Temporal lobe epilepsy and affective disorders: the role of the subgenual anterior cingulate cortex

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ABSTRACT
Objective Reduced deactivation within the default mode network (DMN) is common in individuals with primary affective disorders relative to healthy volunteers (HVs). It is unknown whether similar network abnormalities are present in temporal lobe epilepsy (TLE) patients with a history of affective psychopathology.
Methods 17 TLE patients with a lifetime affective diagnosis, 31 TLE patients with no formal psychiatric history and 30 HVs were included. We used a visuospatial ‘n-back’ paradigm to compare working memory (WM) network activation between these groups. Post hoc analyses included voxel-based morphometry and diffusion tensor imaging. The Beck Depression Inventory-Fast Screen and Beck Anxiety Inventory were completed on the day of scanning.
Findings Each group activated the fronto-parietal WM networks and deactivated the typical DMN in response to increasing task demands. Group comparison revealed that TLE patients with lifetime affective morbidity showed significantly greater deactivation in subgenual anterior cingulate cortex (sACC) than either the TLE-only or the HVs (p<0.001). This effect persisted after covarying for current psychotropic medication and severity of current depressive/anxiety symptoms (all p<0.001). Correlational analysis revealed that this finding was not driven by differences in task performance. There were no significant differences in grey matter volume or structural connectivity between the TLE groups.
Conclusions Our results provide novel evidence suggesting that affective psychopathology in TLE has a neurobiological correlate, and in this context the sACC performs differently compared with network activity in primary affective disorders.

INTRODUCTION
Temporal lobe epilepsy (TLE) is associated with marked psychiatric comorbidity.1 2 Affective disorders (depression/anxiety) are the most common interictal psychopathologies,3 leading to a decreased quality of life4 and an increased risk of suicide.5 6 Historically, affective disorders in epilepsy have been conceptualised as a complication of the underlying seizure disorder.6 Recent epidemiological studies however suggest a more complex relationship, as a history of major depression10–11 or anxiety disorders10 11 is associated with an increased risk of developing epilepsy. Moreover, a lifetime history of affective psychopathology has been associated with a poorer response to antiepileptic medication12 and epilepsy surgery.13–16

The primary affective disorder literature suggests that dysfunction within an extended network including the medial prefrontal cortex (mPFC) and anatomically-related limbic, striatal, thalamic and basal forebrain structures is pathogenic in the onset and maintenance of affective morbidity.17 18 In parallel, evidence from structural19–27 and functional neuroimaging28–37 suggests the same structures may be involved in the development and maintenance of affective symptoms in TLE.

More recently, functional imaging studies have focused on the default mode network (DMN),38 39 a resting-state network that putatively mediates task-independent, self-referential cognition and interactive modulation between intrinsic activities and external tasks.40 DMN dysfunction has been implicated in psychiatric diagnoses.41 42 Studies of primary unipolar and bipolar depression have reported reduced deactivation of the DMN during self-referential43 emotional processing44 45 and verbal working memory (WM) tasks46 with altered patterns of functional connectivity at rest relative to healthy brains.47 48 DMN dysfunction has also been demonstrated in anxiety disorders (see49 for review).

Studies of the DMN in TLE have indicated reduced functional connectivity50 51 and altered task-related deactivations compared with healthy controls.52 53 Emerging evidence suggests that DMN connectivity may be further complicated by comorbid psychopathology.54–56 Chen et al54 demonstrated that in depressed mTLE patients, functional connectivity among the anterior prefrontal cortex, limbic system and temporal lobe is significantly reduced compared with non-depressed TLE patients and healthy controls. However, it is still unknown whether comorbid affective morbidity in TLE modulates the behaviour of this neural network.

WM tasks are normally associated with deactivation of the DMN.57 The aim of this study was to examine DMN function and structure in patients with TLE and a history of comorbid affective disorders. Specifically, we hypothesised that patients with a lifetime affective diagnosis would demonstrate reduced deactivation of the DMN during a WM task, similar to patients with primary affective disorders,40–42 and this would be associated with poorer performance.

MATERIALS AND METHODS
Subjects
A total of 48 right-handed patients with medically refractory TLE undergoing presurgical evaluation
Seven of the 17 patients with a psychiatric history had a neuropsychiatric evaluation as part of presurgical investigations. English speakers and had undergone a neuropsychological and EEG had con

All patients were taking antiepileptic medication, were native English speaking healthy volunteers without any history of neurological or psychiatric disease. We also recruited 30 native English speaking healthy volunteers (HVs) without any history of neurological or psychiatric disorder (none-psychiatric history (nPHx) group). We at the National Hospital for Neurology and Neurosurgery participated in this study between 2009 and 2012. Seventeen patients had at least one lifetime episode of an affective disorder (psychiatric history (PHx) group). Thirty-one patients had no history of psychiatric disorder (none-psychiatric history (nPHx) group). We also recruited 30 native English speaking healthy volunteers (HVs) without any history of neurological or psychiatric disease. Clinical and demographic data are detailed in table 1.

All patients had a structural MRI at 3 Tesla (3 T). Video-scalp EEG had confirmed seizure onset in the medial temporal lobe. All patients were taking antiepileptic medication, were native English speakers and had undergone a neuropsychological and neuropsychiatric evaluation as part of presurgical investigations. Seven of the 17 patients with a psychiatric history had a current psychiatric diagnosis (six unipolar depression; one anxiety disorder); 5 (29%) were prescribed antidepressant or anxiolytic medication.

The study was approved by the National Hospital for Neurology and Neurosurgery and the Institute of Neurology Joint Research Ethics Committee, and written informed consent was obtained from all subjects.

### Neuropsychiatric evaluation and analysis

#### Neuropsychiatric diagnosis: lifetime and current

All patients were assessed by a neuropsychiatrist (JF) via a clinical interview. The diagnoses of mood and anxiety disorders fulfilled criteria according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR). Patients with affective symptoms related to antiepileptic (antiepileptic drug (AED)) therapy or the peri-ictal period (symptoms temporally related to seizure activity) were excluded from the study. We also excluded patients with a history of postictal or interictal psychosis.

#### Beck Depression and Anxiety Inventories (BDI-FS and BAI)

All subjects completed the Beck Depression Inventory-Fast Screen (BDI-FS) and Beck Anxiety Inventory (BAI). For both inventories, recommended severity ranges were employed (BDI-FS: 0–3 minimal; 4–6 mild; 7–9 moderate; 10–21 severe. BAI: 0–7 minimal; 8–15 mild; 16–25 moderate; 26–63 severe).

### MR data acquisition

MRI studies were performed on a 3 T General Electric Excite HDx scanner. Standard imaging gradients with a maximum strength of 40 m Tm⁻¹ and slew rate 150 Tm⁻¹s⁻¹ were used. All data were acquired using an eight-channel array head coil for reception and the body coil for transmission. Standard clinical sequences were performed and included a coronal T1-weighted volumetric acquisition with 170 contiguous 1.1 mm thick slices (matrix 256×256, inplane resolution 0.9375×0.9375 mm) used for voxel-based morphometry (VBM) analysis.

For the fMRI task, gradient-echo planar T2*-weighted images were acquired, providing blood oxygenation level-dependent (BOLD) contrast. A total of 272 volumes were acquired over 1 run lasting 11 min 20 s. Each volume comprised 50 oblique axial 2.4 mm slices (with 0.1 mm gap) covering the whole brain, with a 24 cm field of view, SENSE factor 2, 64×64 matrix and an inplane resolution of 3.75×3.75 mm². Echo time was 25 ms and repetition time was 2.5 s.

### Diffusion tensor imaging acquisition

Data were acquired using a cardiac-triggered single-shot spin-echo planar imaging sequence with echo time=73 ms. Sets of 60 contiguous 2.4 mm thick axial slices were obtained covering the whole brain, with diffusion sensitising gradients applied in each of 52 non-collinear directions (b value of 1200 mm²s⁻¹).
Post hoc imaging analyses

Voxel-based morphometry
The T1-weighted images were segmented into grey matter, white matter and cerebrospinal fluid using VBM8. Grey matter segmentations were normalised to MNI space and smoothed with a Gaussian kernel of 8 mm FWHM to produce maps of grey matter volume (GMV). An ANCOVA was performed to determine group differences in GMV.

Fractional anisotropy and structural connectivity analysis
Diffusion tensor imaging data were preprocessed to remove motion artefact and eddy current distortion using the FSL eddy-corrupt routine. Maps of fractional anisotropy (FA) as an indicator of structural integrity were obtained using the FMRIB Diffusion Toolbox. They were non-linearly registered to the FMRIB58 template using FLIRT and FNIRT and smoothed with a Gaussian kernel of 8 mm FWHM. A whole brain voxel-wise ANCOVA of the FA maps between groups was undertaken in SPM18 with gender, BDI-FS and BAI scores included as regressors of no interest.

Tractography was performed in each subject to investigate the connectivity from the region identified by fMRI. A 6 mm sphere was defined in the white matter of the anterior corpus callosum underlying the activation maxima of the general linear model ANCOVA in the normalised space of the FMRIB58 template. This was transformed into each individual’s native space using the inverse of transform calculated using FNIRT. Probabilistic tractography was then performed in native space from this seed using the FSL Diffusion Toolkit. The connectivity maps generated for each subject were scaled by the number of streamlines initiated and normalised to the FMRIB58 template using the previously calculated transformation and smoothed with a Gaussian kernel of 8 mm FWHM. A whole brain voxelwise comparison of the structural connectivity maps between groups was undertaken in SPM8 with gender, BDI-FS and BAI scores included as regressors of no interest.

RESULTS

Beck Depression and Anxiety Inventories
ANOVA revealed both TLE groups had significantly higher BDI-FS and BAI scores than controls on the day of scanning (p<0.01). There were no significant differences between patient groups on these measures (see table 1).

Inscanner performance
ANOVA revealed a main effect of group on the 0-back (F (2, 75)=4.84, p<0.05), 1-back (F (2, 75)=7.18, p<0.05) and 2-back conditions (F (2, 75)=3.52, p<0.05). Post hoc Bonferroni analysis showed the PHx group performed significantly less well than HVs during the 0 dot-back condition (p=0.008). The PHx group also performed less well than HVs during the 0-back condition; however, this was not statistically significant. There was no significant difference between the patient groups during the 0-back condition. In the 1 dot-back condition, the PHx group performed significantly worse than the HVs (p<0.001) and the nPHx group (p=0.049). In the 2 dot-back condition, the PHx group performed significantly less well than HVs (p=.029); however, their performance was not significantly different to the nPHx group (p=.70). There was no significant difference between the HV and nPHx groups in either 1 or 2 dot-back conditions (see figure 1).

fMRI default mode network
Each group progressively deactivated the typical DMN consisting of the precuneus, medial frontal gyrus, anterior cingulate cortex (ACC), superior temporal gyri and hippocampi in response to increasing task demands (figure 2). ANCOVA revealed the PHx group additionally deactivated the subgenual ACC (sACC) (k=x=2, y=28, z=-2) significantly more than the HV and the nPHx groups (figure 3).
Post hoc fMRI analyses
To determine whether the result for the PHx group may be influenced by current affective diagnosis, the data were reanalysed in a separate ANCOVA dividing the PHx group into lifetime (n=10) versus current (n=7) psychiatric diagnosis. There was no significant difference in the deactivation between these groups. Two further ANCOVAs were performed excluding those patients in the PHx group with scores falling in the moderate to severe range on the BDI-FS (n=3 removed) and BAI (n=4 removed). Both analyses revealed the same effect with significantly greater sACC deactivation (x=2, y=28, z=−2) in the PHx group compared with both the HV and nPHx groups.

A further ANCOVA was performed to explore the potential role of current psychiatric medication. The five patients taking antidepressant and anxiolytic medication were removed from the analysis. The same effect was observed in that the PHx group deactivated the same sACC cluster (x=2, y=30, z=−4) significantly more than HV and the nPHx groups.

Finally, to ensure the result was not driven by differences in task performance, correlational analyses were performed between the inscanner performance on each condition and the sACC BOLD parameter estimates for each subject. There was no significant linear correlation between performance and sACC signal in the 0, 1 or 2 dot-back conditions. There were no significant correlations between BDI-FS and BAI scores and sACC signal. In addition, as a manipulation check, all three groups progressively activated the expected fronto-parietal WM networks as a function of increasing WM demand.

Voxel-based morphometry
A whole brain VBM analysis was conducted to examine whether the main effect of group on DMN deactivation in the sACC was associated with structural differences in this region. There were no significant differences in GMV between the groups (all p >0.05).

FA maps
To explore white matter integrity a whole brain voxelwise ANCOVA was performed using the FA maps generated at the individual level. There were no significant group differences in FA between the PHx group and HVs, or the nPHx group.

Structural connectivity
Seeding from the anterior corpus callosum, each group showed structural connectivity to the forceps minor bilaterally. ANCOVA revealed no significant group differences in the structural connectivity of this region.

DISCUSSION
We report task-related DMN deactivation in patients with TLE and a diagnosed history of comorbid affective disorders. Contrary to our prediction, TLE patients with and without a history of affective disorders and HV demonstrated a progressive deactivation of the DMN in response to increasing WM task demands. Furthermore, the PHx group showed additional deactivation in the sACC, a mesolimbic structure implicated in the pathophysiology of primary depression.65–67

Figure 1  Group results across WM dot-back conditions (*=p<.05).

Figure 2  Group results for progressive deactivation of the typical default mode network in response to increasing task demand (p<.001, unc); controlling for both gender and current mood (BDI-FS and BAI scores). The superior temporal gyrus (STG) is not visualised owing to slice selection to show maximum default mode network deactivation.
Increased deactivation within the DMN in the PHx group contrasts with the growing literature demonstrating that the DMN is less deactivated in affective disorders during self-referential, emotional processing, and verbal WM tasks. Available evidence does indicate that DMN activity is significantly attenuated in TLE with seizures that impair awareness (see for review).

EEG-fMRI studies have consistently demonstrated interictal epileptic discharges (IED)-related deactivations in the anterior and posterior nodes of the DMN in TLE patients during rest. Laufs et al suggested DMN deactivation in TLE is facilitated by the propagation of interictal epileptic activity to functionally interconnected default brain regions, resulting in secondary inhibition of non-seizing cortical regions via subcortical structures. We observed task-related deactivation in the PHx group that was significantly greater than that which occurred in the PHx, and in a component of the ‘affective network’ (sACC), supporting an additional, more specific, epilepsy-affected interaction. It is also possible that the rate of IEDs was dissimilar between the patient groups, particularly given the evidence that affective morbidity has been reported as predictive of seizure recurrence in newly treated patients and has been associated with a poorer response to antiepileptic medication and epilepsy surgery. As we did not collect simultaneous acquisition of EEG-fMRI data, we are unable to examine whether interictal epileptiform activity mediated the relation between sACC deactivation and/or cognitive performance in the PHx group.

Our post hoc analyses indicated that the main effect of group on DMN deactivation of the sACC was not related to volumetric or structural connectivity differences of this region, but represents an isolated functional abnormality. Further studies using resting-state EEG-fMRI methodology are needed to explore this interactional physiological interpretation.

Functional neuroimaging techniques suggest that the ACC is functionally and structurally heterogeneous. A meta-analyses of task-based studies demonstrated the functional heterogeneity separating the ACC into cognitive (dorsal) and affective (rostral) subdivisions. In contrast to task-based approaches, Margulies et al used resting-state functional connectivity to examine ACC functional segregation. They replicated a rostral/caudal ACC distinction, but also found a negative relationship (ie, anticorrelation) between the subgenual portions of the ACC and superior parietal regions, which are involved in higher order cognitive processes, such as attentional control and spatial WM. Although the present study was not designed to disentangle task-related reciprocity between brain networks, we hypothesise that the observed additional sACC deactivation in the PHx group reflects the recruitment of additional neuronal resources (via anticorrelation) for successful task performance.

Within the larger context of the limbic-striato-pallidio-thalamic circuits implicated in the pathophysiology of primary depression, the functional implications of cortical-limbic circuits involving the medial prefrontal network merit comment in light of the abundant basic science literature available to guide translational models. Specifically, the ACC receives extensive dopaminergic innervation from the ventral tegmental area (VTA) and sends projections to the VTA that regulate phasic dopamine (DA) release. In rats, stimulation of the mPFC areas elicits burst firing patterns in the VTA-DA neurons while inactivation of the mPFC converts burst firing patterns to pacemaker-like firing activity. The burst firing patterns increase DA release in the nucleus accumbens, which is thought to encode information about reward prediction. The meso-limbic DA projections from the VTA to the nucleus accumbens and the mPFC thus play major roles in learning associations between operant behaviours or sensory stimuli and reward. Further research is required to examine whether sACC dysfunction deleteriously affects the cortical drive on VTA-DA neuronal burst firing activity, which may impair reward learning in TLE patients with affective morbidity.

Previous research indicates that a lack of DMN deactivation, as found in association with psychiatric disturbance, is associated with impaired cognitive performance and deactivation in controls with performance gains. As predicted, we observed poorer WM performance in the PHx group that was related to increased deactivation, indicating that deactivation is not always cognitively advantageous. Whether this is a task-specific effect requires further investigation.

The behavioural performance of the two patient groups, relative to the control group, requires consideration. We found that both patient groups, irrespective of lifetime affective morbidity, performed less well at the 0 dot-back task condition compared...
with controls. We strongly suspect this is due to disease burden and the uncontrolled effects of antiepileptic medication on the attention networks. In the 1 dot-back condition, the PHx group performed more poorly than both control groups; whereas in the 2 dot-back condition, both TLE groups exhibited equal performance level. Collectively, these findings are suggestive of a ‘weighted’ interaction between psychopathology and TLE. Consistent with this hypothesis, previous research has reported that TLE patients per se are poorer on the 2 dot-back condition.

Our findings also challenge the ‘default-mode interference hypothesis’, which proposes that in a normal functioning system, the task-negative (DMN) components will be reduced during the transition from rest to goal-directed action, which is antecorrelated with activation in the task-positive network. Episodic attentional lapses and deficits in performance are considered to be associated with intruding aspects of the task thereby causing distractions. The investigation of these possible explanations requires further research. Although the majority of functional magnetic resonance imaging (fMRI) studies in primary affective disorders have not accounted for the influence of AEDs on the DMN and/or WM function.77 The majority of our patients were taking AED polytherapy in a variety of combinations. There were no significant differences in the number of AEDs between patient groups. This serves to limit the generalisability of the current study to pharmaco-resistant TLE patients. In addition, our fMRI results failed to achieve significance with correction for multiple comparisons. However, the cluster extent was >20 voxels, reducing the likelihood of false positives.88

The present study is the first to address DMN-related deactivation in TLE patients with a lifetime diagnosis of affective psychopathology. We observed significant deactivation of an ‘affective network’ node (sACC) in patients with a lifetime affective diagnosis with increasing task demands that conferred no cognitive benefit. Post hoc imaging analyses indicated that this finding was not associated with structural differences in the sACC. Our findings suggest the combination of an affective disorder and TLE has a unique pathophysiological basis supporting the growing body of research indicating that affective psychopathology in TLE has a neurobiological correlate and, in this context, the DMN performs differently compared with network activity in primary affective disorders (reduced deactivation).40–43 Prospective serial neuroimaging studies are needed to unravel the causal mechanisms underlying task-related DMN functional alterations and affective psychopathology in TLE.

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Competing interests RAP and JS had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Patient consent Obtained.

Ethics approval UCL Hospitals NHS Foundation Trust Ethics Committee.
Epilepsy

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