

RESEARCH ARTICLE

Cognitive impairment in epilepsy: the role of reduced network flexibility

Chris Tailby^{1,2,3} , Magdalena A. Kowalczyk¹  & Graeme D. Jackson^{1,3,4}¹Florey Institute of Neuroscience and Mental Health, Heidelberg, Victoria, Australia²Institute for Social Neuroscience, Heidelberg, Victoria, Australia³Austin Health, Heidelberg, Victoria, Australia⁴The University of Melbourne, Parkville, Victoria, Australia

Correspondence

Chris Tailby, Melbourne Brain Centre, 245 Burgundy St, Heidelberg, Victoria, Australia 3084. Tel: +61 3 9035 7020; Fax: +61 3 9458 5459; E-mail: chris.tailby@florey.edu.au

Funding Information

This study was supported by the National Health and Medical Research Council (NHMRC) of Australia (program grant 628952 and project grant 1081151) and the Victorian Government Operational Infrastructure Support Program. G.D.J. was supported by an NHMRC practitioner fellowship (1060312).

Received: 15 October 2017; Accepted: 18 October 2017

Annals of Clinical and Translational Neurology 2018; 5(1): 29–40

doi: 10.1002/acn3.503

Abstract

Objective: The dominant model of cognitive impairment in focal epilepsy has emphasised structural bases for cognitive deficits. Current theories of cognition in the healthy brain emphasise the importance of the reweighting of brain network interactions in support of task performance. Here, we explore the hypothesis that cognitive deficits in epilepsy arise through abnormalities of dynamic functional network interactions. **Method:** We studied 19 healthy controls and 37 temporal lobe epilepsy (TLE) patients, using a behavioural measure of verbal fluency (the Controlled Oral Word Association Test) and an fMRI verbal fluency paradigm (Orthographic Lexical Retrieval). **Results:** Behaviourally, verbal fluency was significantly impaired in TLE. Psychophysiological interaction analyses of the fMRI data, which capture state-dependent changes in network connectivity, revealed reduced task-dependent modulations of connectivity from left superior medial frontal cortex to left middle frontal gyrus in TLE patients. Individual differences in verbal fluency among TLE cases was correlated with task-dependent changes in connectivity from left posterior cingulate to left superior medial frontal cortex, and from left superior medial frontal cortex to a range of right predominant brain areas. **Interpretation:** These data reveal that the typical pattern of task-driven shifts in network connectivity is not observed in TLE. Our observations go beyond simple structure-function associations and suggest that failure of network flexibility can be an important contributor to cognitive impairment in epilepsy.

Introduction

Cognitive dysfunction is a common comorbidity in temporal lobe epilepsy (TLE).¹ Memory impairment is considered the characteristic cognitive feature of TLE.^{2,3} However, impairments in non-mnemonic cognitive domains – such as processing speed, confrontation naming, verbal fluency, executive functioning, and general intelligence – are also common.^{1–3} Memory impairment is most strongly associated with pathology in the mesial temporal region⁴ suggesting a direct causal relationship between structural integrity and cognition. Non-mnemonic impairments, however, are less readily reconciled as a direct consequence of primary mesial temporal lobe damage.

It has been argued² that non-mnemonic deficits in TLE might reflect extra-temporal *structural* pathology,^{5–7}

giving rise to the notion of TLE as a structural “network disease”.⁸ While structural “network disease” is unlikely to explain cognitive impairment in all cases,⁹ the underlying concept can be expanded to incorporate functional network disease as well. From this perspective some of the cognitive deficits in TLE, and indeed in epilepsy more generally, represent alterations in *functional* networks.^{9–11}

Cognition requires dynamic reshaping of network interactions in support of task demands.¹² While functional connectivity has been extensively studied in TLE, this has generally been with steady state connectivity,^{11,13,14} rather than dynamic or task modulated connectivity; little is known about task-dependent modulations of connectivity.^{15–17} A reduced ability to implement dynamic task-appropriate network reshaping (‘network

flexibility') might be an important mechanism by which epilepsy results in disturbances of cognitive function,¹⁶ over and above deficits caused by focal structural pathology.

Psychophysiological interaction (PPI) analysis provides a tool for investigating task-related modulations in functional connectivity.¹⁸ PPI analyses estimate how the relationship between neural activity in a seed region and other brain areas is modulated by psychological state.^{18,19} Thus, PPI analyses enable hypothesis driven testing of the context dependent influence of one brain area on the rest of the network to which it connects. A set of midline brain regions, including posterior cingulate cortex and medial superior frontal cortex, have been implicated as important hubs for setting overall brain network configuration. Anterior cingulate/medial superior frontal cortex has been identified as a key region that implements "task sets", setting brain state in a domain independent manner.^{20,21} Posterior cingulate cortex, a major hub of the default mode network, plays a central role in cognition, modulating interactions between the default mode network and cognitive networks that are important for task performance.²² Furthermore, steady state connectivity analyses in epilepsy have repeatedly pointed to the presence of dysfunction within the default mode network.²³

Here we use verbal fluency, in the form of the Controlled Oral Word Association Test, as a model cognitive paradigm to test the hypothesis that abnormal state-dependent changes in functional connectivity contribute to cognitive impairment in TLE. Specifically, we hypothesise that, relative to healthy controls, (1) verbal fluency will be impaired in TLE, (2) task-dependent changes in connectivity (i.e. network flexibility) from midline hub areas will be abnormal in TLE and (3) greater task-dependent changes in connectivity will be associated with better verbal fluency.

Methods

Participants

Nineteen healthy controls and 37 patients with temporal lobe epilepsy participated in this study. Of these 37 patients, 32 had a lateralised epileptic focus (one was bilateral, four were of uncertain lateralisation). We restrict subsequent analyses to 32 unilateral TLE patients with diagnosis confirmed on inpatient video-EEG monitoring at the Austin Hospital Melbourne (see Table 1). Ten patients had hippocampal sclerosis, fifteen had focal MRI temporal lobe abnormalities, and seven were MRI negative. Controls and patients did not differ in age (*t*-tests, all *P* > 0.05), or in gender or handedness (Fisher's exact test, all *P* > 0.05). All participants provided written informed consent. All participants provided written informed consent in accordance with the Declaration of Helsinki, with the study approved by the relevant Human Research Ethics Committees.

Behavioural assessment of verbal fluency

Verbal fluency was measured with the Controlled Oral Word Association Test (COWAT),²⁴ using the letters F, A, S. The COWAT was collected prior to scanning, to obtain a behavioural measure of fluency, and to ensure understanding of the in-scanner fluency task (described next). Of the 19 Controls, 16 had a COWAT score recorded. Among the TLE patients, eighteen of the 20 left lateralised cases, and all 12 of the right lateralised cases had COWAT scores recorded.

Verbal fluency fMRI paradigm

All participants completed a block design, covert verbal fluency paradigm (Orthographic Lexical Retrieval). During the active periods (30 sec) of the OLR paradigm,²⁵ participants were instructed to (silently) generate words

Table 1. Participant details.

	<i>N</i>	Age ($\mu \pm \text{SD}$) ³	Gender (F/M) ⁴	Hand (L/R) ⁴	Epileptic focus (Left/Right)	Age of onset ($\mu \pm \text{SD}$)	Duration of epilepsy ($\mu \pm \text{SD}$)	No. of AEDs ($\mu \pm \text{SD}$)
OLR ¹								
TLE	32	38.1 $\pm$ 10.0	14/18	5/27	20/12	20.2 $\pm$ 12.9	16.6 $\pm$ 13.3	2.3 $\pm$ 0.9
Controls	19	33.5 $\pm$ 7.6	8/11	3/16	NA	NA	NA	NA
COWAT ²								
TLE	30	38.0 $\pm$ 9.4	13/17	4/26	18/12	20.3 $\pm$ 13.1	16.9 $\pm$ 13.3	2.3 $\pm$ 1
Controls	16	33.4 $\pm$ 7.6	6/10	2/14	NA	NA	NA	NA

¹Data used in Figure 2.

²Data used in Figure 3 and in Table 2.

³No differences in age between patients and controls in the OLR or COWAT based analyses (*t*-tests, *P* > 0.05).

⁴No differences in gender or handedness between patients and controls in the OLR or COWAT based analyses (Fischer's exact test, *P* > 0.05).

beginning with the letter that was displayed on a monitor viewed, via mirrors, down the bore of the magnet. Two letters were presented successively, for 15 sec each, during each active period. During the baseline periods (30 sec) participants fixated on a “+” sign. Four active periods were interleaved within five baseline periods.

MRI acquisition

MRI was performed on a 3T Siemens Tim Trio scanner (Erlangen, Germany). Functional images were acquired using a whole-brain gradient-echo single shot echo-planar imaging sequence (echo time 30 msec, repetition time 3000 msec, field-of-view 72×72 voxels in-plane, 44 slices, voxel size 3 mm isotropic).

Preprocessing of functional images

Data were preprocessed using SPM12. Images were slice time corrected, motion corrected, warped to MNI space, resampled to 2 mm isotropic voxels, and smoothed (8 mm FWHM). To define a group wise brain mask for voxel-wise statistical testing (see next section), within brain masks for each participant were generated using the brain extraction tool from FSL,²⁶ their intersection calculated, and posterior venous sinuses (mainly torcula and transverse sinuses) manually excluded.

Task activation analysis

Images acquired during execution of the OLR paradigm were analysed via the general linear model, using SPM12. The design matrix included: an HRF convolved boxcar regressor modelling task active periods (each letter coded separately), temporal parametric modulation of the task regressor, parametric modulation of the task regressor based on the “difficulty” of the letters used (according to individual letter norms provided in Borkowski et al.²⁷), and the motion parameters estimated during preprocessing. For activation analyses the contrast of interest was the beta estimate for the task regressor.

Psychophysiological interaction analyses

We hypothesised that reconfiguration of brain network interactions in the service of task demands, which we refer to here as ‘network flexibility’, is compromised in TLE. We therefore selected seeds in axial regions considered important for such reconfiguration (see Introduction), identified as midline maxima of de/activation in a one sample *t*-test on the task-related activation images obtained in patients and controls. Specifically, from the resulting spm-*t* image we chose the two strongest midline

activation maxima and the two strongest midline deactivation maxima as seeds for the PPI analyses (Fig. 1). While an obvious extension would have been to also include seeds in language areas on the convexity, such as inferior and middle frontal gyri, we elected not to as our primary hypothesis concerns the setting of network configuration by midline brain regions. We also reasoned that if there were abnormal network interactions involving task-specific language regions this would manifest as reduced PPIs from midline cortex to language areas on the convexity, which our analyses would be able to detect (see Fig. 2). Furthermore, the inclusion of additional seeds would necessitate further multiple comparisons corrections, diminishing statistical power. For these reasons, we elected to restrict our analyses to midline seeds.

Using these seeds, we ran PPI analyses on the data from each participant using the gPPI toolbox.¹⁹ Each seed region was defined as a 6 mm radius ROI centred on the de/activation coordinates identified above, with the seed time-series calculated as the first eigenvariate as specified in the gPPI toolbox. The PPI model included the regressors used in the initial first level activation analyses, described above, along with the two additional regressors required for PPI analyses: one containing the seed timeseries, the other containing the PPI term itself. In calculating the PPI term, the HRF was first deconvolved from the seed timeseries. This estimate of neural activity was then multiplied element-wise with the boxcar function describing the task periods (i.e. the task regressor prior to convolution with the HRF). The resulting product was then convolved with the HRF to yield the PPI regressor used in the model.¹⁹

The principal contrast of interest was the beta estimate for the PPI regressor, which estimates the task-induced *change* in the slope (gain) of the relationship between activity in the seed region and activity in voxel *x*. The slope (gain) of this relationship during the baseline period (G_{rest}) was estimated as the beta value obtained for the seed regressor.²⁸ Similarly, the slope (gain) of this relationship during the task period (G_{task}) was estimated as the sum of slope during baseline, G_{rest} , and the beta estimate for the PPI regressor.

Group comparisons

For each seed we used *t*-tests (spm-*t* images) to contrast PPI estimates in controls and TLE patients. The model also included laterality of epileptic focus as a covariate (dummy coded as: left = 1, right = -1, control = 0). The four resulting spm-*t* images were thresholded at an exploratory feature threshold of $P < 0.005^{29-31}$ followed by cluster correction at $P < 0.00625$ (Bonferroni corrected for the eight comparisons performed: the four *t*-tests used here and the four regression analyses described in the next section).

Seed selection from maxima of de/activation

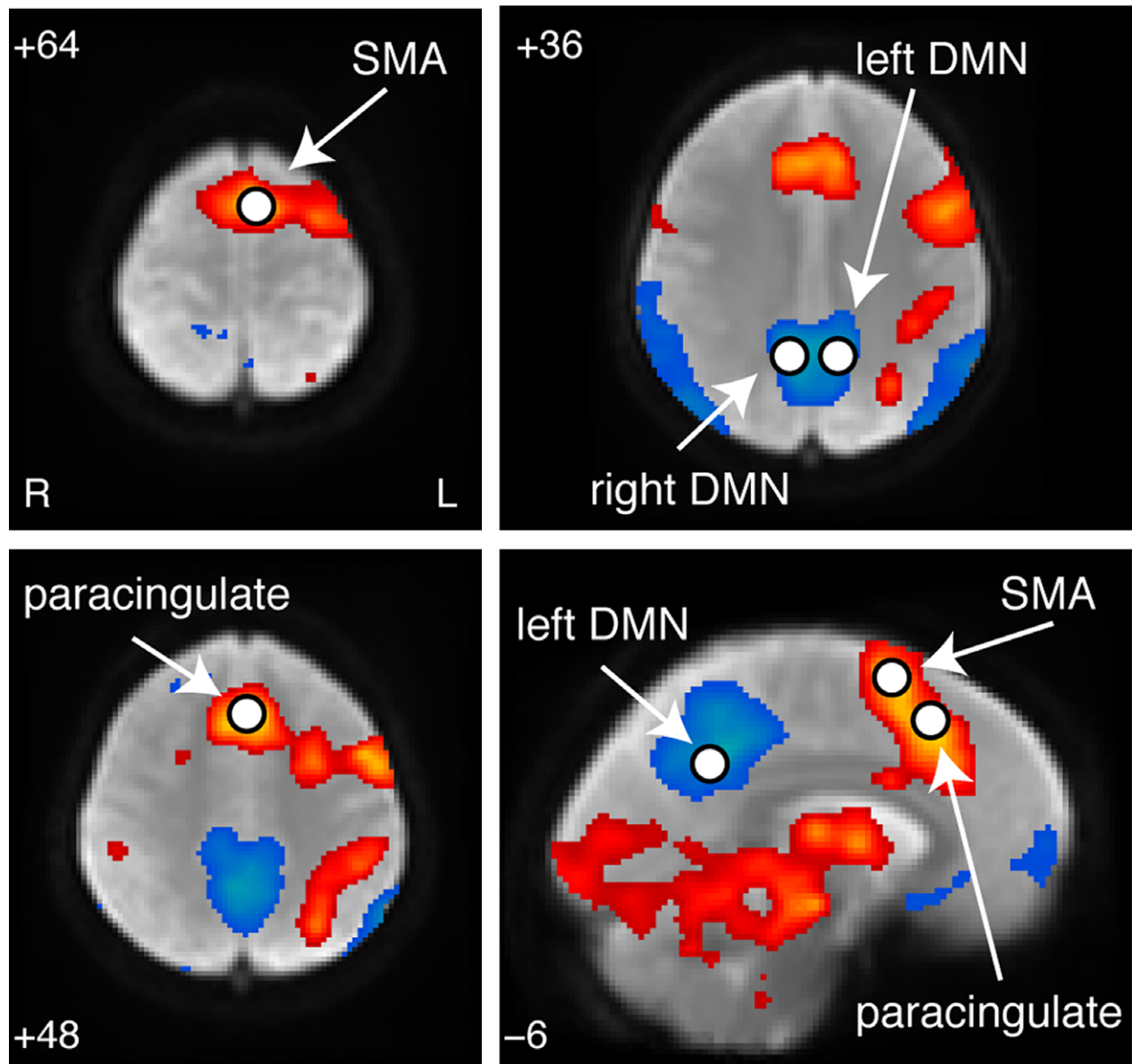


Figure 1. PPI seed selection. Panels show seeds (white circles) overlaid on activation (hot colours) and deactivation (cool colours) during the OLR task. Seeds for the PPI analyses were selected as midline de/activation maxima. Activations and deactivations were derived from a one-sample t -test including all participants (controls and TLE patients). The spm- t map was thresholded at $P < 0.000001$, uncorrected for display purposes, to enable visualisation of seeds relative to underlying activation and anatomy; the map is not interpreted statistically.

Regression analyses of PPI estimates against fluency

To investigate the relationship between PPI estimates and verbal fluency in TLE we regressed COWAT scores against PPI estimates for each of the four seeds. The model also included laterality of epileptic focus as a

covariate (dummy coded as: left = 1, right = -1). COWAT measures were available in 30 of the TLE patients (18 left, 12 right). The four resulting spm- t images were thresholded at a feature threshold of $P < 0.001$ followed by cluster correction at $P < 0.00625$ (Bonferroni corrected for eight comparisons as described above).

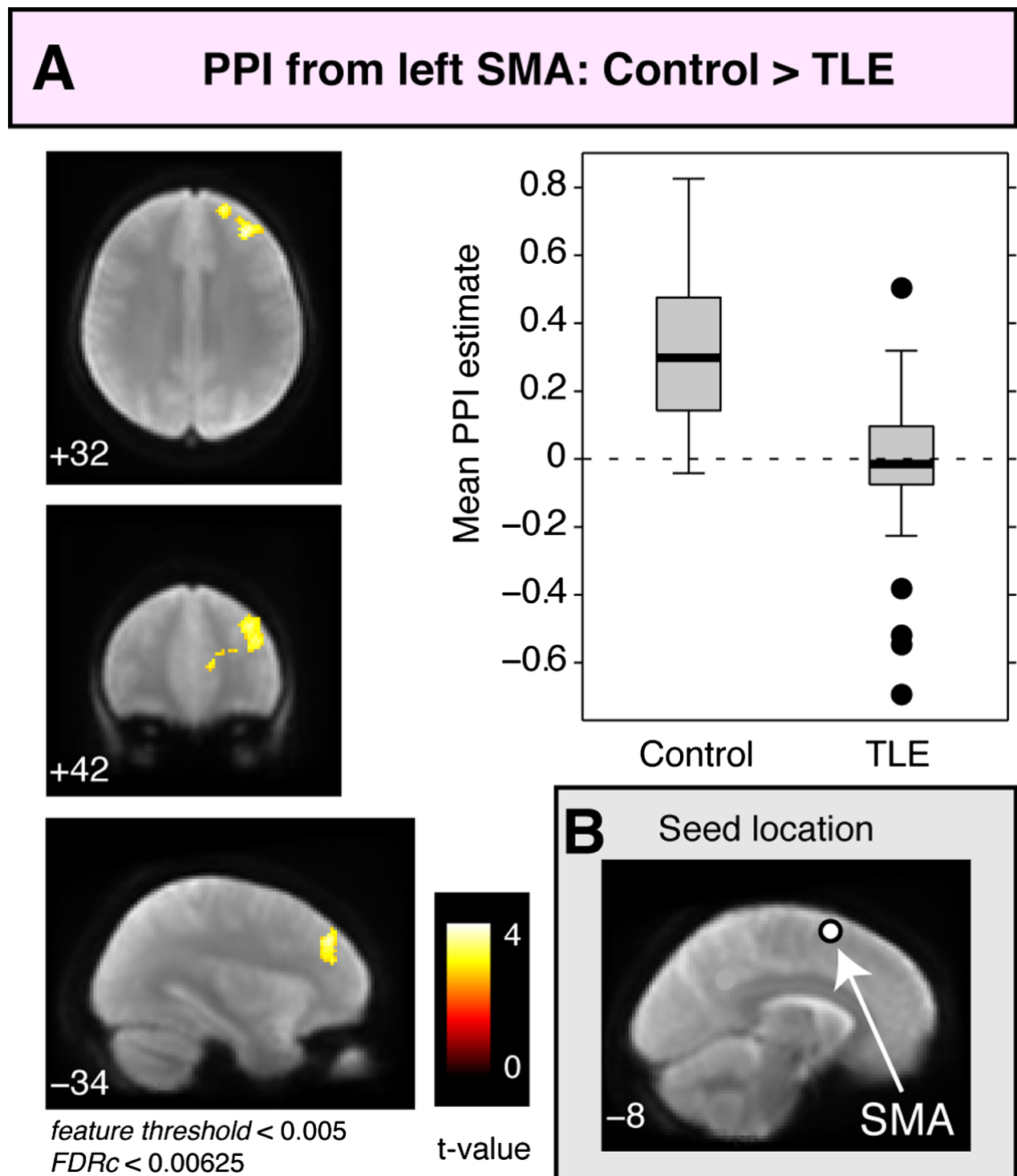


Figure 2. Stronger PPIs from left SMA to left middle frontal gyrus in controls relative to TLE patients. (A) spm-t image showing left frontal cluster within which PPIs from the left SMA seed are significantly stronger in controls. Boxplots show average PPI estimates within the cluster. (B) parasagittal slice showing locations of the SMA seed.

Results

Worse verbal fluency in TLE patients

Verbal fluency (COWAT) scores in patients with unilateral TLE were significantly lower than in controls ($t(44) = 5.34$, $P < 0.001$; see Table 2). COWAT scores did not differ between left and right TLE ($P > 0.05$).

Comparable activation patterns in TLE patients and controls

As we have shown previously,²⁵ activation on the OLR task in patients and controls is left dominant (Fig. 1), with major foci of activation in medial superior frontal cortex, left middle and inferior frontal gyri, left intraparietal sulcus and bilateral cerebellum (right stronger than left).

Activation in controls and TLE patients were not different in language areas. A single medial occipital cluster of weaker activation was present in TLE patients ($XYZ = [-2, -68, 6]$, cluster size = 548 voxels); as our main interest in this paper lies in the PPI effects we do not interpret this activation-related result here.

Task-dependent connectivity changes are stronger in controls than TLE patients

We compared PPI estimates in TLE patients and controls for the four seed regions shown in Figure 1. Significant differences (at an exploratory feature threshold of $P < 0.005$; FDRc, $P < 0.00625$) were observed for one of the seeds: that in left SMA.

For the left SMA seed, PPI estimates were greater in controls in a single cluster of voxels within left middle frontal gyrus (Fig. 2; peak $XYZ = [-32, 38, 32]$, $z = 3.70$). During the baseline period the mean gain (G_{rest}) of the relationship between activity in the seed and activity in voxels within this cluster was weakly positive in patients (0.25 ± 0.17 , mean $\pm$ standard deviation) and controls (0.20 ± 0.13). During the task period the gain (G_{task}) was essentially unchanged in patients (0.22 ± 0.24), but increased substantially in controls (to 0.53 ± 0.23), giving rise to the significantly stronger PPI estimates in controls in this region. In other words, TLE patients did not show

the task-associated increases in connectivity exhibited by controls in this region.

Behavioural correlations

If state dependent changes in connectivity from midline regions are important contributors to verbal fluency in TLE patients then variability in PPI estimates should covary with COWAT scores. We therefore ran regressions of the COWAT scores obtained by individual TLE patients against their corresponding PPI estimate, for each of the four seeds. Two of the four seeds revealed significant clusters (feature threshold, $P < 0.001$ (unc.); FDRc, $P < 0.00625$); the seeds in left DMN and left SMA (Fig. 3 and Table 3).

For the left DMN seed, higher COWAT scores were associated with stronger PPIs to the left medial superior frontal region (left SMA; Fig. 3A). The mean gain of the connectivity to this cluster at rest was weakly positive ($G_{rest} = 0.14 \pm 0.2$). Thus, the positive relationship between PPIs and COWAT scores indicates that better verbal fluency was associated with increasingly positive connectivity of the left DMN seed with the left SMA during the task periods. The mean beta estimate for the OLR task regressor within the left SMA cluster was also positive ($\mu = 0.6$), indicating that stronger connectivity from DMN to SMA occurred during task-related activation of the left SMA.

For the left SMA seed, higher COWAT scores were associated with stronger PPIs to a range of cortical areas, including right lateral and mesial parietal cortex, posterior cingulate cortex, medial occipital cortex, and left and right dorsal somatosensory cortex (Fig. 3B). In all of these clusters the mean slope (gain) at rest was positive (ranging from 0.17 to 0.38), so again the positive relationship between PPI and COWAT score indicates that better verbal fluency was associated with increasingly positive connectivity of left SMA to these clusters during the task periods. The mean beta estimates for the OLR task regressor within these clusters were all negative (ranging from -0.13 to -0.79), indicating that there is increasingly positive connectivity from SMA to these clusters during task-related *deactivation* in these clusters.

Discussion

We found that letter-based verbal fluency is impaired in TLE patients relative to healthy controls. We also observed that at the group level healthy controls, but not TLE patients, exhibited task-dependent increases in the gain of the connectivity (PPI) from left SMA to left prefrontal regions during execution of a verbal fluency paradigm. Within the TLE group, PPI magnitude was

Table 2. COWAT scores.

	<i>n</i>	COWAT score ($\mu \pm SD$) ¹
TLE	30	28.0 ± 11.1
Controls	16	47.7 ± 13.2

¹ $P < 0.001$.

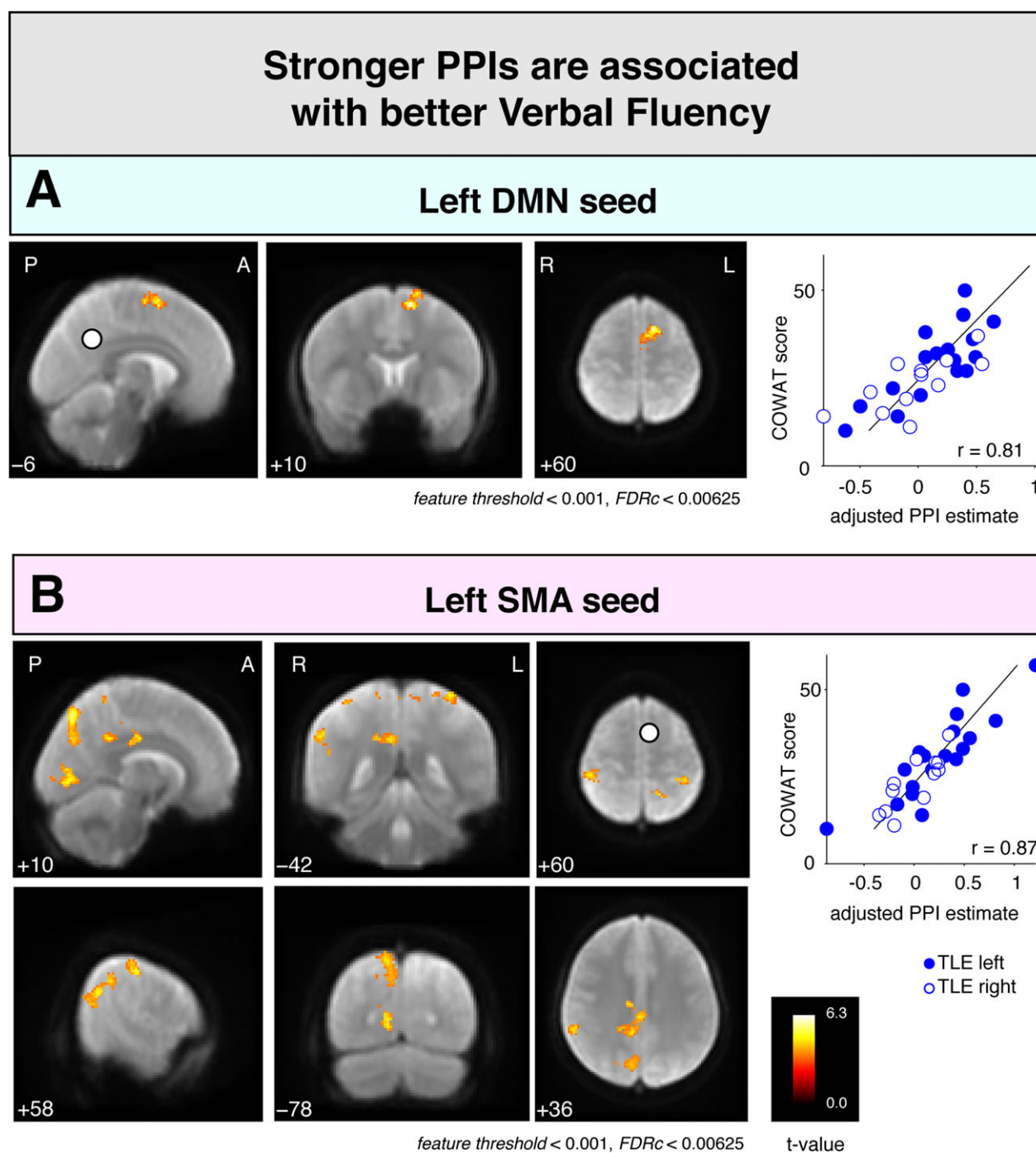


Figure 3. Regressions of COWAT against PPI estimate in TLE patients. (A) spm-t image showing single superior medial frontal cluster within which PPIs from the left DMN seed are significantly correlated with COWAT scores. Scatterplot at right plots each subjects' COWAT score against their average PPI estimate within the cluster. (B) spm-t image showing clusters within which PPIs from the left SMA seed are significantly correlated with COWAT scores. Scatterplot at right plots each subjects' COWAT score against their average (across clusters) PPI estimate (see Supplementary Information for separate scatterplots for each cluster).

positively correlated with verbal fluency ability (from left DMN to left SMA, and from left SMA to a network of areas including right occipital and parietal regions and

bilateral sensorimotor cortex). Our data speak to the importance of network dysfunction – in particular, reduced task-dependent reshaping of network interactions

Table 3. Peak coordinates, z values, neuroanatomical location and voxel extent for clusters of significant PPI-behavioural correlation.

Seed	Cluster location	XYZ	z	n voxels
Left DMN (Fig. 3A)	Superior frontal gyrus	−12,12,62	5.13	340
Left SMA (Fig. 3B)	Lateral occipital cortex	20,−68,44	4.91	654
	Posterior cingulate gyrus	6,−24,32	4.77	394
	Angular gyrus	60,−52,26	4.75	315
	Supramarginal gyrus	60,−20,44	4.26	323
	Occipital pole	16,−88,4	4.07	227
	Superior parietal lobule	−36,−42,68	4.03	397

– in the cognitive deficits observed in TLE. Furthermore, they show that this network dysfunction is present in brain regions remote from the presumed epileptogenic focus in the temporal lobe.

Reduced top-down influence on executive contributions to verbal fluency in TLE

While sometimes characterized as a language task the COWAT is multi-determined, depending upon a range of cognitive abilities including processing speed, sustained attention, working memory, lexical access, set-shifting, strategic processing, self-monitoring and inhibition.³² Letter-based verbal fluency is impaired following left frontal lesions, likely related to the strong executive demands.³³ The weaker PPIs from SMA to MFG that we observed in TLE patients could reflect reduced top-down mediated engagement of strategic processes in TLE patients.³²

Cooperation, rather than antagonism, between task-negative and task-positive regions

Better verbal fluency in TLE was associated with increased gain of the connectivity between the DMN and SMA during the task-active period. The DMN is usually considered antagonistic to, indeed was originally defined by anticorrelation with, a ‘task positive’ network (TPN) encompassing (among other areas) the superior medial frontal region.³⁴ While it may seem surprising that better cognitive performance should be associated with increased cooperation between DMN and TPN, a number of previous studies have reached similar conclusions.^{35–38} Findings such as these have led to the hypothesis that the dorsal posterior cingulate cortex (a key DMN hub) influences whole-brain network meta-stability, ‘tuning’

network interactions throughout the brain, thereby enabling rapid transitions between different neural states.²² Such dynamics have been argued to constitute the essence of the network basis of cognition.^{12,39}

An important role for superior medial frontal cortex in setting task-state

One of the most striking findings that we observed in the TLE group was the right predominant, post-central pattern of PPI-fluency correlation for the SMA seed (Fig. 3B). The vast majority of voxels (2017 of 2310) within the clusters of significant PPI-fluency correlation (Fig. 3) lay outside of the clusters of significant task-related activity (Fig. 1; partial overlap was observed in right occipital cortex [which was task-activated] and right lateral parietal cortex [which was task-deactivated]). Thus, overall PPI-behaviour correlations for the SMA seed were observed most prominently in regions that were, on average, not strongly modulated by the task per se.

The right-predominant, post-central pattern can be interpreted from the perspective of a model of brain function that posits an important role for superior medial frontal cortex (SMA) in setting overall brain state according to task demands.²⁰ The right hemisphere bias may reflect active disengagement of the non-dominant hemisphere during language task execution. Under this hypothesis, this purported ‘brain state’ setting role – effectively a dynamic reconfiguring of brain network architecture appropriate to task demands¹² – would include not just the enlistment of task appropriate regions, but also the disengagement of task-antagonistic or task-irrelevant regions. Such a role for the superior medial frontal region is also suggested by research in healthy controls and in clinical populations,⁴⁰ where lesions in this area are associated with deficits in the voluntary over-riding of automatic responses⁴¹ and, in extreme cases, a lack of spontaneous, goal directed behavior.⁴²

The between groups comparison of PPIs (Fig. 2) indicated that relative to controls the TLE group showed weaker PPIs from SMA to MFG. We did not observe a significant association between SMA-MFG PPIs and fluency in TLE patients (there is no MFG cluster in Fig 3). Together these two findings suggest that while task-related modulations of connectivity from SMA to MFG contribute grossly to fluency differences between patients and controls, they do not explain individual differences in fluency among TLE cases. These individual differences in fluency are better predicted by the degree to which SMA influences activity in non-task essential areas.

Relation to previous studies of network flexibility in epilepsy

We are aware of one other study using a verbal fluency paradigm to study task-based connectivity in TLE.¹⁰ These authors concluded that, “impaired language function may not necessarily be reflected by altered patterns or levels of cerebral activation, but may be characterized by improperly orchestrated activity in the language network”.¹⁰ Our results – using an analysis paradigm that enabled us to go a step beyond previous work and focus on task-related connectivity after first factoring out any main effects of the task itself – are consistent with this conclusion.

O’Muircheartaigh et al.⁴³ used PPI analyses to study connectivity changes during a fluency task in juvenile myoclonic epilepsy. They found significantly stronger PPIs in patients from anterior thalamus to right superior frontal cortex, attributing altered cognitive function to abnormal patterns of brain network dynamics.

Considering cognition in epilepsy more broadly, it would seem reasonable to expect that the abnormal task-related network dynamics we have observed in the setting of verbal fluency translate to other cognitive domains. Aberrant network organisation may underlie other cognitive impairments that are frequently observed in TLE, but that are difficult to reconcile with a presumed focal temporal lobe abnormality.² There is some evidence for this, in the form of abnormal network interactions in the contralesional hemisphere, in the context of working memory impairments¹⁶ and autobiographical memory impairments¹⁵ in TLE.

Causes of reduced network flexibility in TLE

What gives rise to the reduced network flexibility we have observed in our sample of TLE patients? One possibility is a remote (yet undefined) network effect propagated from the epileptic focus. This would be akin to the notion of seizure spread from the focus propagating through and affecting intrinsic large scale brain networks. To cause inter-ictal cognitive disturbance, this effect must persist through the inter-ictal period. Such network effects could be due to spread of inter-ictal discharges disrupting the normal network functioning that supports cognition,⁴⁴ peri-ictal effects such as up- or down-regulated cortical excitability, apparent in the hours to days prior to and following a seizure,⁴⁵ or secondary to network adaptations to epileptic phenomena.⁴⁶

Increased local network segregation in focal epilepsy has been observed in focal epilepsy and interpreted as an attempt to isolate the epileptic network from the rest of the brain.⁴⁶ While such re-organisation might be

protective, in the sense of minimising the propagation of epileptic activity throughout the brain, it may come at an important cost: namely, reduced network flexibility, with attendant effects on cognitive, emotional and behavioural functioning⁴⁷ (Fig. 4). Altered network organisation could also be an intrinsic property of the disease itself, as described in the recent ILAE position paper on classification of the epilepsies.⁴⁸

Medication effects might also contribute to reduced network flexibility. Cognitive and behavioural side effects of antiepileptic drugs are well documented.⁴⁹ One might expect that medication related effects would be more widespread than the effects observed here, though our use of a single cognitive paradigm may limit our ability to reveal such diffuse effects (by restricting the observable changes to those networks associated with the particular paradigm).

Moving beyond structure-function relationships of cognition in epilepsy

The basis of cognitive impairments in TLE has traditionally been studied in the framework of relatively simple structure-function correlations where impaired function is seen as a consequence of damage to the structure that supports that function.⁵⁰ More recently, with brain functions increasingly understood as engaging identifiable intrinsic ‘brain networks’, accounts of impairment based on network effects have emerged. For instance, in their review of anatomical abnormalities and cognitive disorders in TLE, Bell et al.² stated that, “substantial evidence is now available to show that cognitive impairment in TLE is a result of network disruption rather than specific damage to a certain brain structure.”

In the current study, we highlight the potential importance of disturbed dynamic network interactions as a pathophysiological basis of cognitive impairment. Our analysis of context-dependent functional connectivity suggests that changing cognitive demands are met by abnormal and limited network flexibility in our epilepsy patients. Normal cognitive performance depends on network flexibility, with changed demand being matched by changed weighting of network connections. This dynamically regulated variability in network configuration is likely to be important for optimum cognitive performance,¹² with reduced flexibility in responding to task demand leading to reduced cognitive performance.²³ This dynamic brain network account may also allow consideration of cognitive and emotional disturbances in epilepsy as problems of network malleability and adaptiveness. In other words, our findings suggest that impaired cognition may be seen as a disturbance of the brain’s capacity to dynamically reshape its network organisation in support

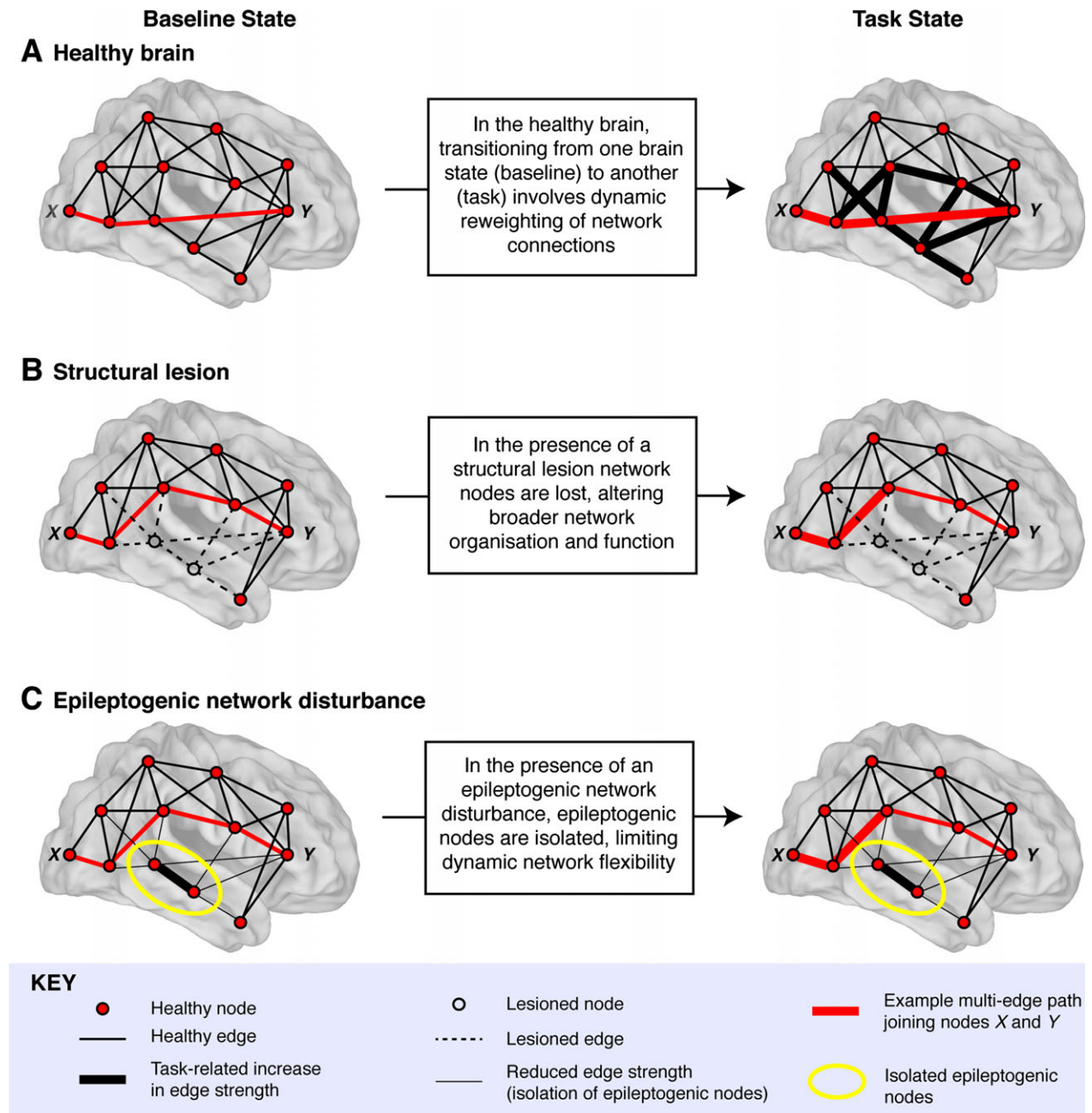


Figure 4. Caricature of potential network bases of cognitive impairment in epilepsy. Network organisation is shown during the baseline state (left column) and task-active state (right column). (A) healthy control brain. During task-active periods (right) network-specific increases in connection strength occur (thick lines). This is measured as significant increases in PPIs. (B) brain with structural epileptogenic lesion (e.g. hippocampal sclerosis). Lesioned tissue corresponds to removal of nodes from the network (with corresponding loss of function), and deletion of edges to/from the removed nodes. Such disruption of the network could affect the normal pattern of task-dependent changes in connection strength (absence of PPIs; represented by absence of thick lines in right panel of (B)). Loss of nodes could also result in lengthening of paths between distal nodes, with attendant reduction in efficiency of information exchange (e.g. minimum path length between X and Y increases from 3 to 4 edges; red edges). (C) epileptogenesis within a region of tissue (nodes enclosed by yellow border) can lead to isolation of the epileptogenic region from the remainder of the network.^{46,47} This is achieved by dampening of edges to/from the epileptogenic region. This “firewalling off” of the epileptogenic region could disrupt task-dependent changes in connection strength that normally support cognitive function (absence of thick lines in right panel of (C)), giving rise to the reduced PPIs observed here (in addition to increases in path length). These network changes could, in principle, reflect intrinsic epilepsy mechanisms and/or homeostatic mechanisms initiated as adaptive responses to epileptic activity.

of cognition, either as a result of epileptic effects on networks or as a consequence of the structural or genetic pathophysiology that gives rise to the epileptic condition.

Acknowledgements

This study was supported by the National Health and Medical Research Council (NHMRC) of Australia (program grant 628952 and project grant 1081151) and the Victorian Government Operational Infrastructure Support Program. G.D.J. is supported by an NHMRC practitioner fellowship (1060312). We thank the patients and clinicians of the Austin Hospital Comprehensive Epilepsy Programme and M. Semmelroch for assistance with coordination of participants and data processing.

Author Contributions

Concept and study design: C.T., G.D.J. Data acquisition and analysis: C.T., M.K. Drafting the manuscript and figures: C.T., G.D.J.

Conflicts of Interest

Nothing to report.

References

- Oyegbile TO, Dow C, Jones J, et al. The nature and course of neuropsychological morbidity in chronic temporal lobe epilepsy. *Neurology* 2004;62:1736–1742.
- Bell B, Lin JJ, Seidenberg M, Hermann B. The neurobiology of cognitive disorders in temporal lobe epilepsy. *Nat Rev Neurol* 2011;7:154–164.
- Hermann BP, Seidenberg M, Schoenfeld J, Davies K. Neuropsychological characteristics of the syndrome of mesial temporal lobe epilepsy. *Arch Neurol* 1997;54:369–376.
- Saling MM. Verbal memory in mesial temporal lobe epilepsy: beyond material specificity. *Brain* 2009;132(3):570–582. awp012.
- Keller SS, Roberts N. Voxel-based morphometry of temporal lobe epilepsy: an introduction and review of the literature. *Epilepsia* 2008;49:741–757.
- Vaughan DN, Raffelt D, Curwood E, et al. Tract-specific atrophy in focal epilepsy: disease, genetics or seizures? *Ann Neurol* 2016. Available from: <http://onlinelibrary.wiley.com/doi/10.1002/ana.24848/full>. [Last accessed 2017 Jan 10]
- Briellmann RS, Jackson GD, Kalnins R, Berkovic SF. Hemispheric volume deficits in patients with temporal lobe epilepsy with and without hippocampal sclerosis. *Epilepsia* 1998;39:1174–1181.
- Bonilha L, Nesland T, Martz GU, et al. Medial temporal lobe epilepsy is associated with neuronal fibre loss and paradoxical increase in structural connectivity of limbic structures. *J Neurol Neurosurg Psychiatry* 2012;83(9):903–909. jnnp-2012.
- Vlooswijk MC, Jansen JF, Jeukens CR, et al. Memory processes and prefrontal network dysfunction in cryptogenic epilepsy. *Epilepsia* 2011;52:1467–1475.
- Vlooswijk MCG, Jansen JFA, Majoie HJM, et al. Functional connectivity and language impairment in cryptogenic localization-related epilepsy. *Neurology* 2010;75:395–402.
- Waites AB, Briellmann RS, Saling MM, et al. Functional connectivity networks are disrupted in left temporal lobe epilepsy. *Ann Neurol* 2006;59:335–343.
- Park H-J, Friston K. Structural and functional brain networks: from connections to cognition. *Science* 2013;342:1238411.
- Zhang Z, Lu G, Zhong Y, et al. Impaired attention network in temporal lobe epilepsy: a resting fMRI study. *Neurosci Lett* 2009;458:97–101.
- Vaughan DN, Rayner G, Tailby C, Jackson GD. MRI-negative temporal lobe epilepsy a network disorder of neocortical connectivity. *Neurology* 2016;87:1934–1942.
- Addis DR, Moscovitch M, McAndrews MP. Consequences of hippocampal damage across the autobiographical memory network in left temporal lobe epilepsy. *Brain* 2007;130:2327–2342.
- Campo P, Garrido MI, Moran RJ, et al. Network reconfiguration and working memory impairment in mesial temporal lobe epilepsy. *NeuroImage* 2013;72:48–54.
- Doucet GE, He X, Sperling MR, et al. From “rest” to language task: task activation selects and prunes from broader resting-state network. *Hum Brain Mapp* 2017;38:2540–2552.
- Friston KJ, Buechel C, Fink GR, et al. Psychophysiological and modulatory interactions in neuroimaging. *NeuroImage* 1997;6:218–229.
- McLaren DG, Ries ML, Xu G, Johnson SC. A generalized form of context-dependent psychophysiological interactions (gPPI): a comparison to standard approaches. *NeuroImage* 2012;61:1277–1286.
- Dosenbach NUF, Visscher KM, Palmer ED, et al. A core system for the implementation of task sets. *Neuron* 2006;50:799–812.
- Tang Y-Y, Rothbart MK, Posner MI. Neural correlates of establishing, maintaining, and switching brain states. *Trends Cogn Sci* 2012;16:330–337.
- Leech R, Sharp DJ. The role of the posterior cingulate cortex in cognition and disease. *Brain* 2014;137:12–32.
- Stam CJ. Epilepsy: what can we learn from modern network theories? *Epileptologie* 2016;33:38–43.
- Benton LA, Hamsher KD, Sivan AB. Controlled oral word association test. AJA Associates, Iowa City: Multiling Aphasia Exam, 1994.

25. Tailby C, Weintrob DL, Saling MM, et al. Reading difficulty is associated with failure to lateralize temporooccipital function. *Epilepsia* 2014;55:746–753.
26. Smith SM. Fast robust automated brain extraction. *Hum Brain Mapp* 2002;17:143–155.
27. Borkowski JG, Benton AL, Spreen O. Word fluency and brain damage. *Neuropsychologia* 1967;5:135–140.
28. Harding IH, Corben LA, Storey E, et al. Fronto-cerebellar dysfunction and dysconnectivity underlying cognition in friedreich ataxia: the IMAGE-FRDA study. *Hum Brain Mapp* 2016;37:338–350.
29. Canli T, Qiu M, Omura K, et al. Neural correlates of epigenesis. *Proc Natl Acad Sci* 2006;103:16033–16038.
30. Hare TA, Camerer CF, Knoepfle DT, et al. Value computations in ventral medial prefrontal cortex during charitable decision making incorporate input from regions involved in social cognition. *J Neurosci* 2010;30:583–590.
31. Humbert IA, McLaren DG. Differential psychophysiological interactions of insular subdivisions during varied oropharyngeal swallowing tasks. *Physiol Rep* 2014;2:e00239.
32. Wood AG, Saling MM, Abbott DF, Jackson GD. A neurocognitive account of frontal lobe involvement in orthographic lexical retrieval: an fMRI study. *NeuroImage* 2001;14:162–169.
33. Baldo JV, Shimamura AP, Delis DC, et al. Verbal and design fluency in patients with frontal lobe lesions. *J Int Neuropsychol Soc* 2001;7:586–596.
34. Fox MD, Snyder AZ, Vincent JL, et al. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proc Natl Acad Sci USA* 2005;102:9673–9678.
35. Hearne L, Cocchi L, Zalesky A, Mattingley JB. Interactions between default mode and control networks as a function of increasing cognitive reasoning complexity. *Hum Brain Mapp* 2015;36:2719–2731.
36. Fornito A, Harrison BJ, Zalesky A, Simons JS. Competitive and cooperative dynamics of large-scale brain functional networks supporting recollection. *Proc Natl Acad Sci* 2012;109:12788–12793.
37. Leech R, Kamourieh S, Beckmann CF, Sharp DJ. Fractionating the default mode network: distinct contributions of the ventral and dorsal posterior cingulate cortex to cognitive control. *J Neurosci* 2011;31:3217–3224.
38. Leech R, Braga R, Sharp DJ. Echoes of the brain within the posterior cingulate cortex. *J Neurosci* 2012;32:215–222.
39. Deco G, Jirsa VK, McIntosh AR. Emerging concepts for the dynamical organization of resting-state activity in the brain. *Nat Rev Neurosci* 2011;12:43–56.
40. Nachev P, Kennard C, Husain M. Functional role of the supplementary and pre-supplementary motor areas. *Nat Rev Neurosci* 2008;9:856–869.
41. Stuss DT, Floden D, Alexander MP, et al. Stroop performance in focal lesion patients: dissociation of processes and frontal lobe lesion location. *Neuropsychologia* 2001;39:771–786.
42. Bogousslavsky J, Regli F. Anterior cerebral artery territory infarction in the Lausanne Stroke Registry: clinical and etiologic patterns. *Arch Neurol* 1990;47:144–150.
43. O'Muircheartaigh J, Vollmar C, Barker GJ, et al. Abnormal thalamocortical structural and functional connectivity in juvenile myoclonic epilepsy. *Brain* 2012;135:3635–3644.
44. Trenité DK-N, Riemersma JBJ, Binnie CD, et al. The influence of subclinical epileptiform EEG discharges on driving behaviour. *Electroencephalogr Clin Neurophysiol* 1987;67:167–170.
45. Badawy R, Macdonell R, Jackson G, Berkovic S. The perictal state: cortical excitability changes within 24 h of a seizure. *Brain* 2009;132:1013–1021.
46. Pedersen M, Omidvarnia AH, Walz JM, Jackson GD. Increased segregation of brain networks in focal epilepsy: an fMRI graph theory finding. *Neuroimage Clin* 2015;8:536–542.
47. Rayner G, Tailby C. Current concepts of memory disorder in epilepsy: edging towards a network account. *Curr Neurol Neurosci Rep* 2017;17:1–9.
48. Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: position paper of the ILAE commission for classification and terminology. *Epilepsia* 2017;58:512–521.
49. Ortinski P, Meador KJ. Cognitive side effects of antiepileptic drugs. *Epilepsy Behav* 2004;5:60–65.
50. Scoville WB, Milner B. Loss of recent memory after bilateral hippocampal lesions. *J Neurol Neurosurg Psychiatry* 1957;20:11–21.