Temporal Lobe Interictal Epileptic Discharges Affect Cerebral Activity in Default Mode Brain Regions

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A cerebral network comprising precuneus, medial frontal, and temporoparietal cortices is less active both during goal-directed behavior and states of reduced consciousness than during conscious rest. We tested the hypothesis that the interictal epileptic discharges affect activity in these brain regions in patients with temporal lobe epilepsy who have complex partial seizures. At the group level, using electroencephalography-correlated functional magnetic resonance imaging in 19 consecutive patients with focal epilepsy, we found common decreases of resting state activity in 9 patients with temporal lobe epilepsy (TLE) but not in 10 patients with extra-TLE. We infer that the functional consequences of TLE interictal epileptic discharges are different from those in ... 61(di(AfF3)0(nt)-268.180(of)-283.6)-43ting

et al., 1997). This network expresses strong functional connectivity at rest (Greicius et al., 2003; Laufs et al., 2003) and has higher overall activity during resting wakefulness than in states of impaired consciousness such as sleep, anaesthesia, and coma (Laureys et al., 2004) or during generalized spike and wave discharges (GSW) (Archer et al., 2003; Gotman et al., 2005; Hamandi et al., 2006; Laufs et al., 2006). Activity in these regions also decreases during a wide range

Fz (ground) and Pz as the reference (10…20 system), and bipolar electrocardiogram (Krakow et al., 2000). Seven hundred and four T_2*-weighted single-shot gradient-echo echo-planar images (EPI; TE/TR: 40/3000, ”ip angle: 90°, 21 5 mm interleaved slices, FOV $= 24 \times 24$ cm^2, 64^2 matrix) were acquired continuously over 35 min on a 1.5 Tesla Horizon EchoSpeed MRI scanner (General Electric, Milwaukee, WI). Patients were asked to rest with their eyes shut and to keep their head still. After gradient and pulse artifact reduction (Allen et al., 1998, 2000), IED were individually identi“ed and the fMRI data were preprocessed and analyzed using SPM2 (http://www.“l.ion.ucl.ac.uk/spm/). After discarding the “rst four image volumes, the EPI time series were realigned, normalized (MNI305 space, SPM2) and the images spatially smoothed with a cubic Gaussian Kernel of 8 mm full width at half maximum.

Statistical Parametric Mapping

IED onsets were used to build a linear model of the effects of interest by convolution with a canonical hemodynamic response function (HRF, event-related design) and its temporal derivative to account for possible variations in the blood oxygen level-dependent (BOLD) response delay. Motion realignment parameters were modelled as a confound (Friston et al., 1996).

A single T-contrast image was generated per subject from the “rst (single-subject) level and the images used to inform a second level (group effect) analysis to test for any common patterns. Analyses were performed for both TLE and extra-TLE groups. A random effects model was used to identify any typical responses consistent across the patients (Friston

Figure 1.

Random effects group analysis blood oxygen level-dependent signal decreases in temporal lobe epilepsy with focal interictal epileptic discharges (IED) in comparison with classic ••default mode•• brain regions. A: Brain areas where blood oxygen level-dependent signal is signi“cantly negatively correlated with IED are projected onto axial slices Z (coordinates given below each slice) of a template average brain. B:

mon activations across this group of patients and found signi“cant positive IED-related BOLD signal changes in the left anterior medial temporal lobe (Fig. 2, Table III). The same analysis for the heterogeneous group of patients with extra-TLE showed common activations in the left subthalamic nucleus, superior temporal gyrus bilaterally, right middle temporal gyrus, medial frontal gyrus bilaterally, anterior cingulate, and the right postcentral gyrus (Fig. 3, Table III).

Complex Versus Simple Partial Seizures

Activity in default-mode brain regions is correlated with consciousness (Laureys et al., 2004) and so we looked at the differences in habitual seizure-types between these groups. We found that simple partial seizures (SPS) were more frequent in the patients with extra-TLE (5/10 patients) and were the single focal seizure type in three of them. Only 3 of 9 patients with TLE had SPS, and these always occurred in addition to complex partial seizures (CPS).

Aetiology

Apart from localization, etiology was assessed as a possible explanatory variable accounting for the differing BOLD response patterns. We found hippocampal sclerosis to be the prevalent pathology in the TLE group (5 of 9 patients), while malformations of cortical development (MCD) were the prominent pathology in the extra-TLE group (5 of the 10 patients, Table I).

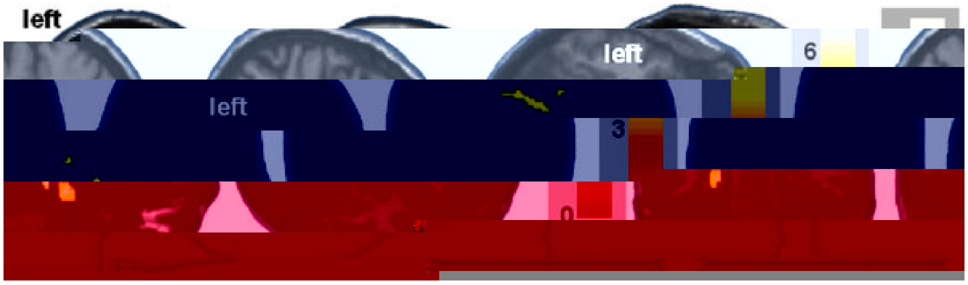

Figure 2.

DISCUSSION

Principal Findings

In patients with TLE, IED were associated with signi“cant deactivation in default mode brain areas and with signi“cant activation in the ipsilateral medial temporal lobe. In the patients with extra-TLE no signi“cant deactivations were found, and there were activations in the subthalamic nucleus, the superior aspects of both temporal and medial frontal lobes. The “ndings indicate that deactivations in default mode brain regions are characteristic of IED in TLE while not seen in extra-TLE, and that different common activation patterns were seen in the two groups.

Methodological Considerations

EEG-fMRI can be used to investigate the electrical and hemodynamic aspects of brain activity changes during task-free rest such as those associated with individual IED. To facilitate intersubject comparison we restricted our analyses to experiments with 1…20 IED per minute. This enabled us to make valid inferences at the group level using a two-stage procedure but restricted the group size to 19 patients (Friston et al., 2005).

Violations of homoscedasticity implicit in the loss of balance at the “rst level can make the second level inference less ef“cient, but would not bias or invalidate it. A full mixed-effect analysis could improve the power of the inference but this is not necessary because we already have signi“cant results using the more conservative summary-statistic approach (Penny and Holmes, 2006).

The distributed and distinct areas of the brain involved in default mode activity were originally identi“ed by positron emission tomography and fMRI meta analyses that included studies with block designs (Gusnard and Raichle, 2001). Stimulus-correlated motion and circulation or respiration effects are thus unlikely to cause the observed signal changes. Nevertheless we took the precaution of modelling realignment parameters re”ecting motion as a potential confound. Likewise, the signal changes observed during resting state brain activity do not originate from the aliasing of physiological noise (De Luca et al., 2006).

A group analysis emphasizes features common to all group members while supressing the individual variability at the same time. Such an approach will be less sensitive to

IED-correlated BOLD signal changes re”ecting potentially different irritative zones but will rather indicate common pathways of IED propagation or their associated effects on ongoing brain function, that fail to reach statistical signi“cance at the single subject level. A group analysis will therefore highlight common features (••typical effects••) for a group of patients investigated.

Previous Work

Deactivations in relation to IED were found in default mode brain areas in 10 of a series of 60 analyzed scanning sessions, mostly associated with bilateral or generalised bursts of spikes (Kobayashi et al., 2006). IED localization however was not further speci“ed nor a group analysis performed. Meanwhile, the same group has recently also found ipsilateral medial temporal activation in a group of patients with temporal lobe IED (Grova et al., 2006).

Using Single Photon Emission Computed Tomography (SPECT), Van Paesschen and coworkers described signi“cant ictal hypoperfusion in the superior frontal gyrus and the precuneus in 90% of TLE patients with complex partial seizures studied, plus hypoperfusion in temporal, occipital, and cerebellar regions (Van Paesschen et al., 2003). Blumenfeld et al., using EEG-SPECT found that temporal lobe seizure-related loss of consciousness was associated with bilateral decreases in cerebral blood ”ow in the frontal and parietal association cortex and retrosplenium. In contrast, however, when consciousness was preserved, such widespread changes were not seen (Blumenfeld et al., 2004). The distribution of these ictal perfusion decreases is consistent with our interictal “ndings in those with TLE who mainly had CPS. Although failure to detect deactivations in default mode brain areas in those with extra-TLE does not translate to their absence, it does suggest that IED do not in”uence brain function in this network to the degree IED do in TLE.

IED Propagation Affects Default Mode Network in TLE

In TLE, epileptic activity may spread from the temporal lobe into one or more functionally interconnected default mode brain regions and the effect of propagated activity can be measured by fMRI. Epileptic networks can lead to widespread secondary inhibition of nonseizing cortical regions via subcortical structures (Norden and Blumenfeld, 2002). It has previously been reported that„even very short (Laufs et al., 2006)„GSW were associated with deactivations in default mode brain regions (Gotman et al., 2005; Hamandi et al., 2006; Laufs et al., 2006; Salek-Haddadi et al., 2003b).

Alarcon and colleagues proposed that in TLE a lesion may affect remote, functionally coupled normal brain regions and that IED may originate from separate regions, resulting in propagation to and recruitment of other neuronal assemblies (Alarcon et al., 1997). Indeed Ebersole and colleagues suggested that scalp EEG changes in TLE principally re”ect propagated epileptic activity (Pacia and Ebersole, 1997). The current study supports the notion that temporal lobe IED affect an epileptic network rather than a circumscribed focus. Further, it may be inferred that the medial anterior temporal lobe structures are a crucial part of such a network in this group of patients with TLE, who had a variety of underlying pathologies at varying locations within the temporal lobe.

The (left) Temporal Lobe and the Default Mode Brain Network

Functional connectivity studies have identi“ed the temporal lobe (Fox et al., 2005; Fransson, 2005), and more speci“cally the hippocampus (Greicius and Menon, 2004), as another part of the default mode network. Activity changes in the default mode network could thus be a consequence

(Wang et al., 2006)„the result of disturbed functional connectivity between the hippocampus and other default mode regions. In patients with left TLE, Waites and colleagues have recently demonstrated that functional connectivity in the ••language network•• was disturbed (Waites et al., 2006). As our subjects all had left-biased IED, we could not investigate laterality in”uences on default mode activity. This would be interesting especially since verb generation tasks, for example, lead to left-lateralized temporal lobe activations (Rowan et al., 2004) and classically deactivate default mode brain regions (Burton et al., 2004).

Our “ndings do not address the issue of causality, but indicate a correlation between IED in TLE and default mode network ”uctuations. A hypothetical alternative explanation is that alteration of the default mode (e.g. by an external cause) facilitates IED. In the case of GSW, a link with sleep spindles and arousal has already been demonstrated (Steriade, 2005).

An Analogy between the Thalamus in GSW and the Hippocampus in TLE

The hippocampus plays a central role in propagation of epileptic activity in TLE, and hippocampal sclerosis often accompanies different pathologies in the temporal lobe (Duncan and Sagar, 1987; Thom et al., 2005). An analogy could be drawn between the role of the thalamus in the propagation of GSW and the role of the hippocampus in the propagation of IED in TLE, with both resulting in antidromic deactivation of default mode brain regions.

Similarly, the activations seen in association with IED in the extra-TLE group suggest a different ••propagation network•• consisting of subthalamic nuclei, superior temporal lobe and medial frontal structures (Figure 3, Table III). This group however was more heterogeneous and this possibility remains speculative until a higher number and more de“ned groups of epilepsy syndromes have been studied.

Lack of Default Mode Deactivation in Extratemporal Lobe Epilepsy

Possible reasons for the lack of deactivations associated with IED in extra-TLE need consideration. These include a lack of sensitivity and the failure of scalp EEG to detect deep IED. Extratemporal IED propagation to the default mode network might not occur so readily and so may not have distant effects: Blume at al. showed that interictal activity in extra-TLE mainly remains within the lobe of origin (Blume et al., 2001).

As much as propagation of IED might depend on the lobe

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