Seizure: European Journal of Epilepsy 101 (2022) 244–252

Contents lists available at ScienceDirect

Seizure: European Journal of Epilepsy

journal homepage: www.elsevier.com/locate/seizure

Increased cortical thickness in nodes of the cognitive control and default mode networks in psychosis of epilepsy

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ARTICLE INFO

Keywords:
Cortex
Epilepsy
Psychosis
Postictal psychosis
Interictal psychosis

ABSTRACT

Objective: To explore the cortical morphological associations of the psychoses of epilepsy.
Methods: Psychosis of epilepsy (POE) has two main subtypes - postictal psychosis and interictal psychosis. We used automated surface-based analysis of magnetic resonance images to compare cortical thickness, area, and volume across the whole brain between: (i) all patients with POE ($n = 23$) relative to epilepsy-without psychosis controls (EC; $n = 23$), (ii) patients with interictal psychosis ($n = 10$) or postictal psychosis ($n = 13$) relative to EC, and (iii) patients with postictal psychosis ($n = 13$) relative to patients with interictal psychosis ($n = 10$).
Results: POE is characterised by cortical thickening relative to EC, occurring primarily in nodes of the cognitive control network; (rostral anterior cingulate, caudal anterior cingulate, middle frontal gyrus), and the default mode network (posterior cingulate, medial paracentral gyrus, and precuneus). Patients with interictal psychosis displayed cortical thickening in the left hemisphere in occipital and temporal regions relative to EC (lateral occipital cortex, lingual, fusiform, and inferior temporal gyri), which was evident to a lesser extent in postictal psychosis patients. There were no significant differences in cortical thickness, area, or volume between the postictal psychosis and EC groups, or between the postictal psychosis and interictal psychosis groups. However, prior to correction for multiple comparisons, both the interictal psychosis and postictal psychosis groups displayed cortical thickening relative to EC in highly similar regions to those identified in the POE group overall.
Significance: The results show cortical thickening in POE overall, primarily in nodes of the cognitive control and default mode networks, compared to patients with epilepsy without psychosis. Additional thickening in temporal and occipital neocortex implicated in the dorsal and ventral visual pathways may differentiate interictal psychosis from postictal psychosis. A novel mechanism for cortical thickening in POE is proposed whereby normal synaptic pruning processes are interrupted by seizure onset.

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https://doi.org/10.1016/j.seizure.2022.09.006
Received 19 July 2022; Accepted 7 September 2022
Available online 8 September 2022

1. Introduction

The neuroanatomical basis of psychosis of epilepsy (POE) is not well understood. As POE is more prevalent in temporal lobe epilepsy [1], most structural neuroimaging studies have examined structural changes in the temporal lobe, particularly the hippocampus, with conflicting results [2–7]. Given that epilepsy is now understood as a disease of brain networks [8,9], pathology in network hubs beyond the hippocampus in POE is likely [10]. Indirect support for this idea comes from evidence of structural changes in patients with schizophrenia, the paradigmatic psychotic illness, in key hubs of two brain networks - the cognitive control network and the default mode network [17–21,23,24,30,31].

Early neuropsychological theories posited that while sensory and motor functions are highly localised, more complex cognitive functions depend upon the coordinated function of multiple, interconnected brain regions [11]. Recent studies using functional magnetic resonance imaging (fMRI) support this idea, identifying brain network dubbed the 'cognitive control network' [14]. The key nodes of the cognitive control network are the dorsolateral prefrontal cortex (DLPFC) anterior cingulate cortex, and parietal cortices which demonstrate increased activation during a variety of cognitive tasks [12–14] including working memory, error detection, response inhibition, sustained attention, and the flexible switching of attention [15,16]. This network is hypothesised to co-ordinate and support cognition and goal-directed, purposeful behaviours [14]. In support of this, lesions in nodes of the cognitive control network produce deficits on multiple cognitive functions [14,16]. In schizophrenia, cortical abnormalities have been identified in cognitive control network nodes in frontal [17–21], cingulate [22,23], and parietal [21,24] cortices and associated with poor cognitive function and increased symptom severity, suggesting a link between the symptoms of psychosis and cognitive control network pathology in the cerebral cortex [24].

When the human brain is not engaged in a specific task and recruiting the cognitive control network, other regions of the brain, now known as the 'default mode network', are consistently *activated*. In contrast, the default mode network is consistently *deactivated* during goal-directed cognitive processing [25]. The default mode network thus comprises a set of interconnected brain regions that are preferentially *active* when individuals are *not engaged* in cognitively demanding tasks [26]. The key nodes of the default mode network are the hippocampus, lateral temporal lobe, medial prefrontal cortex, posterior cingulate cortex, precuneus, and inferior parietal lobule [25–29]. Cortical abnormalities in these nodes have been repeatedly identified in patients with schizophrenia [20,30,31] and bipolar disorder [32], suggesting that variation in cortical morphology in the default mode network may be common across the psychosis spectrum, potentially including POE.

Only two studies have examined surface-based morphology in POE. Though they used the same method – surface-based morphometry (SBM) – they studied different POE subtypes [33,37]. DuBois et al. analysed cortical thickness in 11 patients with postictal psychosis compared to epilepsy patients without psychosis (EC) and a matched healthy control (HC) group [33]. Postictal psychosis is the more acute subtype of POE: it is time-limited, occurs within 7 days of a seizure or cluster of seizures, and usually involves delusions, hallucinations, and/or changes in affect or behaviour [34]. Compared to EC, the postictal psychosis group displayed cortical *thickening* in the right lateral prefrontal cortex, right rostral anterior cingulate cortex (i.e. in cognitive control network hubs), and right middle temporal gyrus. Relative to both groups, postictal psychosis patients showed increased cortical thickness in right rostral anterior cingulate cortex (cognitive control network hub), and thinner cortex in the right angular gyrus and left anterior inferior temporal gyrus. Because cortical thickness and area are thought to reflect distinct cellular mechanisms underpinned by different genetic influences [35,36], this study was limited in that it did not report cortical area, which may have been differentially affected. The second study, Gutierrez-Galve et al., tested 22 epilepsy patients with interictal psychosis, compared to EC and HC [37]. Interictal psychosis is the more chronic and severe form of POE, commonly presenting with paranoid delusions and hallucinations that do not resolve, and being more disabling to patients' psychosocial functioning. Twenty-two cortical parcellations were compared across groups, revealing cortical thinning in the pars opercularis in interictal psychosis patients compared to HC. This difference was not observed between epilepsy patients and healthy controls. Importantly, this study did not include patients with extra-temporal seizure foci, which are relatively common in POE [38], thus limiting findings to the particular syndrome of temporal lobe epilepsy. Also, by preselecting cortical parcellations, this study may not have detected areas of change in cortical morphology that could be identified by examining the entire cerebral cortex. Despite their limitations, the results of these two previous studies of surface-based cortical morphology in POE suggest that episodic, postictal psychosis is characterised by cortical thickening, primarily in nodes of the cognitive control network, while continuous, interictal psychosis is characterised by cortical thinning. This distinction is intuitively appealing because interictal psychosis is more akin to the psychosis seen in schizophrenia [39,40], in which cortical thinning in the cognitive control network and default mode network has been predominantly reported.

The aim of the present study was to: (1) further explore the cortical morphological profile of POE while addressing the limitations of past studies and; (2) specifically confirm whether postictal psychosis is characterised by cortical thickening and interictal psychosis by cortical thinning. We hypothesised that: (i) the POE group overall would display cortical abnormalities relative to EC, (ii) patients with postictal psychosis would display cortical thickening relative to EC, (iii) patients with interictal psychosis would display cortical thinning relative to EC, (iv) patients with postictal psychosis would display cortical thickening relative to patients with interictal psychosis, and (v) clusters of cortical change for all analyses would occur primarily in nodes of the cognitive control network and the default mode network.

2. Methods and materials

2.1. Subjects

The study was approved by the relevant Human Research Ethics Committees at The Royal Melbourne Hospital, Austin Health, and St Vincent's Hospital, Melbourne, Australia. Inclusion criteria for the POE group were: (i) presence of a psychotic disorder and (ii) diagnosis of epilepsy based on clinical features and scalp video-EEG recording of seizures. The specific relationship between the patient's epilepsy and psychotic disorder was established according to the proposed criteria of the International League Against Epilepsy Commission on Psychobiology of Epilepsy.[41] Interictal psychosis was defined as a psychotic episode temporally independent of seizures (ie, occurring beyond seven days). Postictal psychosis was defined as a psychotic episode occurring within seven days of a seizure (or cluster of seizures) after a lucid interval of no more than 48 h, and lasting no longer than two weeks [41]. Patients were excluded if they: (i) had psychogenic non-epileptic seizures; (ii) experienced psychotic symptoms as part of ictal semiology only; (iii) had medication (including anti-epileptic medication) or substance-induced psychoses; (iv) had an organic illness (in addition to epilepsy) with known psychiatric symptoms; or (v) if there was no T1-weighted MRI scan available. Details of subject selection, inclusion and exclusion criteria, and classification of seizures and psychoses are outlined in depth in a previous study [42]. In brief, file review was undertaken by expert neuropsychiatrists and epileptologists at the three sites based on the inclusion and exclusion criteria, identifying a total of 54 cases. MRI scans for all patients with epilepsy who developed psychotic symptoms and met diagnostic criteria for POE between January 1993 and September 2014 were extracted from hospital databases. Twelve POE patients were also prospectively recruited to the study between January 2015 and January 2017, and scanned at The Florey human MRI facility

(Austin Campus) bringing the total number of participants to 66. All scans were reviewed by J.A. for image quality, with 16 scans subsequently excluded on that basis. A further 18 POE scans were excluded due to prior surgical resection of brain tissue (precluding accurate measurement of cortical thickness across the whole brain), and 9 due to errors in the reconstruction of the white matter and pial surfaces which could not be manually corrected. The remaining 23 POE patients were compared to EC patients individually matched on the following variables: hospital site, MRI scanner, age (+/- 5 yrs), gender, lobe of epileptogenesis, laterality, and lesion status on MRI (positive or negative). A flow diagram of the recruitment, screening, exclusion, and matching process is presented in Fig. 1.

2.1.1. Demographic and epileptological variables

Demographic and epileptological characteristics of the sample are presented in Table 1. Chi-squared analyses were employed to examine differences between the groups on categorical variables and independent samples t-tests for continuous variables. There was a significant difference between the PIP and IP groups in lesion status, χ^2 (1, n = 23) = 7.07, p = 0.008 (Table 1). There were no other significant differences between the POE and EC groups, or between the postictal psychosis and interictal psychosis groups on the remaining demographic or epileptological variables (p >0.05 for all comparisons).

2.2. MRI analysis

2.2.1. Image acquisition

There were four participant groups scanned at different sites. T1-weighted sequences with a magnetic field strength of 1.5T or 3T were utilised to obtain images for all volumetric estimations. POE and EC scans were matched by scanner to control for scanner variance. For the Royal Melbourne Hospital cohort, all 6 scans (3 POE, 3 EC) were acquired on a 1.5T GE Signa scanner. For the St Vincent's cohort, 12 scans were acquired on a 1.5T Siemens Symphony scanner (6 POE, 6 EC), 2 scans were acquired on a 1.5T Siemens Magnetom Vision scanner (1 POE, 1 EC), 2 scans were acquired on a 1.5T Siemens Avanto scanner (1 POE, 1 EC), and 2 scans were acquired on a 3T Siemens Skyra scanner (1 POE, 1 EC). Finally, 22 scans (11 POE, 11 EC) were acquired at The Florey human MRI facility (Austin campus) on a 3T Siemens Trio scanner.

2.2.2. Image processing

The FreeSurfer software package version 6.0 (http://surfer.nmr.mgh.harvard.edu) was used for cortical reconstruction and volumetric

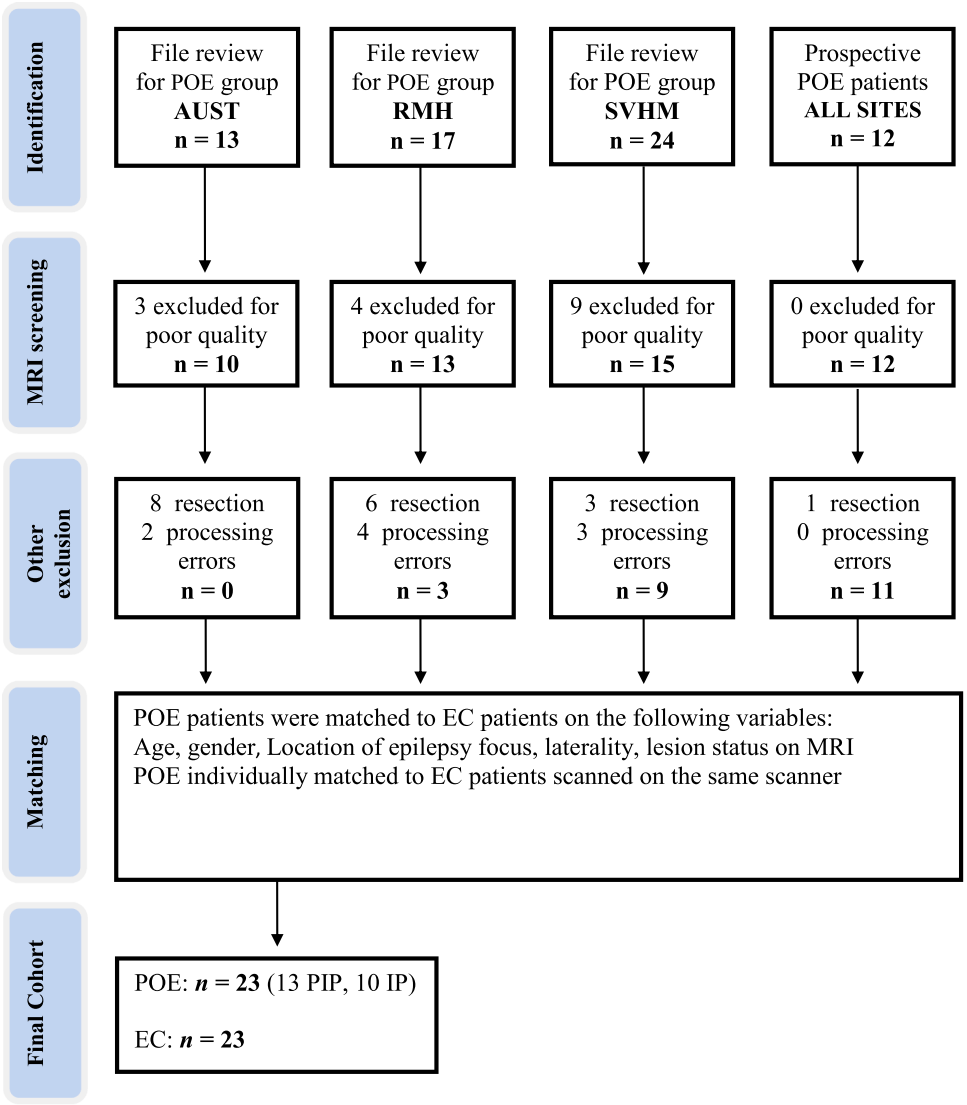

Fig. 1. Flow diagram depicting the recruitment, screening, exclusion, and matching process. POE = psychosis of epilepsy, EC = epilepsy patients without psychosis, PIP = postictal psychosis, IP = interictal psychosis, AUST = Austin Health, RMH = Royal Melbourne Hospital, SVHM = St Vincent's Hospital Melbourne.

Table 1
Demographic and epileptological characteristics of the groups.

Groups	POE (n = 23)			EC (n = 23)
POE Subgroups		**PIP (n = 13)**	**IP (n = 10)**	
Age in years (±SD)	40.91 (12.52) Range: 18–63	42.46 (11.11) Range: 26–62	38.90 (13.66) Range: 18–63	38.83 (12.52) Range: 19–65
Gender, male, n (%)	14 (60.9%)	9 (69.2%)	5 (50.0%)	14 (60.9%)
Epilepsy syndrome, n (%)				
Temporal	14 (60.9%)	8 (61.5%)	6 (60.0%)	15 (65.2%)
Extra-temporal	5 (21.7%)	3 (23.1%)	2 (20.0%)	4 (17.4%)
Generalised	3 (13.0%)	1 (7.7%)	2 (20.0%)	3 (13.0%)
Unclear	1 (4.3%)	1 (7.7%)	0 (0%)	1 (4.3%)
Side of epilepsy focus, n (%)				
Right	7 (30.4%)	4 (30.8%)	3 (30.0%)	8 (34.8%)
Left	8 (34.8%)	3 (23.1%)	5 (50.0%)	9 (39.1%)
Bilateral	4 (17.4%)	4 (30.8%)	0 (0.0%)	2 (8.7%)
GGE	3 (13.0%)	1 (7.7%)	2 (20.0%)	3 (13.0%)
Unclear	1 (4.3%)	1 (7.7%)	0 (0.0%)	1 (4.3%)
Age at seizure onset (±SD)	17.54 (14.39)[a]	22.33 (16.50)[c]	11.78 (9.11)	22.67 (6.36)[b]
Duration of illness	23.37 [a]	18.87 [c]	28.91	16.56 [b]
Lesion on MRI, n (%)				
Lesion positive	9 (39.1%)	2 (15.4%)	7 (70.0%)	7 (30.4%)
Lesion negative	14 (60.9%)	11 (84.6%)	3 (30.0%)	16 (69.6%)

Note, SD = standard deviation, POE = psychosis of epilepsy; EC = epilepsy control patients without psychosis; PIP = postictal psychosis; IP = interictal psychosis;.
[a] 1 missing case;.
[b] 13 missing cases;.
[c] 1 missing case.

segmentation. This process utilises image intensities and continuity information to reconstruct the pial surface and the boundary between grey and white matter. Briefly, processing includes motion correction and averaging [43], removal of non-brain tissue, automated Talairach transformation, segmentation of grey matter structures and subcortical white matter [44,45], intensity normalization, tessellation of the grey-white matter boundary, automated topology correction, [46,47] and surface deformation. Cortical thickness was calculated as the average of the shortest distance from each point on the white matter surface to the pial surface, and the shortest distance from each point on the pial surface to the white matter surface. A gaussian smoothing kernel (FWHM = 10 mm) was used to smooth the data. FreeSurfer morphometric procedures have good test-retest reliability between different scanner types and field strengths [48,49]. A validating study found no significant difference between FreeSurfer estimates and manual histologic measurements (P = 0.32) [50]. Author J.A inspected all surfaces for errors in the pial and white matter surface estimation whilst blind to group membership. Errors were manually corrected using standard procedures (as described in http:// surfer.nmr.mgh.harvard.edu/fswiki/Edits).

2.2.3. Statistical analysis

Analysis of group surface-based morphometry data was performed using the Qdec application within FreeSurfer. Data were visually inspected and checked for outliers. A general linear model was used to compare cortical thickness, area, and volume at each surface vertex between the POE and EC groups. The morphometric variable was the dependant variable, diagnosis (POE or EC) was the categorical predictor, and intracranial volume (ICV) was entered as a nuisance variable. The cortical surfaces of the left and right hemispheres were analysed separately. Monte Carlo null-z simulation was employed to determine significance of each cluster [51], and cluster threshold set at $p<0.05$ for each pairwise group comparison. The results of each analysis (volume, area, and thickness) were mapped to the partially inflated white matter surface for optimal visualisation.

3. Results

3.1. Cortical thickness, area, and volume in POE relative to controls

Compared to the EC group, the POE group overall displayed increased cortical thickness in two data-driven clusters in the right hemisphere. Cluster A included rostral anterior cingulate cortex, caudal anterior cingulate cortex, and posterior cingulate, and extended into the medial aspect of the superior frontal gyrus, the paracentral gyrus, and the precuneus posteriorly (p = 0.0001; Fig. 2). Cluster B included the rostral middle frontal gyrus and the superior frontal gyrus (p = 0.003; Fig. 2). There were no significant differences in cortical thickness in the left hemisphere, nor were there any significant differences in cortical area or volume in the right or left hemispheres.

3.2. Subgroup analyses

3.2.1. Cortical thickness, area, and volume in interictal psychosis relative to controls

The POE group was split into interictal psychosis and postictal psychosis subgroups for analysis. Compared to EC, the interictal psychosis subgroup displayed increased cortical thickness in the left hemisphere in two data-driven clusters. The first cluster (Cluster C) included the lateral occipital cortex posteriorly, and extended anteriorly along the lingual, fusiform, and inferior temporal gyri (p = 0.0001; Fig. 3). The second cluster (Cluster D) also included the lateral occipital cortex, and extended anteriorly into the superior parietal lobule, the cuneus, and the precuneus (p = 0.0007; Fig. 3). The interictal psychosis subgroup also displayed increased cortical thickness in the right hemisphere in a single cluster (Cluster E), which included the inferior and superior parietal lobules, and the precuneus (p = 0.003; Fig. 3). There were no significant differences between the interictal psychosis and EC groups in cortical area or volume ($p > 0.05$ for all comparisons).

3.2.2. Cortical thickness, area, and volume in postictal psychosis

There were no significant differences between the postictal psychosis and EC groups in cortical thickness, area, or volume ($p > 0.05$ for all comparisons). Similarly, there were no significant differences between the postictal psychosis and interictal psychosis groups in cortical thickness, area, or volume in the left or right hemispheres ($p > 0.05$ for all comparisons).

4. Discussion

This study utilised a well-validated, automated, data-driven methodology to examine whether POE was associated with changes in cortical thickness, area, and volume across the whole brain relative to a well-matched EC group, and whether there were differences in cortical morphology between the main POE subtypes (postictal psychosis and interictal psychosis) relative to EC. Key findings of this study are summarised in box 1. Thicker cortex was identified in POE patients compared to EC in the right rostral anterior cingulate cortex, right caudal anterior cingulate cortex, right superior frontal gyrus, and right rostral middle frontal gyrus (cognitive control network nodes), and right posterior cingulate, right precuneus (default mode network nodes), and right medial paracentral gyrus relative to EC. There were no differences in cortical thickness between the POE and EC groups in the left hemisphere, or in area or volume in either hemisphere. Patients with interictal psychosis demonstrated cortical thickening relative to EC that was not evident in postictal psychosis patients after correction for multiple comparisons. Specifically, the interictal psychosis group had thicker cortex in the right inferior parietal lobule (default mode network /

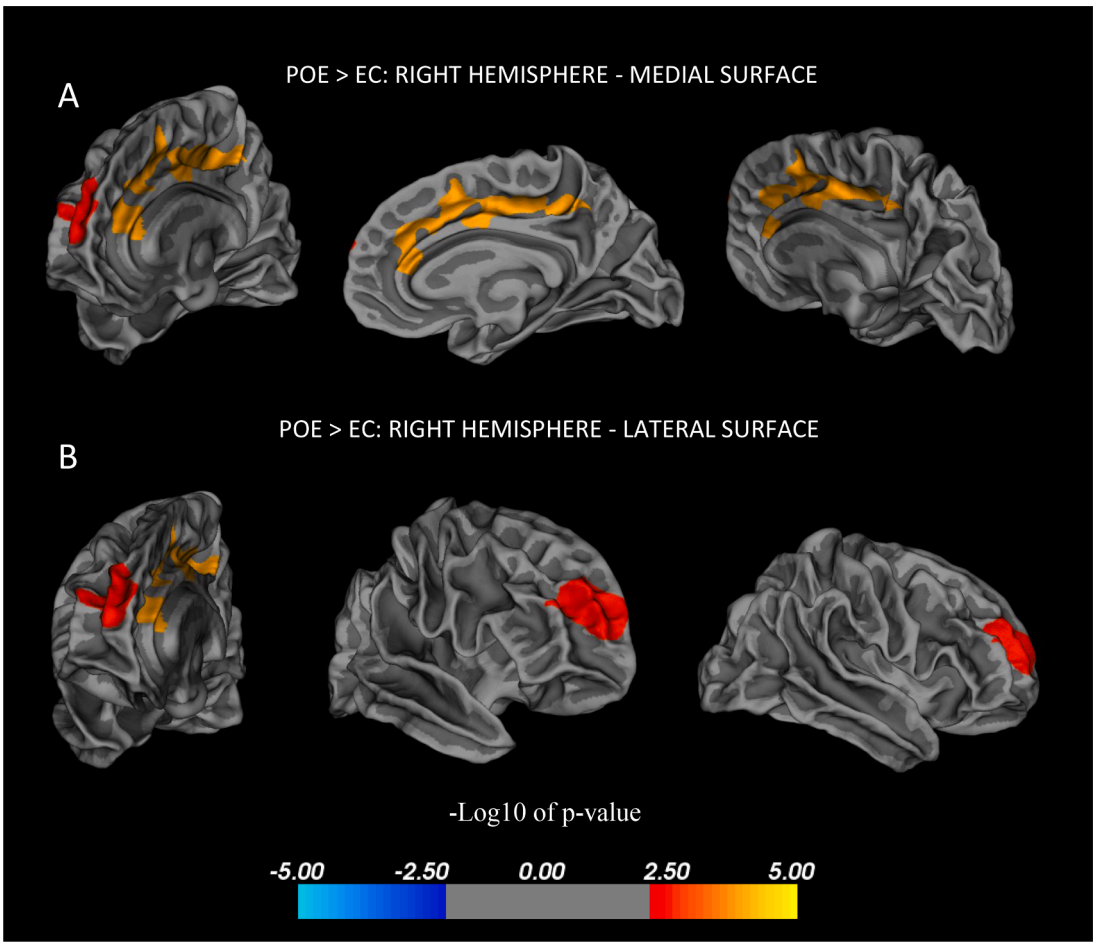

Fig. 2. Differences in cortical thickness between the POE and EC groups were found in the right hemisphere only. Light grey defines the crowns of the gyri and dark grey defines the sulci. The POE group had a thicker cortex (as indicated by yellow/red) in the right hemisphere in two clusters**. Cluster A** was thicker (yellow) in POE patients and included the rostral anterior cingulate cortex, caudal anterior cingulate cortex, posterior cingulate, medial superior frontal gyrus, medial paracentral gyrus, and precuneus. **Cluster B** was also thicker (red) in POE patients and included the rostral middle frontal gyrus and superior frontal gyrus.

cognitive control network), the precuneus (default mode network), right superior parietal lobule (cognitive control network), left lateral occipital cortex, lingual gyrus, fusiform gyrus, inferior temporal gyrus, superior parietal lobule (default mode network), cuneus (default mode network), and the precuneus (default mode network).

As there were no significant differences between groups in cortical area or volume, cortical thickness was the only relevant metric of cortical change in POE. Cortical thickness and cortical area are thought to be driven by distinct cellular mechanisms with unique genetic etiologies [35]. Future studies examining genetic influences on brain structure in POE should separately examine cortical thickness and area, as unique genetic influences would be obscured by the use of cortical volume, which conflates thickness and area. Isolating the distinct genetic factors that contribute to cortical abnormalities in POE may lead to a more accurate endophenotype, which could be utilised to identify epilepsy patients at risk of psychosis.

4.1. Cortical thickening in the default mode network and cognitive control network in POE

The regions of cortical thickening identified in the present study are highly similar to those reported by DuBois et al. [33] in their morphology study of postictal psychosis, i.e., the right lateral prefrontal cortex (cognitive control network), rostral anterior cingulate cortex (cognitive control network) and middle temporal gyrus. Cortical thickening was more widespread in our study, including caudal anterior cingulate cortex (cognitive control network), posterior cingulate (default mode network), and precuneus (default mode network). This may reflect increased power to detect changes due to our larger sample size, and the inclusion of interictal psychosis patients in the overall POE group. We did not confirm the cortical thinning found in the other morphology study [37]. However, that study excluded patients with extra-temporal seizure foci, and did not examine cortical morphology across the entire brain, which may partially explain these divergent results. Most of the regions identified in the present study are known cognitive control network and default mode network hubs, suggesting that cognitive control network and default mode network pathology is implicated in the pathogenesis of POE. In particular, our findings suggest that POE is underpinned by network level pathology rather than localised structural deficits [10] - an idea that is well-established in the schizophrenia literature [24,31,52,53]. An obvious extension of our work would be to examine whether these structural cortical changes are reflected in altered brain function within the default mode network and cognitive control network using functional MRI and neuropsychological measures of cognitive control, and default mode network functions such as verbal and visual memory, autobiographical recall, and prospective memory [26,54].

4.2. Potential mechanisms of cortical thickening in POE

Given that studies of surface based cortical morphometry in schizophrenia consistently report cortical thinning, it is striking that both

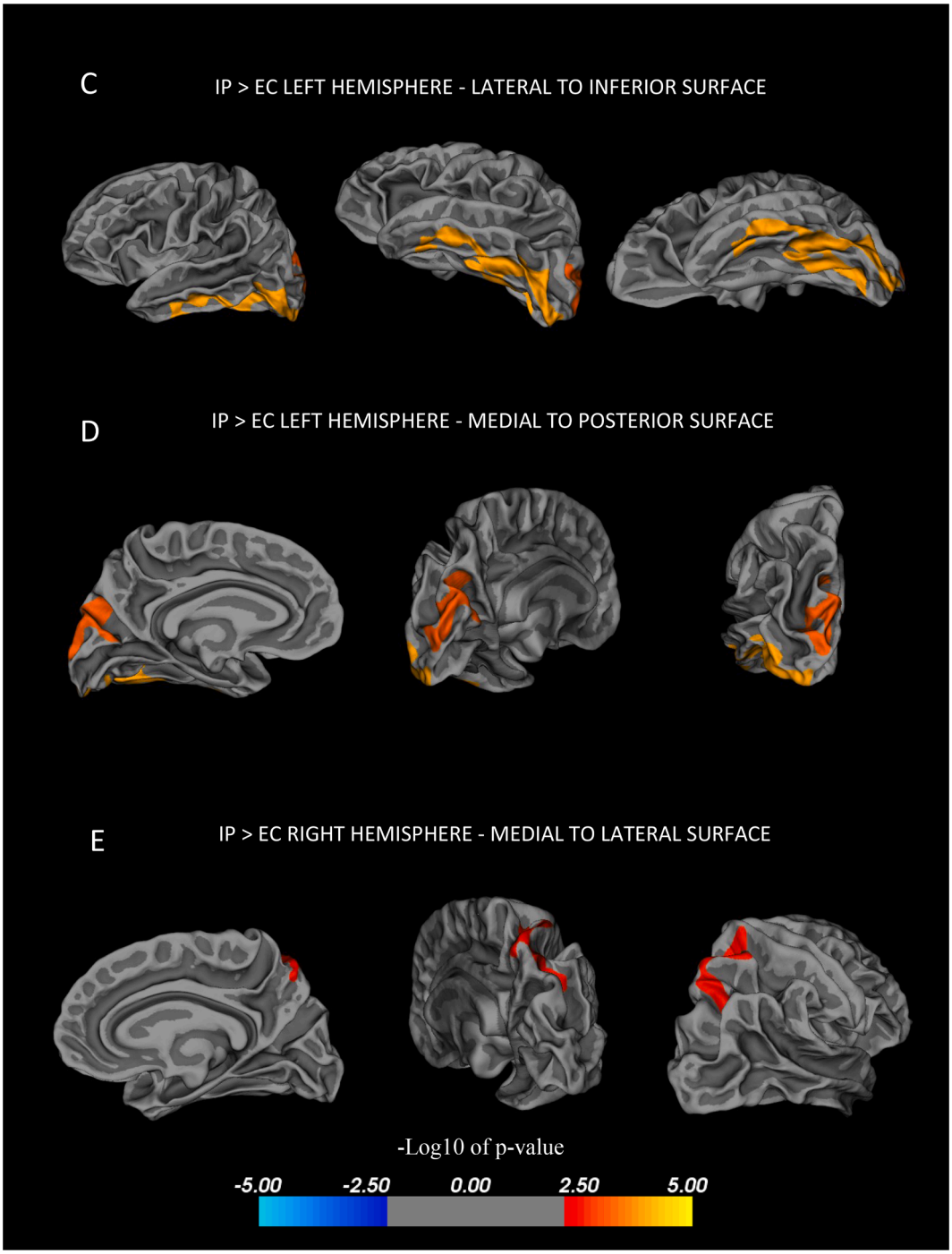

Fig. 3. Differences in cortical thickness between the interictal psychosis (IP) and EC groups. The interictal psychosis group had a thicker cortex (as indicated by yellow/red) in two clusters in the left hemisphere. **Cluster C** (top, yellow) included the lateral occipital cortex, the lingual gyrus, the fusiform gyrus, and inferior temporal gyrus. **Cluster D** (middle, orange) included the superior parietal lobule, the cuneus, and the precuneus. The interictal psychosis group also had a thicker cortex in the right hemisphere in a single cluster (**Cluster E)** which included the inferior and superior parietal lobules, and the precuneus (bottom, red).

studies of whole-brain surface based cortical morphology in POE to date have identified thickening, both in similar cortical regions, primarily in the right hemisphere. These findings suggest that grey matter abnormalities in POE and schizophrenia are driven by fundamentally different processes, although the ability to definitely make this conclusion was limited by a lack of a non-epilepsy psychosis/schizophrenia group. A number of candidate mechanisms for thickening of cortical grey matter have been suggested including swelling, inflammation, and focal cortical dysplasia [33]. An alternative possibility is that cortical thickening reflects incomplete synaptic pruning, leading to deviations in normal brain development. Grey matter development follows a non-linear process, beginning with a pre-pubertal increase followed by post-pubertal grey matter loss [55,56]. In the healthy brain, reduction in cortical grey matter begins primarily in dorsal parietal and frontal regions [57], accelerating in frontal and striatal regions post-adolescence [55]. Cortical thickening in POE may thus reflect pathological processes (e.g. seizures and their secondary effects) interrupting synaptic pruning [58], leading to abnormally thickened cortex. This is supported by the relatively younger mean age of epilepsy onset in the POE group (17.5 years), relative to the EC group (22.7 years), and in the interictal

Box 1
Key findings of this study

Key findings

· POE is characterised by cortical thickening relative to EC
· Thickening occurs primarily in nodes of the CCN and DMN
· Interictal psychosis is characterised by cortical thickening in left occipital and temporal regions relative to EC
· This was also evident to a lesser extent in postictal psychosis
· A novel mechanism for cortical thickening in POE is proposed whereby normal synaptic pruning processes are interrupted by seizure onset.

EC, epilepsy controls; CCN, cognitive control network; DMN, default mode network; POE, psychosis of epilepsy

psychosis group (11.8 years) relative to the postictal psychosis group (22.3 years), perhaps suggesting that seizure onset during the adolescent period interrupts synaptic pruning, leading to abnormally thickened (unpruned) cortex. While this hypothesis cannot be directly explored in the present study, it could be investigated in future longitudinal neuroimaging studies of POE.

4.3. Cortical thickening in lateral temporal and occipitotemporal regions in interictal psychosis

Patients with interictal psychosis had thicker cortex in regions heavily implicated in visual processing. For example, the lingual gyrus supports object colour processing [59] and the encoding and retrieval of visual memories [60], while the fusiform gyrus is involved in face perception [61]. The inferior temporal gyrus is a key node in the ventral visual pathway, performing higher level processing on visual information projected from primary visual cortex to allow identification of perceptual objects [62], while the inferior parietal lobule, which was also thicker in interictal psychosis, is a key node in the dorsal visual pathway. It receives information from striate cortex and facilitates motor action towards objects recognised via the ventral pathway [63]. Areas of thicker cortex identified in both the ventral and dorsal visual pathways in interictal psychosis may be implicated in visual hallucinations in patients with interictal psychosis, a possibility which could be investigated in future studies incorporating measures of the quality and frequency of hallucinations in interictal psychosis. The interictal psychosis group also displayed cortical thickening in the right cuneus and precuneus (default mode network nodes). However, these regions were also thicker in the POE group overall and thus less likely to be specific to interictal psychosis.

The finding of no significant difference between postictal psychosis and EC, or between postictal psychosis and interictal psychosis groups is likely due to the small sample of postictal psychosis patients once the POE group was subdivided. This is supported by the finding that when less stringent statistical criteria were employed, the postictal psychosis group displayed a similar pattern of cortical thickening to that seen in the interictal psychosis group, but without thickening in lateral and occipital regions (see supplementary material for uncorrected results). This suggests that cortical thickening in postictal psychosis follows a similar, but less severe pattern of cortical changes to than that seen in interictal psychosis. Furthermore, prior to correction for multiple comparisons the postictal psychosis group displayed *unthickened* cortex relative to interictal psychosis in areas identified as thicker in the interictal psychosis group relative to EC (lateral occipital cortex, fusiform gyrus, and inferior temporal cortex). Although these uncorrected results must be interpreted with caution, they provide tentative support for the hypothesis that postictal psychosis and interictal psychosis may be differentiated by the degree of cortical thickening in the lateral temporal and occipital neocortex.

4.4. Limitations

The primary limitation of the paper is the small size of the subgroups (postictal psychosis = 13 and interictal psychosis = 10), meaning that the possibility of Type 1 or Type 2 errors cannot be excluded. Nonetheless, tests were corrected for multiple comparisons, minimising the probability of false discoveries. A further limitation of this study is that, due to limited access to the records of some participants, we were unable to retrieve information regarding seizure frequency and treatment with antiepileptic and neuroleptic medication. Nonetheless, treatment with antipsychotic medication is overwhelmingly associated with cortical grey matter reduction in schizophrenia [64–66]. As such, antipsychotic medication treatment is unlikely to underpin cortical thickening in POE. Antiepileptic drug use has been associated with cortical thinning [67] or have no effect on cortical morphology [68]. Therefore it is unlikely that antiepileptic use underpins the cortical thickening seen in POE. Differences between MRI procedures between sites may have been a source of error especially given the small sample size, however POE and EC scans were matched by scanner in order to control for scanner variance. Finally, the lack of a non-epilepsy psychosis group limits the ability to determine whether the morphological brain changes identified are specific for POE.

5. Conclusion

In conclusion, this study identified cortical thickening in psychosis of epilepsy, primarily in nodes of the cognitive control network and default mode network, compared to control patients with epilepsy without a history of psychosis. Patients with interictal psychosis also displayed cortical thickening in occipital and temporal regions relative to epilepsy controls, which may be related to visual hallucinations in interictal psychosis. The results of this study suggest that the transition from postictal psychosis to interictal psychosis may reflect the spread of cortical pathology from frontal and parietal regions to temporal and occipital neocortex. Longitudinal work with larger numbers is warranted to investigate this possibility, and to further elucidate the basis of changes in surface-based cortical morphology in people with psychosis of epilepsy.

Disclosure

None of the authors have any conflict of interest to disclose.

Funding

J.A was supported by an Australian Postgraduate Award.

Conflicts of interest

None of the authors have any conflict of interest to disclose.

Acknowledgments

The authors acknowledge the facilities and scientific and technical assistance of the National Imaging Facility, a National Collaborative Research Infrastructure Strategy (NCRIS) capability, and support from the Victorian Government Operational Infrastructure Support Program at The Florey Institute of Neuroscience and Mental Health. We extend our gratitude to the patients of the Comprehensive Epilepsy Programmes at Austin Health, the Royal Melbourne Hospital, and St Vincent's Hospital Melbourne for their time and participation in this research. We also thank the staff of the Programmes for their ongoing support.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.seizure.2022.09.006.

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