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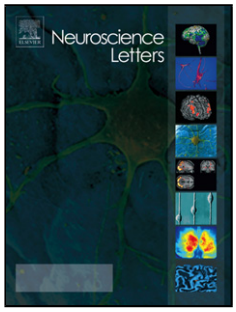

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Title

Cortical thickness and gyrification patterns in patients with psychogenic non-epileptic seizures

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Highlights

- Our findings partly corroborate but also differ from two previously published brain morphometry studies in PNES.
- These findings point to a highly heterogeneous biopsychosocial disorder in terms of phenomenology, outcome and presumably aetiology.
- The results of this study contradict highly reductionist views and dualistic approaches to our understanding of PNES.

Abstract

Psychogenic non-epileptic seizures (PNES) are often viewed as manifestations of altered motor and sensory function resulting from psychological responses to adverse experiences. Yet many patients and non-expert healthcare professionals find it difficult to understand how severe disturbances in normal neurological functioning can solely result from underlying psychological mechanisms to the exclusion of other physical causes. Perhaps importantly, recent advances using neuroimaging techniques point to possible structural and functional correlates in PNES. In an attempt to further our understanding of the neurobiological correlates of this condition, we compared the brain scans of 20 patients with PNES (14 females, mean age 41.05, range 19 – 62) and 20 age- and gender-matched healthy controls (14 females, mean age 40.65, range 21 - 61) to investigate group differences for cortical thickness and gyrification patterns using FreeSurfer. Compared to controls, patients with PNES showed cortical thickness increases in motor, sensory and occipital areas as well as cortical thickness decreases in temporal and frontal brain regions. In addition, we observed age-related changes in cortical thickness in the right lateral occipital area in PNES. However, contrary to our prediction that atypical gyrification may be present, we did not find any evidence of abnormalities on a measure thought to reflect prenatal and early childhood cortical development and organization. Nor did we find significant correlations between cortical thickness results and clinical features. These findings partly corroborate, but also differ from previous morphometric studies in PNES. These inconsistencies likely reflect the aetiology and phenomenological heterogeneity of PNES.

Keywords

Cortical thickness; FreeSurfer; Local gyrification index; Psychogenic non-epileptic seizures; Structural magnetic resonance imaging

1. Introduction

Psychogenic non-epileptic seizures (PNES) are characterized by seizures which superficially resemble epileptic seizures but in which seizure-like episodes are thought to result from underlying psychological mechanisms rather than being caused by epileptic discharges in the brain [1]. In the absence of a clear and easily discernible "organic" cause, current medical nosologies class PNES as a conversion/somatoform [2] or dissociative disorder [3]. In light of this, explanations of this diagnosis have largely been rooted in psychoanalytic or psychological accounts [4], often characterizing these disorders as medically unexplained [5]. While the latter categorization is a diagnosis of convenience based on a highly reductionist view of what is considered medically explained, the former accounts reflect a contested, dualistic approach to the understanding of functional neurological disorders like PNES [6]. However, there is now a growing body of evidence from structural and functional studies in PNES which suggests that PNES is best understood as a biopsychosocial disorder, a disorder in which structural and persistent or recurrent functional changes in the brain may act as predisposing or precipitating factors for PNES [7,8].

The present study was intended to add to this evidence by employing whole-brain cortical surface morphometric analyses of T1-weighted structural magnetic resonance imaging (sMRI) brain scans of individuals with PNES and age- and gender-matched healthy controls. First we examined whether age-related changes in cortical thickness (controlling for gender) would differ between patients with PNES and controls. This is important because age-related changes in cortical thickness are well documented [9], and disparity between groups in this regard would have significant implications for how subsequent group comparisons of cortical thickness are conducted. Secondly, the present study examined

whether group differences in cortical thickness (controlling for age and gender) would differ between PNES patients and controls. Based on the two published morphometric studies in patients with PNES [10,11], it was predicted that we would see group differences in motor, frontal and occipital regions in addition to brain regions involved in emotion processing.

In addition to cortical thickness measures, we utilized a local gyrification index (lGI) measure based on that of Schaer et al. [12]. Because the degree of gyrification (gyral and sulcal formations) is largely determined early in life (primarily during the third trimester with additional changes during early childhood) and remains relatively stable from adolescence to adulthood [13], this sensitive measure is thought to be particularly useful for investigating aberrant early neurodevelopmental changes, traces of which may be identifiable at any age [12]. While a later age at onset is more common, PNES manifestations have also been observed during early childhood [14], and given the link between trauma and PNES [15] and atypical gyrification patterns previously described in children exposed to maltreatment [16] and in individuals with panic disorder [17], it was predicted that individuals with PNES compared to controls may show atypical levels of gyrification. Finally, we conducted correlational analyses to explore the relationship between cortical thickness and PNES clinical features in cortical regions that showed increases or decreases in cortical thickness in PNES patients compared to controls.

2. Methods

2.1. Participants

Fifty-three 3T T1-weighted MRI brain scans of patients with PNES acquired between 2009 and 2016 were retrieved retrospectively from the Radiology Department, Royal Hallamshire Hospital, United Kingdom. Inclusion of MRI brain scans was based upon (a) confirmed PNES clinical diagnosis by a Consultant Neurologist at the Royal Hallamshire

Hospital (b) video-EEG recordings of typical attacks with semiological features of non-epileptic attacks and no associated electro-encephalographic (EEG) or electrocardiographic (ECG) changes suggestive of epilepsy (c) minimum age of 16 at the time of the scan. MRI brain scans were excluded if the patient was (a) likely to have had a mixed seizure disorder (epilepsy and PNES) or (b) had an MRI brain scan showing clinically significant abnormalities. From this initial PNES sample, twelve scans were excluded due to possible or definite co-existing epilepsy. Eight scans were excluded due to lack of video-EEG recordings showing habitual seizure-like episodes. Based upon visual inspection of the MRI scans, three scans were excluded due to MRI results showing clinically significant brain abnormalities (two for hippocampal reductions suggestive of mesial temporal sclerosis, and one 76 year old with T2 hyperintensities which may have reflected a mini stroke), four scans were excluded due to blurring of the image, and six scans were excluded due to portions of the brain not being captured in the field of view. No cases were excluded due to age. In addition, fifty-six 3T T1-weighted MRI brain scans of age- and gender-matched healthy controls were retrieved retrospectively from an existing database of individuals who had previously volunteered for brain imaging studies (Radiology Department, Royal Hallamshire Hospital). In total, twenty patients with a "gold standard" PNES diagnosis and twenty age- and gender-matched healthy controls were included in the analyses. All of the patients with PNES were right-handed. Age- and gender-matched healthy controls were free from neurological disease or psychiatric disorders. The retrospective retrieval of archival data was conducted in accordance with the guidelines set out by the NHS ethical approval granted by the South West – Exeter Research ethics committee and carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

2.2. PNES clinical features

Semiology features were categorized as 1) generalized motor seizures: seizures mainly characterized by tonic, clonic, or dystonic-like generalized movements, 2) akinetic seizures: seizures mainly characterized by unresponsiveness and the absence of movement with the exception of minor limb tremors, 3) seizures with subjective symptoms: seizures were mainly characterized by experiential phenomena reported by the patients during video-EEG recordings, and 4) focal motor seizures: seizures with focal motor movements [18]. Symptom severity was assessed using a symptom severity scale, in which symptom severity was based upon the summation of previously described clinical features relevant to PNES: 1) ictal loss of consciousness 2) ictal incontinence 3) ictal tongue-biting 4) ictal injury 5) accident and emergency attendance for seizures 6) seizure episodes more than thirty minutes in duration 7) the continuation of symptoms without periods of remission up to the time of the MRI brain scan [19]. Age at onset, symptom duration, number of anti-epileptic and anti-depressant drugs taken at time of MRI, clinical psychiatric diagnosis and reports of trauma exposure were extracted retrospectively from patients' medical records. Types of trauma exposure were documented as 1) sexual abuse 2) physical abuse 3) psychological abuse 4) loss of child 5) other noted but unspecified traumatic experience 6) suicide attempt.

2.3 Image acquisition and FreeSurfer analyses

All brain MRI T1-weighted volumetric scans were acquired using the same Phillips 3 Tesla scanner at The Royal Hallamshire Hospital, Sheffield, U.K. For all participants, brain MRI was performed using matrix size 256 x 256, field of view 256, slice thickness 1mm, voxel size 1x1x1, flip angle 8º, coronal plane. Due to the retrospective nature of this study, it was not possible to limit the MRI pulse sequence parameters used to exactly the same timings across all of the subjects. Slight differences in echo time (TE) and repetition time (TR) were

present in our PNES group (TE 3.75 – 4.86 ms, TR 8.16 – 10.42 ms) compared to controls (TE 4.80 ms and TR 10.50 ms). However, it is important to note that cortical thickness measurements remain relatively robust even when different MRI protocols or scanners are used [20].

MRI-based measurements for each participant were obtained using FreeSurfer version 5.30 (http:// www.surfer.nmr.mgh.harvard.edu). In brief, Freesurfer consists of two processing streams, a surface-based stream and a volume-based stream. The surface-based stream constructs models of the white matter/gray matter boundary and the boundary between the gray matter and cerebralspinal fluid (pial surface) from which cortical thickness measures are taken as the shortest distance between the two. The volume-based stream preprocesses MRI volumes and labels subcortical tissue classes allowing for the representation and measurement of subcortical structures (putamen, hippocampus, amygdala, ventricles etc.). Both cortical and subcortical labelling is based on a subject-independent atlas and the subject-specific values. These labels are then morphed onto a common space (average subject) to achieve a common point of reference for each subject. This coordinate system can be subsequently used to examine group differences by creating group maps. A full description of this procedure has been published elsewhere [20,21].

Following surface reconstruction and segmentation, the resulting output was visually inspected for quality and accuracy. If needed, edits were made to adjust for skull strip errors, intensity normalization failures (requiring addition of white matter control points), incorrect white matter segmentation, automated topological fixer errors, and pial surface inaccuracies. In the PNES group one skull strip error was adjusted. Edits to the pial surface were required in seven scans, topological defects (holes or handles) adjusted in eleven scans, and control points added in nine scans (263 in total). In the healthy control group, no skull strip errors occurred, edits to the pial surface were made in twelve scans, topological defects adjusted in

thirteen scans, and control points added in eleven scans (277 in total). The recon-all processing stream was re-run from the appropriate stage to recreate the final surfaces in brains which required corrections to the initial segmentation. To achieve a common point of reference for each subject the recon-all –qcache flag was used to smooth and resample the data onto the FreeSurfer fsaverage (average subject made in MNI305 space). Prior to general linear model analyses (GLM), cortical thickness maps were smoothed with a 10-mm full-width at half-maximum (FWHM) Gaussian Kernel. No additional smoothing was applied in relation to *l*GI. This is because the final FWHM is a composite of the applied FWHM and the smoothness inherent in the data and *l*GI has a lot of inherent smoothness. In effect, this resulted in the degree of smoothness in our *l*GI data corresponding to a smoothing kernel of 10-mm. Analysis was run on the University of Sheffield high performance computing cluster (Iceberg; OS 64-bit Scientific Linux (Redhat); 2 X Intel Ivy bridge E5 2650V2 8-core processors based nodes).

GLM analyses to assess group differences in age-cortical thickness interactions and *l*GI-age interactions was run by implementing the mri_glmfit script, with DODS (different offset, different slope) as design matrix, diagnosis and gender as discrete factors, and age as covariate. DODS assumes a different offset but predicts a different effect of ageing in both groups (different slope). To examine group differences in cortical thickness and *l*GI (controlling for age), mri_glmfit was used with DOSS (different offset, same slope) as design matrix, diagnosis and gender as discrete factors, and age as nuisance factor. DOSS also allows for group differences to start at different points (different offset) but constrains the group data to change in a similar way, that is, a similar impact of ageing in both groups (same slope). DODS/DOSS are specific to FreeSurfer (for a detailed description see https://surfer.nmr.mgh.harvard.edu/fswiki/DodsDoss).

All of the vertex-wise group analyses were corrected for multiple comparisons using mri_glmfit-sim in FreeSurfer, with a cluster forming threshold of 3 ($p < 0.001$) and cluster-wise probability set to $p < 0.05$. P values were adjusted for both hemispheres using --s 2spaces flag in order to correct for the full search space. This was repeated for 10,000 iterations to derive the location of cluster sizes under the null hypothesis. Clusters surviving cluster-wise correction were then superimposed on fsaverage inflated surfaces using tksurfer, a GUI application available in FreeSurfer.

2.4 Correlation analyses with clinical features

We conducted correlational analyses to investigate the relationship between brain regions that showed increases or decreases in cortical thickness in patients with PNES compared to controls with clinical features in patients with PNES (age at onset; duration of symptoms; symptom severity; number of antiepileptic drugs taken). Regions of interest (ROIs) based on significant cluster-wise corrected cortical thickness results were manually drawn on the fsaverage inflated surfaces in tksurfer and subsequently mapped back to each hemisphere for each subject using the mri_label2label command. The average cortical thickness for each cluster for each subject was then extracted using the mris_anatomical_stats command. Correlations were conducted using a bivariate nonparametric correlation procedure (Spearman's coefficient) with an alpha of 0.05 and subsequently corrected for multiple comparisons using Bonferroni correction. Kolmogorov-Smirnov and Shapiro-Wilk were used to test for normality. All statistical analyses were two-tailed and conducted using the Statistical Package for Social Sciences (IBM SPSS Statistics for Macintosh, Version 24. Armonk, NY: IBM Corp.).

3. Results

3.1 Demographics

In total twenty patients with PNES (14 females, mean age at time of scan 41.05, standard deviation, SD 12.50, age range 19 - 62) and twenty age- and gender-matched healthy controls (14 females, mean age at time of scan 40.65, SD 12.40, age range 21 - 61) were included. The mean age at onset of PNES was 27.80 (SD 11.84, range 9 - 51) with a mean duration of symptoms in years prior to MRI of 10.18 (SD 13.73, range 0.25 – 50). Nine patients were taking anti-depressants (Supplementary Table 1) and one patient was taking antipsychotic medication (Quetiapine). Telemetry data capturing typical attacks was available for all twenty PNES patients. The mean number of PNES habitual attacks recorded was 2.5 (range 1 – 8, Supplementary Table 1). Based on the video-EEG recordings, 45% of patients (n = 9) were characterized as having predominantly generalized motor seizures/positive motor phenomena, 35% of patients as having predominantly akinetic seizures characterized mainly by blank spells with reduced responsiveness (n = 7), and 20% were characterized as having predominantly seizures with subjective symptoms only but not loss of awareness (n = 4). None were characterized as having focal motor seizures. In all patients, brain MRI was visually inspected by an experienced neuroradiologist for signs of pathological brain abnormalities or brain injury. Three patients showed some abnormality. However, these abnormalities were not deemed clinically significant to the extent that these changes could explain their symptoms. Given that they affected the white matter and cerebellum they are unlikely to have affected our cortical thickness analyses. The same morphological analyses were run with these three missing in addition to their matched healthy controls. Exclusion or inclusion of these patients resulted in the same clusters and their order for both the left and right hemisphere. All other patients had unremarkable brain MRI results. PNES group characteristics are presented in Table 1. The results of PNES symptom severity scale are presented in Table 2.

3.2 Morphological analyses

Age-related changes in cortical thickness were first examined after we had controlled for gender. This analysis identified a single significant cluster surviving cluster-wise correction in the right lateral occipital area, where patients with non-epileptic seizures showed greater decreases in cortical thickness with increasing age compared to controls (Figure 1A & B, Table 3). Group differences in cortical thickness, controlling for age and gender, were examined next (Figure 1C, Table 3). Cluster-wise corrected results showed bilateral structural changes in PNES patients compared to controls, with cortical thickness increases in the cuneus bilaterally, the left paracentral, and left lingual regions. Decreases in cortical thickness were observed in PNES patients compared to controls in the inferior frontal gyrus (pars opercularis) bilaterally, right superior temporal region, and the right medial orbitfrontal cortex. Analysis of gyrification patterns revealed no significant group differences surviving cluster-wise correction for age-related *l*GI while controlling for gender or *l*GI group comparisons controlling for gender and age. Due to the number of PNES patients who had reported trauma exposure (Table 1), additional cortical thickness sub-analyses was conducted in the PNES group only (N = 20). The exact same statistical analyses (described above) was conducted for age-cortical thickness interactions (controlling for gender) and cortical thickness controlling for age and gender. The results of these analyses were non-significant.

---------Insert Figure 1 here----------

3.3 Clinical features

Symptom severity positively correlated with cortical thickness in both the left cuneus ($r_s = 0.497$, $p = 0.02$) and right cuneus ($r_s = 0.451$, $p = 0.04$). However, these correlations were not significant following Bonferroni correction for multiple comparisons. No other uncorrected significant correlations were found between cortical thickness results and age at onset, duration of symptoms, or number of antiepileptic drugs taken (Supplementary Table 2). Due to the small number of patients comprising each PNES subtype, it was not feasible to conduct additional analyses based on semiology.

4. Discussion

The first finding of this study concerns age-related changes in cortical thickness. We observed cortical thickness differences between groups in the right lateral occipital area where, compared to controls, patients with PNES showed greater cortical thickness decreases with increasing age. This is in keeping with a previous cortical thickness study which found that, compared to healthy controls, PNES patients showed decreased cortical thickness in this area of the brain [11].

In the second group-level analysis controlling for age and gender, we found that patients with PNES showed decreased cortical thickness compared to controls in the right superior temporal gyrus associated with multisensory integration [22] and the right medial orbitofrontal cortex associated with emotion processing [23], although the direction of the differences with regard to the right medial orbitofrontal cortex was the opposite of the findings in a previous study [11]. However, PNES is highly heterogeneous and therefore, it is possible that this heterogeneity may be the reason for consistent or inconsistent findings across studies that use similar methodological approaches. Additionally, the lack of well

defined and established categorical or dimensional characterizations of specific sub-types of PNES makes it difficult to interpret differing results across studies. We also observed decreased cortical thickness in regions associated with response inhibition [24,25], namely the left and right pars opercularis. Interestingly, Labate et al. [10] found that cortical thickness in the left pars opercularis in PNES patients' negatively correlated with dissociation scores, suggesting that higher dissociation scores were associated with decreases in cortical thickness in this region of the brain. However, it is difficult to make an equivalent inference between dissociation and our results, as we were unable to directly measure the tendency to dissociate in our study.

Increased cortical thickness in PNES patients compared to controls was observed in the left paracentral lobule, with the significant cluster spanning both the primary motor cortex and primary somatosensory cortex. The paracentral lobule has been associated with, amongst other things, the planning, control and execution of motor function [26]. However, this finding differs in terms of both direction and laterality to the findings of Labate et al. [10], who observed cortical thickness decreases in the right paracentral lobule in patients with PNES. Again, differences in group characteristic and PNES heterogeneity may be a plausible explanation for these inconsistencies. Yet, the role of cortical thickness changes in brain regions involved in motor function is of significant interest in PNES [10,11]. Cortical thickness increases in PNES were also observed in occipital regions involved in visual processing [27,28], namely the cuneus bilaterally and the left lingual gyrus. A recent imaging study [29] found that increased long-range functional connectivity density of occipital regions (right calcarine fissure and bilateral lingual gyri) correlated with disease duration in patients with PNES. The authors proposed that changes in functional connectivity in this region may reflect long-term hypervigilance and increased sensitivity to external stimuli. While the present study does provide some support for their findings, we did not find a

significant correlation between cortical thickness results in occipital regions and duration of PNES.

Furthermore, no significant correlations surviving correction for multiple comparisons were found between clinical features in PNES and cortical thickness results, nor did we find cortical thickness differences between patients who had reported traumatic experiences and those who had not. However, the lack of significant correlations is not altogether surprising. A number of previous neuroimaging studies have failed to find any significant relationship between imaging results and clinical features in this disorder, and those that did reported inconsistent findings [8]. Perhaps more importantly, clinical features derived from medical records or indeed self-report measures may not be that reliable, especially if they are applied cross-sectionally in small studies. We must also consider the possibility that changes in cortical thickness may reflect other factors not accounted for in the present study [30,31], especially comorbidities often associated with PNES such as anxiety, depression, posttraumatic stress or personality disorders [32]. Disorders such as these could play an aetiological role in PNES on the one hand and be related to changes in cortical thickness on the other. Therefore, it is not clear whether cortical thickness changes associated with PNES in our study are indeed responsible for PNES or whether changes in cortical thickness reflect other factors not necessarily associated with this disorder. This is a critical consideration which has not been sufficiently addressed by our study, nor indeed most other studies which implicate structural and/or functional brain changes in PNES [8]. This is due to the high levels of co-existing psychiatric disorders, small sample sizes and lack of psychiatric controls free of PNES. However, the high level of psychiatric comorbidity observed in our patient group is in keeping with that observed in most other studies of this disorder and suggests that we have studied a typical patient sample [32].

In addition to looking at cortical thickness, we also conducted a group analysis of gyrification patterns using *l*GI. However, contrary to our prediction that gyrification may differentiate PNES patients from controls, the results suggest that atypical gyrification patterns may not be a contributor to PNES, at least in our sample. Whereas our study therefore provides some support for the idea that PNES may represent an adaptive (or maladaptive) process reflected by plastic structural brain changes in frontal, sensorimotor, temporal and occipital brain regions, we did not find any evidence of abnormalities on a measure thought to reflect prenatal and early childhood cortical development and organization [13]. This finding may be surprising. A range of observations provide indirect evidence for the relevance of neglect and trauma in early life to the development of PNES [33-36]. Additionally, atypical gyrification patterns have been observed in major depressive disorder, bipolar disorder, and schizophrenia [37]. Animal studies provide evidence of life-long structural changes in the brain, neuro-endocrine and behavioural abnormalities after neglect / trauma in early life, which could underpin these findings in humans [38,39]. It is possible that the neglect or trauma which may be relevant to PNES affects individuals after the developmental phase in which gyrification patterns are determined. In addition, neglect or trauma in early life are not considered an obligatory precondition to the subsequent development of PNES, but only an important risk factor [6]. Alternatively, our sample may have been too small or too heterogeneous to pick up relevant structural abnormalities of early brain development.

In conclusion, our findings of cortical thickness differences between patients with PNES and healthy controls partly corroborate, but also differ from, morphometry-based MRI findings in PNES previously described [10,11]. Possible reasons for these variable findings may include sample size, anatomical variation, and likely differences in group characteristics in terms of genetic makeup, medical history, life experiences, semiology, duration of the

disorder, personality characteristics, and co-existing psychopathology. Nonetheless, the key take home message is that these findings support the growing body of evidence suggesting that PNES, rather than being a condition that is medically unexplained, may indeed have physical substrates in the brain. The results of the current study and previous neuroimaging studies of PNES have important implications for the way we think about and treat individuals with PNES and how diagnosis may be better communicated to patients. However, longitudinal morphometric studies prospectively capturing a wide range of demographic, developmental and clinical data are needed to better address the role of ageing and whether changes in cortical thickness represent a predisposition to, or consequence of PNES. Furthermore, PNES are paroxysmal events, which are difficult to investigate through the use of sMRI data alone. As such, interictal data provides only part of the picture and future studies should attempt to map electroencephalography (EEG) ictal data acquired during non-epileptic events to the underlying structure, connectivity and folding patterns of the cerebral cortex. This may shed more light on the pathophysiological mechanisms of PNES. Future studies also need to be large enough and involve relevant control groups to allow a better distinction between the likely associations of PNES itself and of concurrent psychopathology and or trauma exposure. The interpretation of such datasets would be greatly aided by a better categorical or dimensional characterization of PNES, a highly heterogeneous disorder in terms of phenomenology, outcome, and presumably aetiology.

Conflicts of Interest

All authors declare no conflict of interest.

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Figure caption (black and white version for print)

Figure 1. Whole-brain group-level analysis of cortical thickness differences between PNES patients and age- and gender-matched healthy controls. Results depict significant clusters surviving cluster forming threshold of $p<0.001$ and cluster-wise correction for multiple comparisons at alpha 0.05. Cortical thickness maps were smoothed using a 10mm full-width at half-maximum (FWHM) Gaussian kernel. A = anterior, P = posterior. **(A**) Group differences in age-cortical thickness interactions controlling for gender. (**B)** Scatter plot showing age-related changes in average cortical thickness in mm in PNES (triangle) and in age- and gender-matched healthy controls (HC, circle) for the right lateral occipital cluster. (**C)** Group differences in cortical thickness controlling for age and gender.

Figure caption (colour version for online)

Figure 1. Whole-brain group-level analysis of cortical thickness differences between PNES patients and age- and gender-matched healthy controls. Results depict significant clusters surviving cluster forming threshold of $p<0.001$ and cluster-wise correction for multiple comparisons at alpha 0.05. Cortical thickness maps were smoothed using a 10mm full-width at half-maximum (FWHM) Gaussian kernel. Blue and pale blue indicate decreases in cortical thickness. Orange and red indicate increases in cortical thickness. A = anterior, P = posterior. **(A**) Group differences in age-cortical thickness interactions controlling for gender. (**B)** Scatter plot showing age-related changes in average cortical thickness in mm in PNES (blue triangle) and in age- and gender-matched healthy controls (HC, red circle) for the right lateral occipital cluster. (**C)** Group differences in cortical thickness controlling for age and gender.

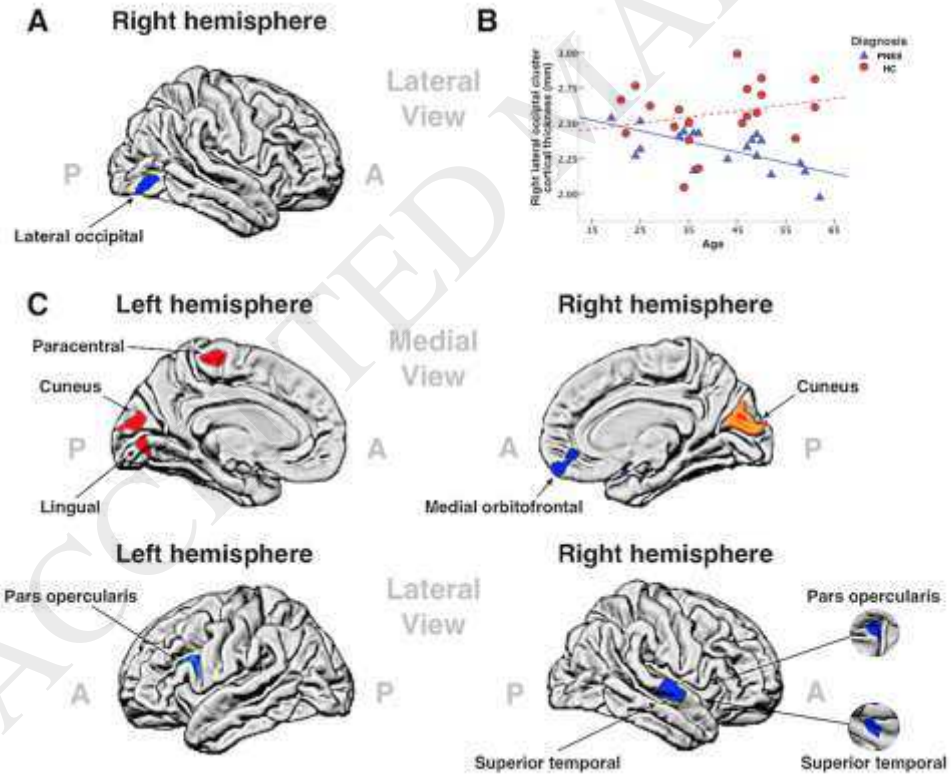

Table 1. PNES group characteristics (n = 20)					
Comorbid conditions (n = 16)					
			Number	**Percentage**	**Range***
Depression			13	81.3%	1 - 4
Anxiety			9	56.3%	
Migraine			5	31.3%	
PTSD			2	12.5%	
Panic disorder			2	12.5%	
Agoraphobia			2	12.5%	
OCD			1	6.3%	
Fibromyalgia			1	6.3%	
Number of AEDs taken at time of MRI (n = 12)					
			Number	**Percentage**	
One			6	50%	
Two			5	42%	
Three			1	8%	
Types of traumatic experiences (n = 10)					
			Number	**Percentage**	**Range***
Sexual abuse			4	40%	1 - 5
Physical abuse			3	30%	
Psychological abuse			2	20%	
Loss of child (miscarriage, cot death, other)			5	50%	
Suicide attempt			3	30%	
Other trauma unspecified			3	30%	
Other features (n = 20)					
			Number	**Percentage**	
History of head injury			1	5%	
Positive family history of epilepsy			0	0%	
PNES = psychogenic non-epileptic seizures; PTSD = post traumatic stress disorder; OCD = obsessive compulsive disorder; AEDs = anti-epileptic drugs; MRI = magnetic resonance imaging; *Range refers to the minimum and maximum number of instances i.e. some patients had more than one psychiatric comorbid condition and some patients had been exposed to more than one traumatic event.					

Table 2. Results of symptom severity scale in PNES patients (n = 20)					
Item			**Number**	**Percentage**	
Ictal loss of consciousness			17	85%	
Ictal incontinence			5	25%	
Ictal tongue-biting			3	15%	
Ictal injury			6	30%	
A&E attendance for seizure episodes			7	35%	
Seizure duration > 30 minutes			6	30%	
Recurrent symptoms without periods of remission			17	85%	
Group scores for symptom severity scale					
			Mean	**Standard deviation**	**Range**
			3.05	1.50	1 - 7
PNES = Psychogenic non-epileptic seizures; A&E = accident and emergency					

Table 3. Significant clusters of cortical thickness difference between PNES patients and age- and gender-matched healthy controls for each hemisphere

Group differences in age-cortical thickness interactions controlling for gender (DODS)								
Cluster No.	**Right hemisphere**	**Max**	**Vtx Max**	**Size (mm^2)**	**MNIX**	**MNIY**	**MNIZ**	$P_{cluster}$
	Annotation							
1	Lateral occipital	-5.425	41725	238.03	43.2	-75.4	-7.2	0.01236
Group differences in cortical thickness controlling for age and gender (DOSS)								
Cluster No.	**Left Hemisphere**	**Max**	**Vtx Max**	**Size (mm^2)**	**MNIX**	**MNIY**	**MNIZ**	$P_{cluster}$
	Annotation							
1	Pars opercularis	-5.217	47493	530.08	-45.6	16.8	21.2	0.00020
2	Paracentral	4.542	116966	174.58	-8.2	-24.6	62.7	0.04996
3	Cuneus	3.938	112494	268.99	-4.4	-84.2	17.8	0.00699
4	Lingual	3.717	114676	193.57	-10.5	-77.7	-4.9	0.03233
Cluster No.	**Right Hemisphere**	**Max**	**Vtx Max**	**Size (mm^2)**	**MNIX**	**MNIY**	**MNIZ**	$P_{cluster}$
	Annotation							
1	Superior temporal	-7.052	17325	271.41	44.8	4.4	-23.5	0.00539
2	Superior temporal	-6.300	149014	335.88	64.3	-17.9	0.3	0.00160
3	Pars opercularis	-5.754	24955	208.01	37.8	19.2	11.3	0.02484
4	Cuneus	5.013	125855	619.63	5.7	-86.9	11.5	0.00020
5	Medial orbitofrontal	-3.788	12607	207.47	9.8	43.7	-7.4	0.02544

Results of significant clusters surviving cluster forming threshold ($p < 0.001$) and cluster-wise correction for multiple comparisons (alpha = 0.05). DODS = different offset different slope; DOSS = different offset same slope; Max = maximum –log10 (p-value) in the cluster with positive and negative values indicating increases or decreases in cortical thickness in patients with PNES compared to controls; Vtx Max = vertex number of the maximum; MNI = Montreal Neurological Institute; MNIX, MNIY, MNIZ = MNI305 coordinates of maximum; $P_{cluster}$ = cluster-wise probability