Positive and Negative Network Correlations in Temporal Lobe Epilepsy

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Temporal lobe seizures are accompanied by complex behavioral phenomena including loss of consciousness, dystonic movements and neuroendocrine changes. These phenomena may arise from extended neural networks beyond the temporal lobe. To investigate this, we imaged cerebral blood flow (CBF) changes during human temporal lobe seizures with single photon emission computed tomography (SPECT) while performing continuous video/EEG monitoring. We found that temporal lobe seizures associated with loss of consciousness produced CBF increases in the temporal lobe, followed by increases in bilateral midline subcortical structures. These changes were accompanied by marked bilateral CBF decreases in the frontal and parietal association cortex. In contrast, temporal lobe seizures in which consciousness was spared were not accompanied by these widespread CBF changes. The CBF decreases in frontal and parietal association cortex were strongly correlated with increases in midline structures such as the mediodorsal thalamus. These results suggest that impaired consciousness in temporal lobe seizures may result from focal abnormal activity in temporal and subcortical networks linked to widespread impaired function of the association cortex.

Keywords: brainstem, consciousness, hypothalamus, seizures, single photon emission computed tomography (SPECT), thalamus

Introduction

The brain contains multiple reciprocal excitatory and inhibitory interconnections both on the scale of local microcircuits, and on the scale of long range network interactions. These same networks, so crucial for normal information processing, may also convey abnormal signals in disorders such as epilepsy. Temporal lobe seizures arising from mesial temporal sclerosis are an important and common form of epilepsy, accounting for the largest group of medically refractory patients treated surgically (Engel, 1987; Williamson *et al.*, 1993). Striking behavioral changes accompany temporal lobe seizures. These include amnesia for the event, automaton-like movements referred to by Penfield as 'automatisms', dystonic posturing of the limbs (Marks and Laxer, 1998), neuroendocrine changes (Bauer, 2001; Quigg *et al.*, 2002), and loss of consciousness. The diverse behavioral repertoire of temporal lobe seizures, and prior human and animal investigations, suggest that more widespread neural networks are recruited during these events (Newton *et al.*, 1992; Cassidy and Gale, 1998; Shin *et al.*, 2001; Lee *et al.*, 2002; Norden and Blumenfeld, 2002; Zhang and Bertram, 2002). However, the relationship between widespread network involvement and impaired consciousness has not been thoroughly investigated.

Temporal lobe seizures typically begin with more focal phenomena such as fear, rising epigastric sensation, indescribable premonitions, or lip smacking automatisms (Park *et al.*, 2001; Janszky *et al.*, 2003). Seizures that terminate without impaired consciousness are classified as simple partial, while those that impair consciousness are classified as complex partial. Impaired consciousness in complex partial seizures is usually most profound late in the seizure and persists for up to several minutes after the end of the seizure, during the postictal period. Is this impaired consciousness related to spread of abnormal activity to networks beyond the temporal lobe?

To address this question, we sought to image temporal lobe seizures in a well defined group of patients with surgically confirmed mesial temporal sclerosis. Cerebral blood flow (CBF) imaging is only indirectly related to neuronal activity, but has been validated, based on comparison to electrophysiological studies, as a method for localizing seizure activity in humans (Spanaki *et al.*, 1999). We used single photon emission computed tomography (SPECT) ictal–interictal imaging because of its unique capacity to take a 'snapshot' of CBF during human seizures. The SPECT radioisotope, injected during a seizure, is rapidly taken up by the brain and does not redistribute (Andersen, 1989). Imaging can then be carried out 60–90 min later, eliminating serious problems with movement artifact and the patient's clinical stability. Other imaging modalities (e.g. fMRI or O-15 PET) would require the actual imaging to be performed *during* seizures, not feasible in temporal lobe epilepsy. SPECT analysis has been greatly facilitated in recent years by difference methods, comparing ictal scans to baseline interictal images in the same patient (Zubal *et al.*, 1995; O'Brien *et al.*, 1998; Spanaki *et al.*, 1999; Chang *et al.*, 2002), and by statistical parametric mapping (SPM), facilitating quantitative analysis of changes in groups of patients (Lee *et al.*, 2000; Chang *et al.*, 2002; Blumenfeld *et al.*, 2003).

Using this approach, we found widespread bilateral cortical and subcortical CBF increases and decreases during, and immediately following complex partial seizures. In contrast, simple partial seizures caused much more limited regions of involve-

ment primarily confined to the temporal lobe. Correlation analyses demonstrated a strong relationship between CBF increases in the upper brainstem and medial thalamus and CBF decreases in higher order association cortex. This suggests that long range network effects may play an important functional role in temporal lobe seizures.

Materials and Methods

Patients

All procedures were in accordance with Yale Human Investigations Committee and NIH guidelines. Informed consent was obtained from all subjects. Inclusion and exclusion criteria were chosen to identify a relatively homogeneous group of patients with surgically proven mesial temporal lobe epilepsy for SPECT analysis. Consecutive patients with the following inclusion criteria were used: ictal SPECT performed during video and scalp EEG monitoring; interictal SPECT performed at least 24 h after the most recent seizure; verbal questions or commands were addressed to patient during the seizure and recorded on video; combination of tests supporting left or right mesial temporal lobe seizure onset (MRI, FGD-PET, neuropsychology testing, angiogram Wada test, scalp EEG, intracranial EEG); surgical pathology demonstrating hippocampal sclerosis; and successful surgery with no seizures during a minimum follow-up period of 1 year following antero-medial temporal lobe resection. Exclusion criteria were as follows: significant anatomical lesion outside the temporal lobe; previous intracranial surgery; inadequate (less than 1 year) follow-up; seizures which secondarily generalized; or SPECT images acquired during intracranial EEG monitoring (Studholme *et al.*, 2001). A total of 24 ictal–interictal image pairs from 21 patients were included in the study, nine males, 12 females with mean age at the time of SPECT imaging of 35 years (range 15–57 years).

Videotape and EEG Review

Videotape and EEG of seizures for all SPECT injections were reviewed by two readers, blinded to the results of the imaging studies. Seizure onset time was defined as the earliest, and seizure end time was defined as the latest EEG or clinical evidence of seizure activity. SPECT injection time was defined as when the syringe plunger was fully depressed. The readers also rated patients' behavior during seizures for evidence of impaired responsiveness, using a simple two-level classification, modified from Lee *et al.* (2002). Seizures in which patients had impaired responsiveness to verbal questions or commands or amnesia were classified as complex partial. Seizures in which patients remained fully alert and interactive throughout were classified as simple partial. All patients included in the study were presented with questions or commands during seizures by either medical staff or family members. EEG localization and frequency patterns were read by consensus of the two reviewers.

Image Acquisition

Ictal SPECT injections were performed during continuous scalp EEG and video recordings. Upon noting seizure onset, a technologist performed an intravenous injection of Tc-99m labeled hexamethylpropylene-amine-oxime (HMPAO) (Medi-Physics, Amersham Healthcare, Arlington Heights, IL). Patients were asked to close their eyes during the injection. Interictal injections were performed in these same patients after at least 24 h of no seizure activity, in a quiet room, while patients were at rest, awake, but with their eyes closed.

SPECT images were acquired within 90 min after injection. Projection data were acquired on a Picker PRISM 3000 (Philips Medical Systems, Best, Netherlands) and transverse slices were reconstructed as described previously (Zubal *et al.*, 1995; Chang *et al.*, 2002). SPECT image data were transferred to personal computer with Linux operating system (Red Hat Software, Inc. Raleigh, NC), and saved in Analyze format using MedX (Sensor Systems, Inc. Sterling, VA).

Image Analysis

Images were analyzed using statistical parametric mapping (SPM99, Wellcome Department of Cognitive Neurology, London, UK http://www.fil.ion.ucl.ac.uk/spm/) on a MATLAB 6.5 (The MathWorks, Inc. Natick, MA) platform, as described previously (Chang *et al.*, 2002; Blumenfeld *et al.*, 2003). Prior to analysis, images from patients with right temporal onset seizures were flipped right to left to enable group analysis of ipsilateral and contralateral changes. Images were realigned, spatially normalized and smoothed using a Gaussian kernel ($16 \times 16 \times 16$ mm). Global intensity normalization to correct for differences in total brain counts between ictal and interictal scans was performed using proportional scaling with an analysis threshold of 0.8 (Friston *et al.*, 1996; Acton and Friston, 1998). A paired *t*-test model was then used in SPM to compare the ictal versus interictal images for groups of patients. Intergroup comparisons were also made among the different subgroups studied with the multi-group conditions and covariates model in SPM. The extent threshold (k) below which clusters were rejected was 125 voxels. This is equivalent to a volume of 1 cc (with SPM voxel dimensions of $2 \times 2 \times 2$ mm). Individual voxel-level significance threshold p was 0.01, corresponding to a Z score of 2.33. Clusters of voxels showing changes were then identified at a significance level $P = 0.05$, after correction for multiple comparisons for the entire brain.

Volumetric Analysis of SPECT Changes in Individual Patients

To enable inter-region correlation analyses, we first performed a volumetric analysis of mean per cent ictal–interictal changes in anatomically defined cortical and subcortical brain regions. The SPM MRI template Colin27 (see http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html and ftp://ftp.mrc-cbu.cam.ac.uk/pub/imaging/Colin/) was manually segmented into 15 anatomical regions on each side of the brain using a three-dimensional multi-modal image registration viewer written by C.S. (http://rview.colin-studholme.net/): frontal association cortex, perirolandic cortex, parietal cortex, mesial temporal cortex, lateral temporal cortex, occipital cortex, basal ganglia, medial thalamus, lateral thalamus, hypothalamus, midbrain–diencephalic junction and pretectal areas ('subthalamus'), midbrain tegmentum, midbrain substantia nigra, pontine tegmentum, and cerebellum (see Supplementary Data online for details). Although the insular cortex has important limbic and multimodal connections, we did not include it in this analysis because insular cortex is not clearly demarcated from frontal and parietal operculum on SPECT imaging. We next calculated the per cent changes between interictal and ictal SPECT for each volumetric region in each individual patient by taking the mean of [(ictal – interictal)/interictal] × 100% for all voxels in each region. Spatial normalization of SPECT images to the MRI template, and global intensity normalization of ictal and interictal images was as described above for the SPM analysis.

Correlation Analyses

Statistical analysis of the per cent changes in the identified volumes was performed using SPSS 11.5 (SPSS Inc., Chicago, IL). We first calculated Pearson correlation coefficients between all possible combinations of cortical and subcortical regions on the side ipsilateral to seizure onset. Principal components analysis was next used to identify groupings of related variables. Three components were identified based on concordance of both the Cattell scree test and the Kaiser rule, retaining only components with eigenvalues > 1.0 without rotations (Tabachnick and Fidell, 1989).

To analyze the partial correlation between medial thalamic changes and changes in all other brain regions, we performed an SPM analysis using the multi-subject, conditions and variates model, entering the ictal–interictal per cent change in the medial thalamus ipsilateral to seizure onset as the covariate. For this analysis, we again used an extent threshold $k = 125$ voxels, voxel-level significance threshold $P = 0.01$, followed by a cluster-level significance level $P = 0.05$ corrected for multiple comparisons for the entire brain.

Results

Complex Partial Seizures

We analyzed SPECT images from groups of patients with complex partial seizures during two time epochs, at 60–90 s

after seizure onset, or >90 s after seizure onset (Figs 1–3). Seizure onset time was used to define patient groups because onset can usually be determined more precisely based on EEG and behavior than seizure end. An injection time of 90 s was chosen as the cut-off because this was approximately equal to mean seizure duration. For the 60–90 s group (n = 8), and >90 s group (n = 10), respectively, the mean seizure durations were 94 ± 17.7 s (mean ± SEM), and 91 ± 12.8 s; mean injection times after seizure onset were 73 ± 8.9 s, and 130 + 10.1 s. Thus, the 60–90 s group consists of patients injected ~30 s before the end of the seizure (28 ± 21.4 s), representing the late ictal period, while the >90 s group consists of patients injected ~40 s after seizure termination (40 ± 13.4 s), representing the early post-ictal period.

In the 60–90 s group, EEG during the seizures in which the SPECT scans were performed showed unilateral rhythmic theta frequency slowing over the temporal lobe on the side of seizure onset in all eight patients. In the >90 s group, EEG during seizures showed unilateral rhythmic theta frequency slowing over the temporal lobe on the side of seizure onset in six patients, bilateral theta frequency slowing over the fronto-temporal regions in one patient, mild diffuse slowing in two patients, and no EEG changes aside from movement artifact in one patient. Of note, secondary generalization did not occur in any of the patients included in the study. Behavior during seizures consisted of sitting in bed with bland staring, unresponsiveness to verbal commands and/or amnesia for the event, with some patients also exhibiting oral automatisms, unilateral arm dystonia, or unilateral low amplitude arm movements (manual automatisms). No patients exhibited clonic or tonic motor activity.

Complex partial seizures were associated with functional imaging changes in widespread cortical and subcortical networks (Fig. 1). In the 60–90 s group, the most significant

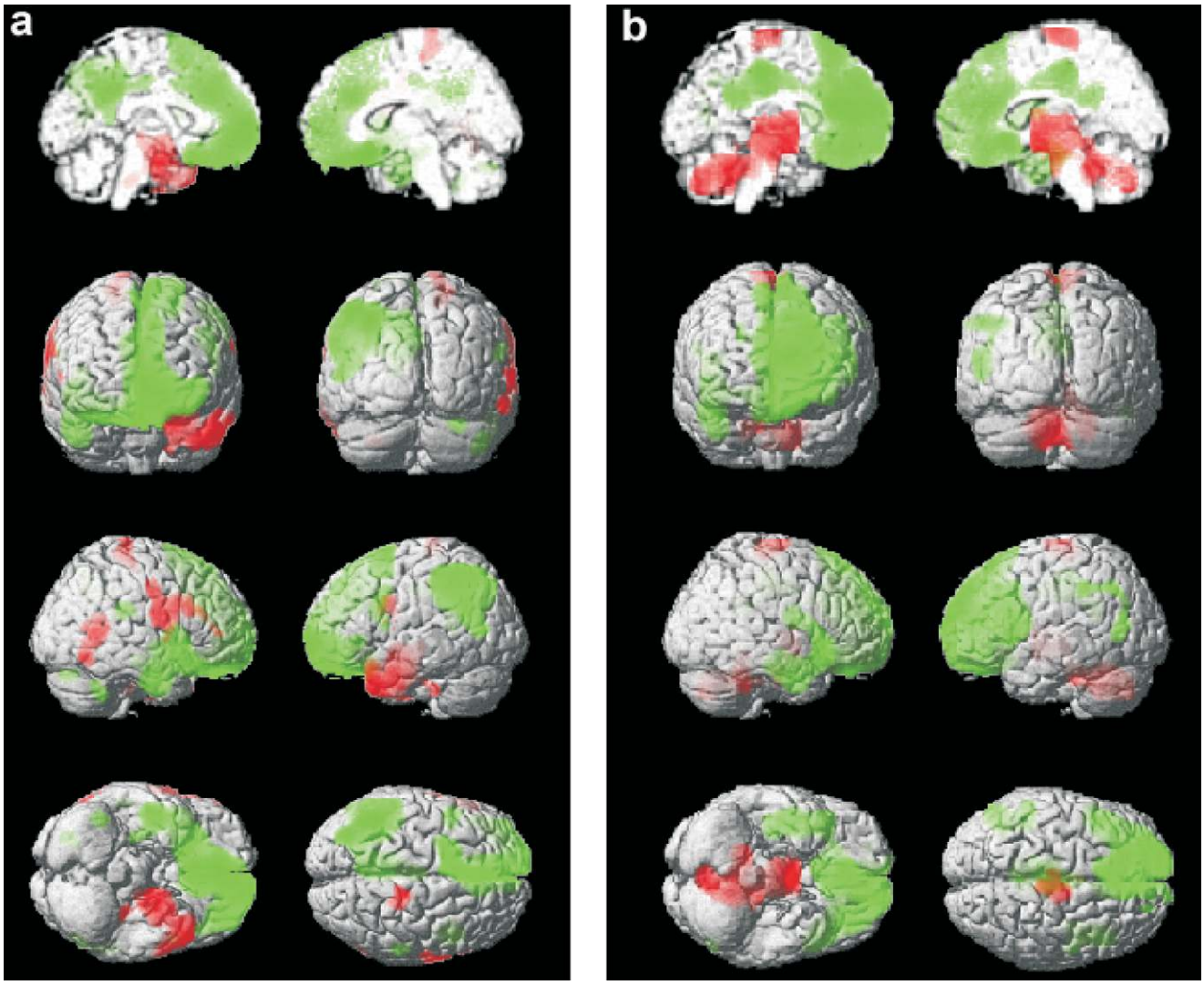

Figure 1. Complex partial seizures arising from the temporal lobe are associated with significant CBF increases and decreases in widespread brain regions. Statistical parametric maps depict CBF increases in red and decreases in green. Changes ipsilateral to seizure onset are shown on the left side of the brain, and contralateral changes on the right side of the brain (combining patients with left and right onset seizures). (*a*) 60–90 s after seizure onset, increases occur mainly in the ipsilateral temporal lobe, while decreases occur in the ipsilateral > contralateral frontal and parietal association cortex (n = 8). (*b*) >90 s after seizure onset, increases occur mainly in the bilateral medial diencephalon, upper brainstem and medial cerebellum, while decreases occur in the ipsilateral > contralateral frontal and parietal association cortex (n = 10). For (*a*) and (*b*), extent threshold, k = 125 voxels (voxel size = 2 × 2 × 2 mm). Height threshold, P = 0.01. Equivalently, only voxel clusters greater than 1 cm^3 in volume and with Z scores greater than 2.33 are displayed.

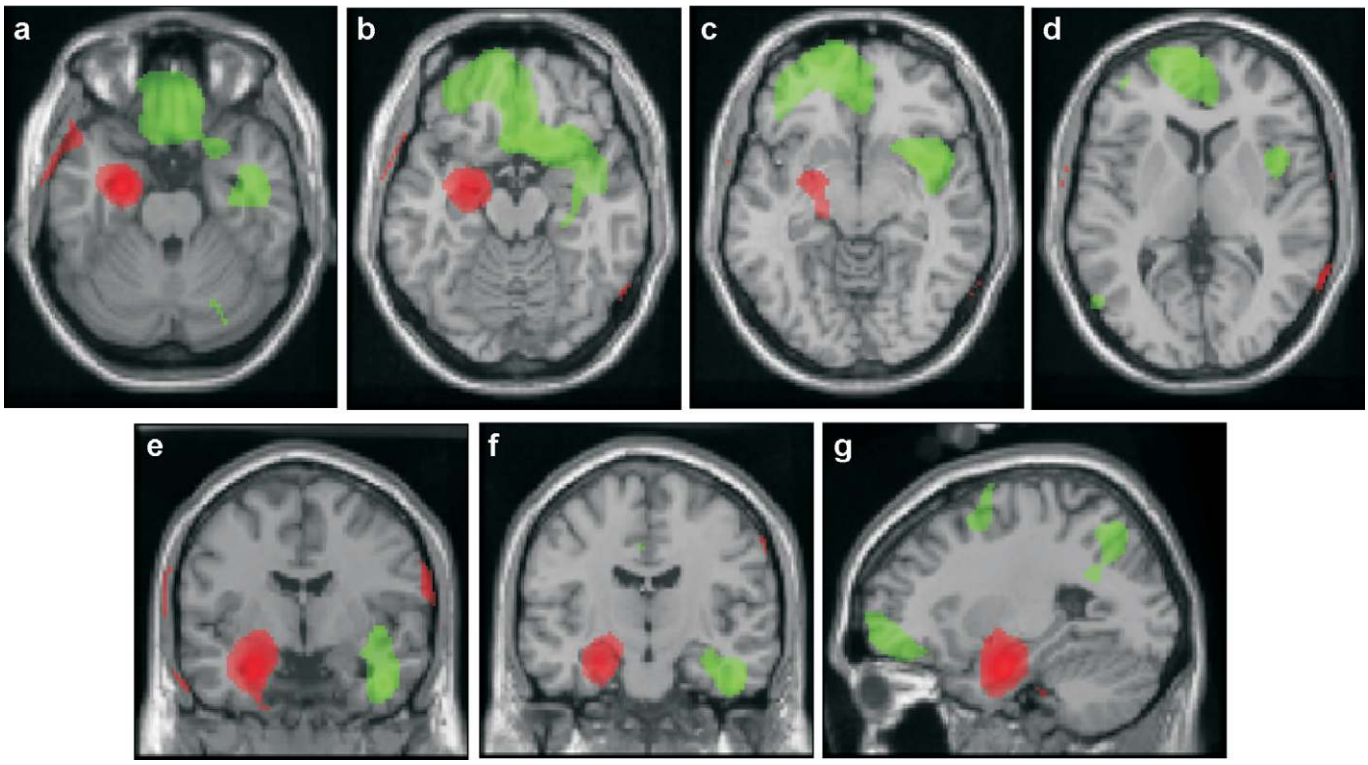

Figure 2. Cortical–subcortical involvement 60–90 s after onset of temporal lobe complex partial seizures. Same patient data as Figure 1*a* ($n = 8$). Statistical parametric maps depict CBF increases in red and decreases in green. Changes ipsilateral to seizure onset are shown on the left side of (*a–f*), and contralateral changes on the right side. (*a–d*) Horizontal sections progressing from inferior to superior showing CBF increases in the ipsilateral temporal lobe and ventral basal ganglia, and decreases in the bilateral association cortex. (*e–f*) Coronal sections progressing from anterior to posterior. (*g*) Sagittal section through the temporal lobe ipsilateral to seizure onset showing maximal involvement of the pes hippocampi. (*a–g*) Extent threshold, $k = 125$ voxels (voxel size $= 2 \times 2 \times 2$ mm). Height threshold, $P = 0.01$. Equivalently, only voxel clusters greater than 1 cm^3 in volume and with *Z* scores greater than 2.33 are displayed.

CBF increases were present in the temporal lobe of seizure onset, maximal in the anterior, or pes hippocampus (Figs 1*a* and 2; Table 1). More minor increases were present in other ipsilateral and contralateral neocortical areas but did not reach statistical significance at the cluster level. Significant subcortical increases in the 60–90 s group were present in the ventral basal ganglia on the side of seizure onset, particularly in the region of the ventral pallidum (Fig. 2*c*,*e*).

Perhaps as important as the CBF increases, were the striking CBF decreases seen during these complex partial seizures in the 60–90 s group in the bilateral orbitofrontal, anterior cingulate, lateral frontal, and parietal association cortex, but of slightly greater magnitude on the side of seizure onset (Fig. 1*a*; Table 1). Of note, primary cortical regions such as the perirolandic cortex, primary auditory, and primary visual cortex were relatively spared by these decreases.

In the >90 s group, representing the early post-ictal period, the temporal lobe is no longer activated (Fig. 1*b*). Interestingly, however, marked increases occur in this group in a variety of subcortical structures with known limbic connections: the bilateral medial thalamus, hypothalamus, subthalamus (midbrain–diencephalic junction), midbrain, and upper pons (Figs 1*b* and 3; Table 1). In addition, the bilateral cerebellar vermis is activated.

In the >90 s group, like the 60–90 s group, marked CBF decreases persist in the bilateral higher order association cortex, including the orbitofrontal, anterior cingulate, lateral frontal and parietal cortex, with slightly greater magnitude on the side of seizure onset (Figs 1*b* and 3; Table 1).

Simple Partial Seizures

We also analyzed SPECT images from a group of simple partial temporal lobe seizures with no impaired consciousness based on independent review of seizure videotapes ($n = 6$). Mean seizure duration was 67 ± 18.5 s (mean ± SEM), mean injection time after seizure onset was 78 ± 6.7 s, and mean time from the end of the seizure until the injection was 11 ± 17.1 s. Thus, injection times after onset were very similar to the 60–90 s complex partial group (78 versus 73 s), while the seizure durations were slightly shorter in the simple partial group (67 versus 94 s), although not significantly so ($P = 0.32$, two-tailed *t*-test). EEG during the seizures in which the SPECT scans were performed showed unilateral rhythmic theta frequency slowing over the temporal lobe on the side of seizure onset in three patients, mild diffuse slowing in one patient, and no EEG changes in two patients. Behavior during seizures consisted of sitting in bed and responding to questions and commands from family or staff.

Individual patients in the simple partial group analyzed by SPECT difference imaging (Zubal *et al.*, 1995; Chang *et al.*, 2002) showed focal CBF increases in the temporal lobe either on the side of seizure onset, or bilaterally in five of six patients (data not shown). However, due to individual variations in the anatomic locations and magnitude of these changes, the group data showed only small increases in the contralateral temporal lobe and cerebral peduncle, none of which reached statistical significance at the cluster level (Fig. 4). Even more strikingly, the widespread bilateral CBF decreases seen in the higher order association cortex with complex partial seizures (Fig. 1)

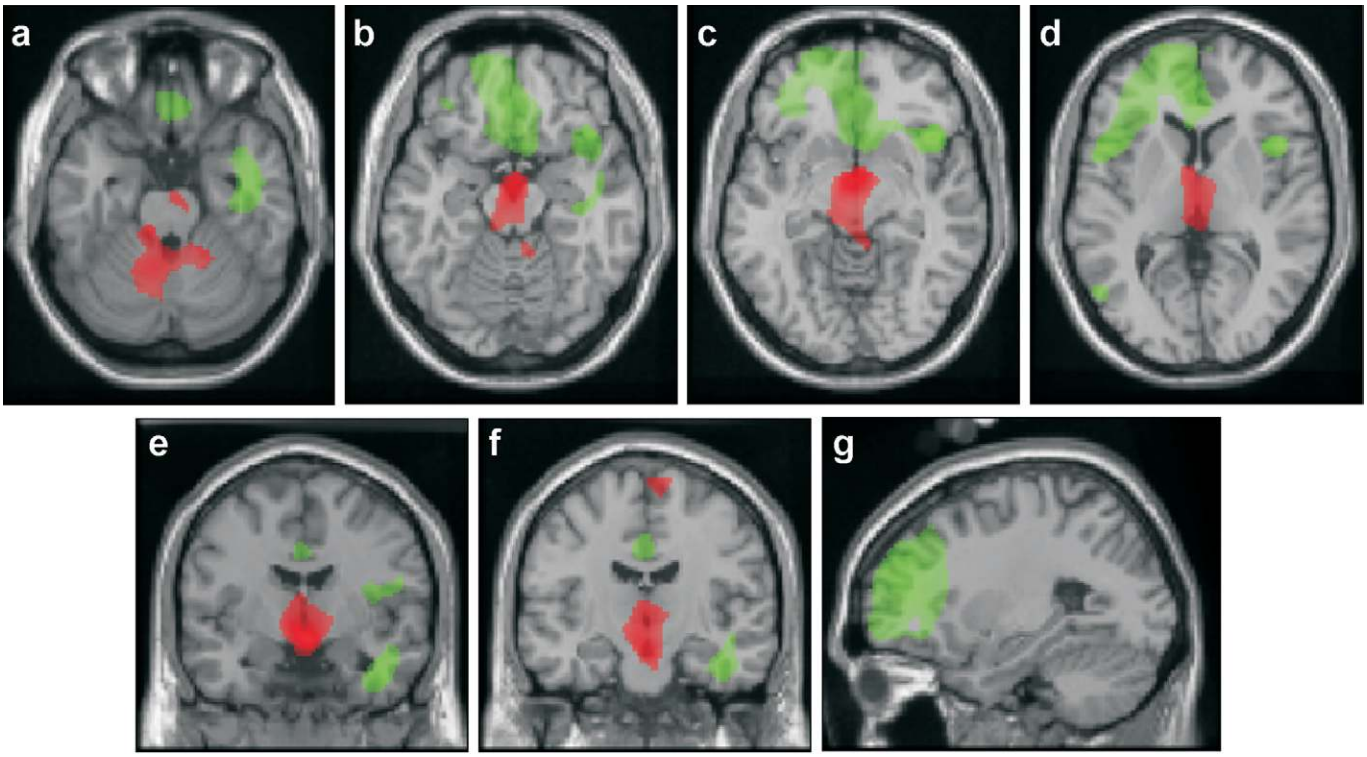

Figure 3. Cortical–subcortical involvement >90 s after onset of temporal lobe complex partial seizures. Same patient data as Figure 1*b* ($n = 10$). Statistical parametric maps depict CBF increases in red and decreases in green. Changes ipsilateral to seizure onset are shown on the left side of (*a–f*), and contralateral changes on the right side. Sections are at the same levels as Figure 2. (*a–d*) Horizontal sections progressing from inferior to superior, and (*e–f*) coronal sections progressing from anterior to posterior showing CBF increases in the bilateral midbrain, hypothalamus, subthalamus (midbrain–diencephalic junction) and medial thalamus. Decreases are present in the bilateral association cortex. (*g*) Sagittal section through the temporal lobe ipsilateral to seizure onset no longer shows increases at this time. Extent threshold, $k = 125$ voxels (voxel size = 2 × 2×2 mm). Height threshold, $P = 0.01$. Equivalently, only voxel clusters greater than 1 cm^3 in volume and with *Z* scores greater than 2.33 are displayed.

Table 1
Brain regions with significant changes during temporal lobe seizures

Brain regions (voxel clusters)	Cluster significance (*P*)	Cluster volume (*k*)	Maximum voxel location	*x*, *y*, *z*	Maximum voxel *Z* score
Complex partial seizures 60–90 s					
Hyperperfusion:					
Ipsilateral temporal lobe, ipsilateral basal ganglia	0.000	4544	ipsilateral pes hippocampi	–26, –8, –24	4.38
Hypoperfusion:					
Bilateral medial and orbital frontal, ipsilateral lateral frontal, contralateral insula, contralateral temporal	0.000	19488	contralateral orbital frontal	14, 16, –14	4.22
Ipsilateral medial and lateral parietal	0.000	8298	ipsilateral precuneus	–6, –46, 32	3.93
Complex partial seizures >90 s					
Hyperperfusion:					
Bilateral medial thalamus, hypothalamus, subthalamus, midbrain, pons, medial cerebellum	0.000	6555	Bilateral hypothalamus	2, –6, –12	4.49
Hypoperfusion:					
Bilateral medial and orbital frontal, ipsilateral lateral frontal, ipsilateral medial parietal, contralateral insula, contralateral temporal	0.000	27717	Contralateral insula	44, 16, –2	4.90

Same data as in Figure 1. *P* = cluster-level significance corrected for multiple comparisons for the entire brain. Only clusters with cluster-level significance $P < 0.05$ are listed. *k* = cluster size in voxels (voxel size = 2 × 2 × 2 mm). *x*, *y*, *z* are coordinates in MNI space of the voxel with maximum *Z* score for the cluster.

were absent in the simple partial seizures, both in the individual (not shown) and group data (Fig. 4).

In addition to the within-group analyses, we also directly compared each of the complex partial seizure subgroups to the simple partial group. Between-group analyses are less sensitive because of inter-subject variability. For example, with the present sample size, no statistically significant differences were found when directly comparing the 60–90 s versus >90 s

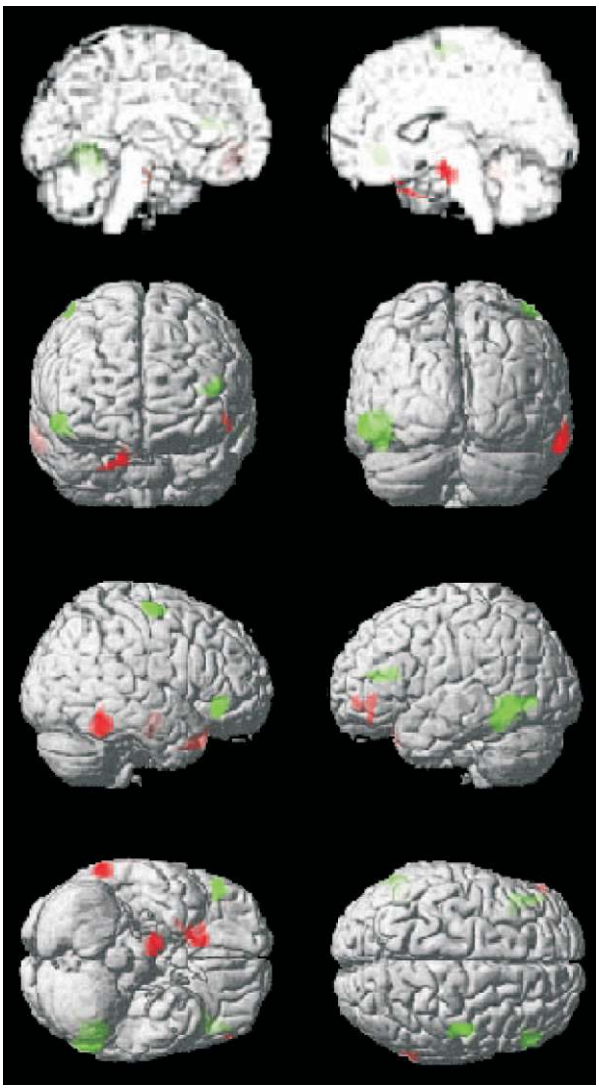

Figure 4. Simple partial seizures arising from the temporal lobe are not associated with widespread CBF changes. Statistical parametric maps depict CBF increases in red, and decreases in green ($n = 6$). Changes ipsilateral to seizure onset are shown on the left side of the brain, and contralateral changes on the right side of the brain. Extent threshold, $k = 125$ voxels (voxel size $= 2 \times 2 \times 2$ mm). Height threshold, $P = 0.01$. Equivalently, only voxel clusters greater than 1 cm^3 in volume and with Z scores greater than 2.33 are displayed. Resulting voxel clusters were not statistically significant after correction for multiple comparisons.

groups to each other. However, SPM analysis did reveal that both the 60–90 s (n = 8) and the >90 s (n = 10) complex partial groups had significantly decreased perfusion in bilateral frontal lobes (cluster-level P = 0.000 corrected for multiple comparisons, k = 8707, maximum voxel Z = 4.48 for 60–90 s; P = 0.000, k = 7544, Z = 3.70 for >90 s) as compared to the simple partial group (n = 6) (data not shown).

Network Correlations

What is the mechanism for the hypoperfusion in frontal and parietal association cortex seen during complex partial seizures? To begin to investigate this, we divided the brain into anatomical regions and calculated the Pearson correlation between perfusion changes in each region and all the others ipsilateral to seizure onset (Table 2). We used the ictal–interictal SPECT scan pairs from all temporal lobe patients at all injection times (n = 24). Although this analysis must be considered exploratory, several clear trends can be seen after roughly correcting for multiple comparisons by increasing the significance threshold to 0.001 (Table 2). There was a strong positive correlation between several midline subcortical structures (medial thalamus, lateral thalamus, subthalamus, hypothalamus, midbrain tegmentum, midbrain substantia nigra, and pontine tegmentum), suggesting that changes in these structures tend to occur in the same direction. Perhaps most interestingly, there was a strong negative correlation between changes in the frontal and parietal cortex and these subcortical structures, especially the medial thalamus ($P < 0.001$, P = 0.008 for frontal and parietal cortex, respectively), as well as a strong positive correlation between the frontal and parietal cortex (P = 0.001, Table 2). This suggests an inverse relationship between changes in perfusion in the midline subcortical structures and the association cortex during temporal lobe seizures. Perfusion changes in the mesial and lateral temporal lobe, on the other hand, were not correlated with changes in the association cortex, but were strongly positively correlated with the ipsilateral basal ganglia ($P <$ 0.001) (Table 2), a finding that has previously been related to dystonic limb movements during temporal lobe seizures (Newton *et al.*, 1992).

Principal components analysis (see Materials and Methods) identified three components, representing three groupings of highly intercorrelated brain regions, which accounted for 78% of the total variance in the data. Variables with greatest factor loading in each component are most highly intercorrelated, and in descending order for each component were as follows: first component, positive factor loading – subthalamus, medial thalamus, midbrain substantia nigra, midbrain tegmentum, lateral thalamus, pons, and hypothalamus; first component negative factor loading – frontal and parietal; second component, positive factor loading – lateral temporal, medial temporal, basal ganglia, and occipital; and third component, positive factor loading – parietal and frontal. Thus, the principal components analysis confirmed the findings based on identification of highly correlated regions (Table 2). These results are summarized in Figure 5. Midline subcortical structures form one network of strong positive correlations, while the frontal and parietal cortices form a second network of positive correlations (Fig. 5*a*). These cortical–subcortical networks appear to interact through negative correlations via the thalamus (Fig. 5*a*,*c*,*d*). Another network of positive correlations is formed by the temporal lobe and basal ganglia (Fig. 5*b*,*e*).

Based on these findings, we selected the medial thalamus ipsilateral to seizure onset as a crucial node with high positive and negative correlations to numerous cortical and subcortical structures. SPM enables analysis of data for the entire brain with correction for multiple comparisons in the entire analysis volume (Friston *et al.*, 1996; Acton and Friston, 1998). We therefore performed an SPM analysis of the partial correlation between medial thalamic changes ipsilateral to seizure onset and changes in all other brain regions bilaterally (Fig. 6). As with the other correlation studies already discussed, we included the entire population in this analysis (n = 24) to include effects of individual patient variation even in patient groups that did not *on average* show significant medial

Table 2
Correlation between CBF changes in cortical and subcortical regions during temporal lobe seizures

	Rolandic	Occipital	Lat temp	Mes temp	BG	Cerebell	Parietal	Frontal	Pons	SN	Mid teg	Subthal	Lat thal	Hypothal
Med thal	–0.379	0.019	0.293	0.188	0.323	0.454	–0.531	**–0.674***	0.586	**0.673***	**0.700***	**0.847***	**0.872***	0.557
	0.068	0.930	0.165	0.378	0.123	0.026	0.008	**<0.001**	0.003	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.005
Hypothal	–0.251	–0.281	–0.060	0.035	–0.004	0.245	–0.343	–0.562	0.595	**0.747***	**0.632***	**0.666***	0.398	
	0.237	0.183	0.781	0.870	0.984	0.249	0.100	0.004	0.002	**<0.001**	**0.001**	**<0.001**	0.054	
Lat thal	–0.362	0.163	0.505	0.405	0.519	0.343	–0.349	**–0.638***	0.494	**0.665***	**0.680***	**0.768***		
	0.082	0.446	0.012	0.050	0.009	0.100	0.094	**0.001**	0.014	**<0.001**	**<0.001**	**<0.001**		
Subthal	–0.300	–0.150	0.295	–0.430	0.255	0.310	–0.430	–0.516	**0.614***	**0.896***	**0.929***			
	0.154	0.486	0.162	0.036	0.229	0.140	0.036	0.010	**0.001**	**<0.001**	**<0.001**			
Mid teg	–0.361	–0.074	0.357	0.190	0.280	0.285	–0.267	–0.350	0.603	**0.922***				
	0.083	0.732	0.087	0.374	0.185	0.177	0.208	0.093	0.002	**<0.001**				
SN	–0.372	–0.134	0.274	0.202	0.143	0.301	–0.319	–0.467	**0.683***					
	0.074	0.532	0.195	0.344	0.506	0.152	0.129	0.021	**<0.001**					
Pons	–0.214	–0.432	–0.135	–0.108	–0.129	0.537	–0.441	–0.477						
	0.315	0.035	0.530	0.616	0.548	0.007	0.031	0.018						
Frontal	0.177	0.062	0.068	–0.089	–0.237	–0.482	**0.625***							
	0.409	0.774	0.753	0.678	0.265	0.037	**0.001**							
Parietal	0.397	0.161	0.174	0.093	–0.001	0.522								
	0.055	0.451	0.416	0.665	0.995	0.009								
Cerebell	0.340	0.079	0.305	–0.249	0.223									
	0.104	0.714	0.147	0.241	0.294									
BG	0.240	0.343	0.757*	**0.677***										
	0.258	0.101	**<0.001**	**<0.001**										
Mes temp	0.392	0.390	**0.856***											
	0.058	0.060	**<0.001**											
Lat temp	–0.366	0.388												
	0.079	0.061												
Occipital	0.357													
	0.087													

Pearson correlation coefficients (*r*) and significance levels (*P*, two-tailed *t*-test) (top and bottom values, respectively) are given. Correlations were calculated between all possible pairs of anatomical regions ipsilateral to seizure onset across all 24 patients.
*Regions with significant correlation at the 0.001 level are shown in bold. For each pair of regions, Lat temp, lateral temporal; Mes temp, mesial temporal; BG, basal ganglia; Cerebell, cerebellum; SN, substantia nigra; Mid teg, midbrain tegmentum; Subthal, subthalamus; Lat thal, lateral thalamus; Hypothal, hypothalamus; Med thal, medial thalamus.

thalamic increases (60–90 s and simple partial groups). Using this approach, we found significant positive correlation between the ipsilateral medial thalamus, and the ipsilateral thalamus, subthalamus, and midbrain, as well as the contralateral medial thalamus (cluster-level $P = 0.001$ corrected for multiple comparisons, $k = 1894$, maximum voxel $Z = 6.71$). A smaller region of significant correlation was also present with the ipsilateral medial cerebellum ($P = 0.015$, $k = 873$, $Z = 3.98$). Significant negative correlation was found between the ipsilateral medial thalamus and the bilateral orbital frontal, ipsilateral lateral frontal and parietal, and the contralateral temporal cortex ($P = 0.000$, $k = 16\,900$, $Z = 5.44$). This more statistically robust approach confirms that changes in medial thalamic perfusion in temporal lobe seizures are positively correlated with ipsilateral midline subcortical structures, as well as with the contralateral medial thalamus, and are negatively correlated with bilateral regions of the association cortex.

Discussion

Consciousness is notoriously difficult to define, and philosophers debate whether the personal and subjective feeling of awareness can ever be causally related to physical phenomena (Chalmers, 1996; Searle, 1997). There is wide consensus, however, that external behaviors related to consciousness and the biological basis of these behaviors can be investigated scientifically (Gray, 1992; Singer, 1998; Rees *et al.*, 2002). In this study, we classified patients during temporal lobe seizures, based on whether they responded normally during seizures (simple partial seizures), or showed impaired responsiveness during seizures (complex partial seizures). We found widespread functional changes in cortical and subcortical networks in complex partial temporal lobe seizures. Simple partial seizures, in contrast, were associated with more limited changes confined mainly to the temporal lobes. Complex

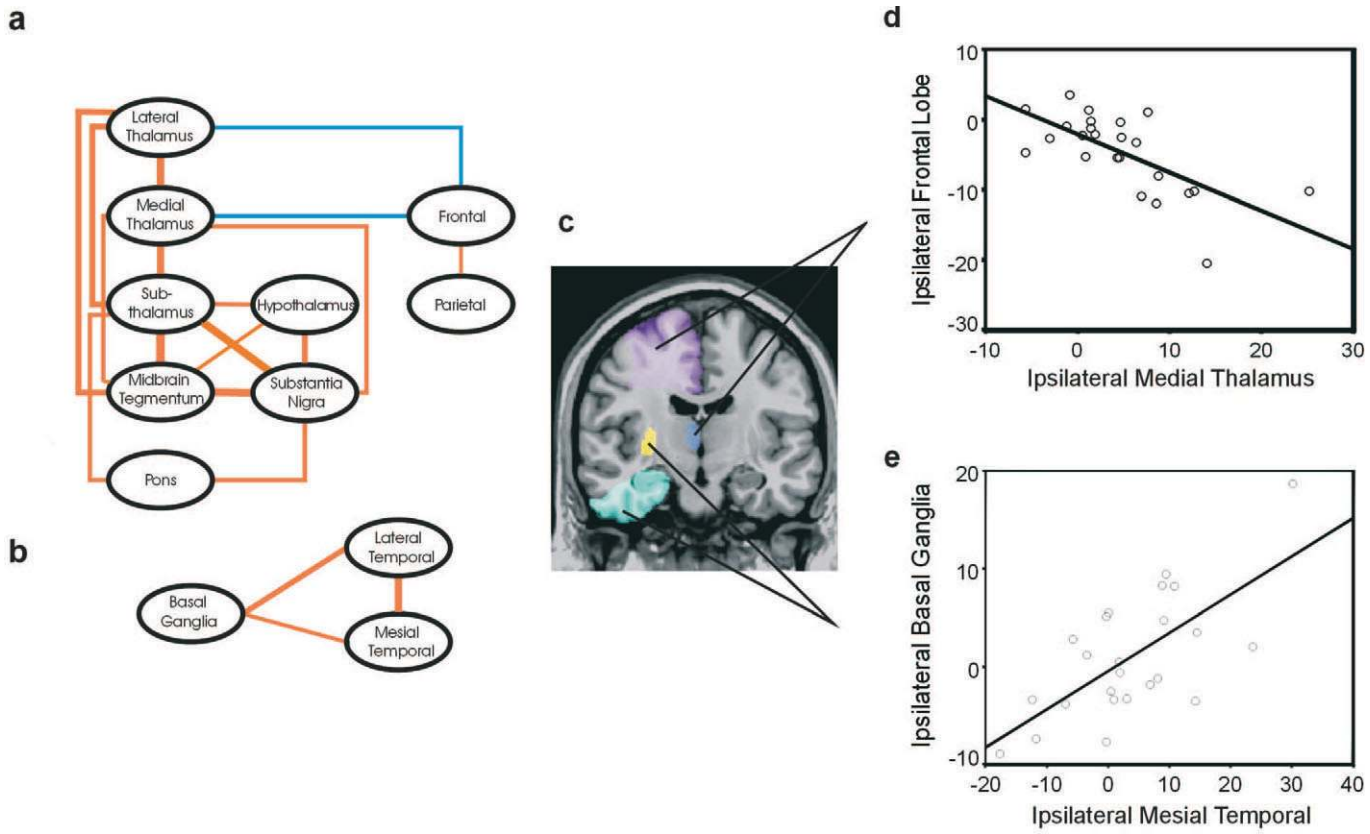

Figure 5. Cortical–subcortical network correlations in temporal lobe seizures. (*a*) Networks of midline subcortical structures, and fronto-parietal cortex ipsilateral to seizure onset showing positive (orange) and negative (blue) correlations (Table 1). Line thickness is proportional to the Pearson correlation coefficient (*r*). (*b*) Basal ganglia and temporal lobe also form a network of positive correlations. (*c–e*) Examples of correlations between pairs of structures ipsilateral to seizure onset. (*d*) Mean per cent change (ictal versus interictal) in the frontal lobe shows a significant negative correlation with mean per cent change in the medial thalamus ($r = -0.67$, $P < 0.001$; $n = 24$). (*e*) Mean per cent change in the basal ganglia shows a significant positive correlation with mean per cent change in the mesial temporal lobe ($r = 0.68$, $P < 0.001$; $n = 24$).

partial seizures were associated with marked decreases in CBF in regions of the association cortex including the lateral prefrontal, anterior cingulate, orbital frontal, and lateral parietal cortex. These decreases occurred bilaterally, but were more profound on the side of seizure onset.

Our results should be considered in light of investigations from normal subjects showing cerebral activation during tasks involving aspects of consciousness. For example, several studies have shown that the same lateral frontal and parietal regions which were hypoperfused during complex partial seizures, are normally activated during tasks that require visual perceptual awareness and discrimination (Lumer *et al.*, 1998; Rees and Lavey, 2001; Rees *et al.*, 2002). Similarly, the anterior cingulate is important in response selection (Bunge *et al.*, 2002), orbital frontal cortex participates in attaching emotional valency to decision making (Moll *et al.*, 2002), and the upper brainstem and thalamus also play a role in normal attention (Kinomura *et al.*, 1996).

What is the mechanism for decreased CBF in fronto-parietal cortex during complex partial seizures? The answer is not definitively known at present, and will need to await further studies. In previous work reporting frontal or parietal hypoperfusion during temporal lobe seizures a mechanism has not been identified (Rabinowicz *et al.*, 1997; Menzel *et al.*, 1998; Chang *et al.*, 2002; Van Paesschen *et al.*, 2003). Interestingly, we found that fronto-parietal hypoperfusion was strongly correlated with hyperperfusion in midline subcortical structures such as the mediodorsal thalamus. We recently proposed a 'network inhibition hypothesis' in which complex partial seizures arising in the temporal lobe propagate to the medial thalamus and upper brainstem reticular formation, disrupting their normal activating functions (Norden and Blumenfeld, 2002; Blumenfeld and Taylor, 2003). This, in turn, may lead secondarily to functional inactivation of widespread regions of frontal and parietal association cortex. Thus, both anatomical structures that are abnormally activated and structures that are abnormally inhibited could contribute to impaired function during epileptic seizures. While it is not clear if the CBF decreases we observed were associated with decreased neuronal activity, 'surround inhibition' has been reported previously in regions outside the zone of seizure activity in electrophysiological, metabolic, and neuroimaging studies (Prince and Wilder, 1967; Collins, 1978; Engel *et al.*, 1982, 1983; Handforth and Ackermann, 1988; VanLandingham and Lothman, 1991a; Schwartz and Bonhoeffer, 2001) and there is some evidence based on animal work that subcortical structures may play a role (VanLandingham and Lothman, 1991b; Ostrand and Cooper, 1994; Redecker *et al.*, 1997; Bruehl *et al.*, 1998). Data from a number of intracranial EEG studies show slow waves in frontal cortex during temporal lobe seizures resembling the EEG activity of sleep (Lieb *et al.*, 1991; Mayanagi *et al.*, 1996; Rivera *et al.*, 2004). One possibility is that regions of 'surround inhibition' outside the seizure onset zone may serve an adaptive function to reduce the likelihood

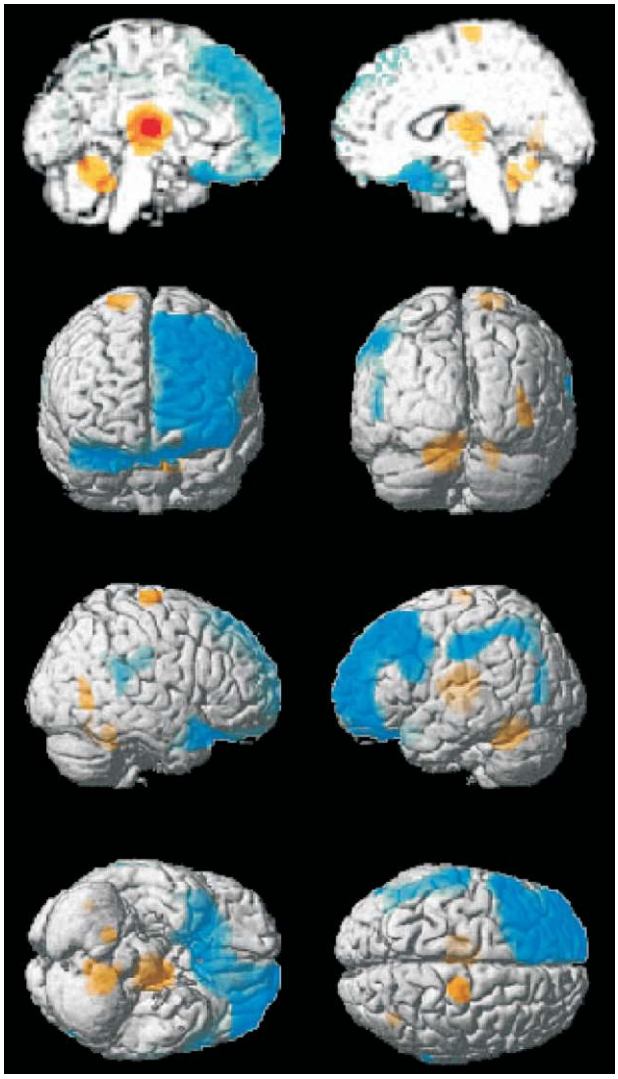

Figure 6. Brain regions showing significant correlation with ipsilateral medial thalamic perfusion changes in temporal lobe seizures. Statistical parametric map depicts positive correlations in orange and negative correlations in blue ($n = 24$). The medial thalamus ipsilateral to seizure onset is shown in red. Significant positive correlations were seen at the cluster level with the ipsilateral thalamus, subthalamus, midbrain and medial cerebellum, as well as with the contralateral medial thalamus. Significant negative correlations were seen at the cluster level with the bilateral orbital frontal, ipsilateral lateral frontal and parietal, and the contralateral temporal cortex. Extent threshold, $k = 125$ voxels (voxel size $= 2 \times 2 \times 2$ mm). Height threshold, $P = 0.01$. Equivalently, only voxel clusters greater than 1 cm^3 in volume and with Z scores greater than 2.33 are displayed.

of seizure spread to other cortical regions (Schwartz and Bonhoeffer, 2001; Van Paesschen *et al.*, 2003). Indeed, temporal lobe seizures are particularly prone to remain confined to limbic cortex, and rarely generalize.

We cannot fully exclude the possibility that the decreases in CBF seen in the frontal and parietal cortex are due primarily to a hemodynamic mechanism. However, we do not believe that the decreases in CBF outside the temporal lobe represent a simple 'steal' phenomenon for several reasons. First of all, the vascular supply of the frontal and parietal cortex (anterior and middle cerebral arteries) differs from the temporal lobe (middle and posterior cerebral arteries) and midline subcortical structures (posterior circulation), making vascular steal an unlikely explanation for the observed hypoperfusion pattern. Of note, some regions within the middle cerebral artery territory are almost entirely spared by the hypoperfusion, most notably the peri-Rolandic cortex (see Fig. 1). In addition, we saw no correlation between the amount of increased CBF in the temporal lobe and decreased CBF in the fronto-parietal association cortex (Table 2). While a simple steal phenomenon is unlikely, other hemodynamic mechanisms could play a role, such as regional vasoconstriction similar to that seen in migraine, triggered by the ictal discharge. Post-ictal migraine is a well known phenomenon, and similar mechanisms may be activated during seizures as well.

Strong involvement of the bilateral medial diencephalon and upper brainstem has important functional implications for understanding temporal lobe seizures. Previous work (reviewed in Norden and Blumenfeld, 2002) and preliminary SPECT studies (Mayanagi *et al.*, 1996; Blumenfeld *et al.*, 2000; Bradley *et al.*, 2000; Paige *et al.*, 2000; Lee *et al.*, 2002) support the importance of medial temporal and medial diencephalic connections in generating limbic seizures. Intense hypothalamic involvement of the kind reported here may play an important role in neuroendocrine changes (Bauer, 2001; Quigg *et al.*, 2002), medial diencephalic changes may contribute to memory impairment, and upper brainstem–diencephalic involvement to impaired consciousness. A recent SPECT imaging study found an association between medial thalamic and upper brainstem involvement during seizures, and loss of consciousness (Lee *et al.*, 2002). However, another recent SPECT imaging study which investigated the early part of temporal lobe seizures, within 30 s of onset, found decreased CBF in the frontal association cortex without significant changes in the brainstem and diencephalon (Van Paesschen *et al.*, 2003). We found that in complex partial, but not simple partial seizures, there is marked hypoperfusion of fronto-parietal association cortex correlated with hyperperfusion of midline subcortical structures late in seizures, progressively intensifying in the post-ictal period. Further studies will be needed to elucidate whether fronto-parietal hypoperfusion early in seizures is related to subtle midline subcortical changes not easily detected by SPECT, or is generated through other mechanisms.

One possible limitation of this study is the small sample size ($n = 24$), particularly in the simple partial group ($n = 6$). Thus, further investigation with a larger sample is warranted. It could be argued that the lack of changes in the simple partial group may be due to the smaller sample size ($n = 6$) compared to the two complex partial groups ($n = 8$, $n = 10$, respectively). However, when we directly compared each complex partial group to the simple partial group we found significantly more decreased perfusion in the frontal lobes in both complex partial groups compared to the simple partial group. Since this effect was detectable despite the reduced sensitivity of between-subject analyses (compared to within-subject analyses), this suggests that the robust hypoperfusion in the complex partial groups was not simply due to larger sample size than in the simple partial group. Another possible concern is that differences other than impaired consciousness may have contributed to the imaging differences between the simple partial and complex partial groups. Although the EEG changes, and overall level of motor activity were similar in the different groups, they were not identical, and we cannot rule out the possibility that additional variables aside from impaired consciousness may contribute to the observed perfusion differ-

ences. In addition, the injections times and seizure durations were not identical in the complex partial and simple partial patient groups. Thus, these results must be considered preliminary, particularly with regard to conclusions about mechanisms of consciousness, until they are replicated with larger and more closely matched groups of patients, and with more sophisticated means of assessing patient awareness during seizures.

If these results are confirmed, we tentatively propose the following model: early in temporal lobe seizures the most intense CBF increases occur in the temporal lobe. In simple partial seizures, physiological changes do not extend significantly beyond the temporal lobes, and consciousness is spared. In complex partial seizures, however, abnormal activity extends to a widespread network, reflected by CBF decreases in the fronto-parietal cortex and CBF increases in the medial diencephalon and upper brainstem. This may lead to disruption of normal information flow in multiple systems and loss of consciousness, which is particularly severe late in seizures, and extends to the early post-ictal period. We recently found that generalized tonic–clonic seizures are associated with abnormal focal CBF increases in regions similar to those reported here to show CBF decreases (Blumenfeld *et al.*, 2003). Based on this, we propose that abnormal increased activity in fronto-parietal association cortex may cause loss of consciousness in generalized seizures, while abnormal decreased activity in these same networks may cause loss of consciousness in complex partial seizures.

Notes

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