in the hippocampus at approximately the 10th week of development [21] due to the infolding of the DG, CA, subiculum, and parahippocampal gyrus. The medial edges of the hippocampus begin to fuse by the second trimester, and by 30 weeks gestation, the hippocampal fissure is reduced to a shallow indentation, having been largely obliterated by the fusion process [46]. In the healthy adult brain, all that typically remains of the hippocampal fissure is a small opening between the DG and the presubiculum and parasubiculum on the medial surface of the hippocampus [21]. As such, residual hippocampal fissure cavities, which are reflected in overall hippocampal fissure volumes, suggest disrupted hippocampal development.

There was no significant difference in hippocampal subfield volumes between the group with POE and control group with epilepsy, suggesting that these subfields are not selectively implicated in the pathogenesis of POE. However, it is important to note that automated segmentation of hippocampal subfields does not calculate the volume of subfields in the tail of the hippocampus. This is due to current lack of knowledge of the neuroanatomical structure of the hippocampal tail and subsequent uncertainty around the boundaries of its subfields [38].

4.2. Theoretical and clinical implications

Given that enlarged hippocampal fissures are thought to reflect abnormal hippocampal neurodevelopment, our primary finding of an enlarged right hippocampal fissure in POE provides support to and expands the neurodevelopmental model of psychosis. According to this model, psychosis is the end state of abnormal neurodevelopmental processes that precede the onset of psychosis by many years [47,48]. Importantly, past studies have shown an association between neurodevelopmental abnormalities of the hippocampus specifically, and psychosis. For example, developmental abnormalities of the hippocampus have been identified in first-episode schizophrenia and linked to psychiatric symptoms [23], while the neurotoxic effects of fetal hypoxia have been linked to neuronal loss in the hippocampus and a higher risk of early onset schizophrenia [49]. Importantly, longitudinal studies have identified progressive volume loss in the hippocampus in patients with childhood onset schizophrenia [50]. Moreover, a greater prevalence of hippocampal shape abnormalities, including abnormalities of the hippocampal fissure, have been identified in familial schizophrenia patients relative to controls [51]. According to the neurodevelopmental model, one of the key antecedent risks for psychosis is exposure to early life stressors. For example, birth complications, maternal infection, and exposure to exogenous glutocorticoids have all been clearly linked to abnormal development of brain structure and connectivity in psychosis [47,52]. Although this cannot be directly investigated in the present study because of its retrospective design, it may be that enlarged hippocampal fissure volume in POE reflects abnormal neurodevelopment due to the impact of early life stressors. Febrile convulsions, which have been linked to hippocampal sclerosis via genetic variation in

the *SCN1A* gene [53], may also contribute to abnormal hippocampal development, and constitute a risk factor for POE. Abnormal neurodevelopment of the hippocampus may also underpin our previous finding in this cohort of reduced posterior hippocampal volume in POE [12].

The validity of extending the neurodevelopmental model of psychosis to POE requires exploration in longitudinal studies incorporating measures of early life stress, and sequential assessment of hippocampal volumetrics in patients with epilepsy, POE, and psychosis without epilepsy. Serial assessment of patients identified as 'at-risk' of POE (i.e., those exposed to early life stressors, febrile convulsions, or with enlarged hippocampal fissures) would provide insight into the developmental timing of hippocampal abnormalities in POE. If hippocampal fissure enlargement was observed over time, this would point to the impact of seizures on hippocampal morphometry, whereas stable hippocampal fissure volumes would suggest that such abnormalities in POE occur during early neurodevelopment.

In terms of clinical implications, the neurodevelopmental model of psychosis and the identification of risk factors for psychosis in schizophrenia have informed the early identification and treatment of people at risk, improving the course of the disease in some cases [54]. Similarly, in epilepsy, the identification of preclinical biomarkers of POE may lead to early monitoring and intervention, and augment decision-making processes around the necessity and timing of treatment, including epilepsy surgery to preclude the onset of POE. We suggest that future studies should investigate whether enlarged hippocampal fissures and smaller posterior hippocampal volumes are preclinical risk factors for POE.

4.3. Limitations

The present study has some limitations. First, because the majority of patients were identified through retrospective file review, we did not have reliable data on medication use and, therefore, could not rule out possible confounding effects of antiepileptic drugs or antipsychotics, which have been linked to altered hippocampal volumes in schizophrenia, and may have affected subfield volumes in the group with POE. Second, the MRI scans for the retrospective cohort with POE and their controls with epilepsy were obtained on 1.5 T scanners, which have a lower signal-to-noise ratio than scanners with higher field strengths (e.g., 3 T or 7 T). Assessment of hippocampal subfields at higher field strengths may allow for subtle changes in hippocampal subfields to be identified. Furthermore, as neuroanatomical knowledge of the hippocampal tail increases, it will become possible to reliably annotate its subfields and thus investigate the relative contribution of individual subfields to reduced posterior hippocampal volumes in POE, which we identified in a previous study in the same cohort of patients [12]. Finally, although we matched patients and controls on MRI scanner parameters as closely as possible, there were small differences in sequence parameters such as repetition time and echo time for some pairs of patients with POE and controls with epilepsy. Prospective studies of POE would address these issues; however, obtaining large prospective samples of POE patients is challenging.

5. Conclusion

This study found that hippocampal subfields were similar between patients with POE and controls with epilepsy; however, there was an enlarged right hippocampal fissure identified in the group POE. In a previous study, we identified bilaterally reduced posterior hippocampal volume in POE, which combined with the present finding suggests abnormal fusion of the hippocampus during early neurodevelopment, with possible concomitant underdevelopment of the hippocampal body and tail. Longitudinal studies are required to directly investigate this possibility, and the applicability of the neurodevelopmental model of psychosis to POE.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2020.107290.

Declaration of competing interest

There is no conflict of interest.

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