Table 2. Seizure characteristics.

Seizure type	Patient no.	Seizure frequency (times/month)	Nocturnal seizure (%)	Aura	Seizure onset	Motor automatism	Facial expressions	Postictal confusion	Seizure duration (seconds)
HMS-1	1	500	90		vocalisation	1, 4	frightened, painful	none	20-30
	2	100	95		sitting up	1, 4	frightened, painful	none	20-45
	3	30	98		vocalisation	1, 3, 4	painful	none	30-40
	4	100	5		vocalisation	1, 2, 4	painful	none	21-35
	10	30	95		vocalisation	1, 4	frightened	none	25-40
	11	30	95		staring	1, 2, 4	none	none	20-40
	12	4	0		staring	1, 4	none	yes	25-40
	13	4	70		Staring	1, 3, 4	none	yes	40-60
HMS-2	5	500	95	fear	vocalisation	1, 5	none	none	30-50
	6	30	99		vocalisation	1, 3, 5	painful	none	30-60
	7	500	98		tonic posturing	1, 3, 5	frightened	yes	40-60
	8	30	95		tonic posturing	1, 3, 5	painful	none	22-31
	9	30	90		vocalisation	1, 2, 5	frightened	none	20-28

1: vocalisation; 2: asymmetric dystonic limb posturing; 3: symmetric dystonic limb posturing; 4: marked agitation, with body rocking, boxing and kicking; 5: mild agitation, with horizontal movements or rotation of trunk and pelvis.

was considered focal or limited, and a focal resection was therefore performed. Surgery was performed twice for Cases 1 and 11. Case 1 showed left frontal FCD. Initially, partial removal of the FCD resulted in poor surgical outcome and after seven months he was re-evaluated and the FCD was removed completely, which rendered the patient seizure-free. Case 11 underwent resection of the parietal cortex, with an Engel class III outcome. After four years, a second resection of the right posterior-superior temporal area was performed under the guidance of MEG and SISCOM, which rendered the patient seizure-free with Engel class I. Ten patients had a good outcome of Engel class I and three had an outcome of Engel class III. In the latter group, one patient had only the left ACC removed, guided by ECoG, and histopathology was negative. The second patient, with a poor outcome, had an EZ in the left inferior frontal gyrus with involvement of Broca's area; only the areas anterior and posterior to Broca's area were removed, with multiple subpial transections in Broca's area and histopathology of FCD2A. The third patient with left anterior temporal resection resulted in an outcome of Engel class III, with histopathology of FCD1A. In this patient, the EZ may have been wider than the original resection, but the patient refused further evaluation. Post-surgical complications were limited to difficulty in naming in one patient (Case 13), which resolved later, and permanent hemianopsia in another (Case 11).

Discussion

Identifying cerebral mechanisms underlying the clinical manifestation of epileptic seizures can provide insight into the physiological processes underlying non-pathological behaviour in the normal brain. The network structures within the brain are connected functionally, and structurally, it is not surprising that seizures arising from different sites can propagate in a variably extensive way to involve the same neural network (Spencer, 2002). Ictal SPECT may provide insight into the functional organisation of more complex seizure-related symptoms such as automatisms and motionless stare (Shin *et al.*, 2002). SPM has been used to evaluate the localisation or lateralisation of seizure foci by ictal SPECT (Knowlton *et al.*, 2004; Chassagnon *et al.*, 2009). In this study, single case analysis was not employed because each patient had only one ictal and interictal image. However, a paired t-test for all 13 patients increased the statistical power to a threshold of $p<0.002$, allowing more reliable results to be obtained.

Clusters of significant hyperperfusion in the OFG, ACC, midbrain, pons, and LFN were documented. The precise symptomatogenic zone for HMS is largely unknown, although there is increasing evidence that it might be located in the ACC (San Pedro *et al.*, 2000; Tao *et al.*, 2010), the OFG (Bartolomei *et al.*, 2002) or both (Rheims *et al.*, 2008). Rheims *et al.*

Table 3. ECoG and SISCOM findings.

Patient no.	Number of subdural electrodes	Number of depth electrodes	Inter-hemispheric electrodes	ECoG result			SISCOM
				Ictal onset zone	Epileptogenic zone	Area of secondary spread	
1	58 20		6	L lat frontal over FCD	L lat frontal FCD	L ACC and all L Lat frontal	L lat frontal over FCD
2	not done		Not done	Not done	Not done	Not done	R medial frontal, ACC, L cerebellum
3	28		4	L ACC	L ACC	L lat frontal	L occipital, R parietal, brainstem
4	80		8	R lat frontal, anterior to tuber	R lat frontal	R ant tip of frontal pole	R lat frontal, small R med frontal, caudate
5	40			R lat. frontal, over FCD	R lat frontal, over FCD	remained localised	ACC B/L, R>L
6	140		12	R SFG	R SFG and R MFG	L frontal B/L ACC	R med frontal up to R ACC
7	96		30	L IFG	L IFG	L ACC and L SMA	L lat med frontal, L ACC
8	68	6x1 R IFS, over FCD		R IFG over FCD	R IFG over FCD	R lat frontal	R med frontal up to R ACC
9	92	4x3 over L lat frontal		L lat frontal	L lat frontal	whole L frontal cortex	L lat frontal, L cerebellum, L ACC
10	86	6x2 R lat frontal		R MFG over FCD	R MFG over FCD	remained localised	B/L occipital
11	126			R parieto-temporal	R post temporal	R post frontal	R post temporal, R parietal
12	98			R ant temporal	R ant temporal	R IFG and whole R lat frontal	R ant temporal, L cerebellum
13	90			L ant temporal	L ant temporal	L ant temporal	L ant temporal, L ACC

ACC: anterior cingulate cortex; ant: anterior; B/L: bilateral; FCD: focal cortical dysplasia; IFG: inferior frontal gyrus; IFS: inferior frontal sulcus; lat: lateral; L: left; MFG: middle frontal gyrus; post: posterior; R: right; SFG: superior frontal gyrus; SMA: supplementary motor area.

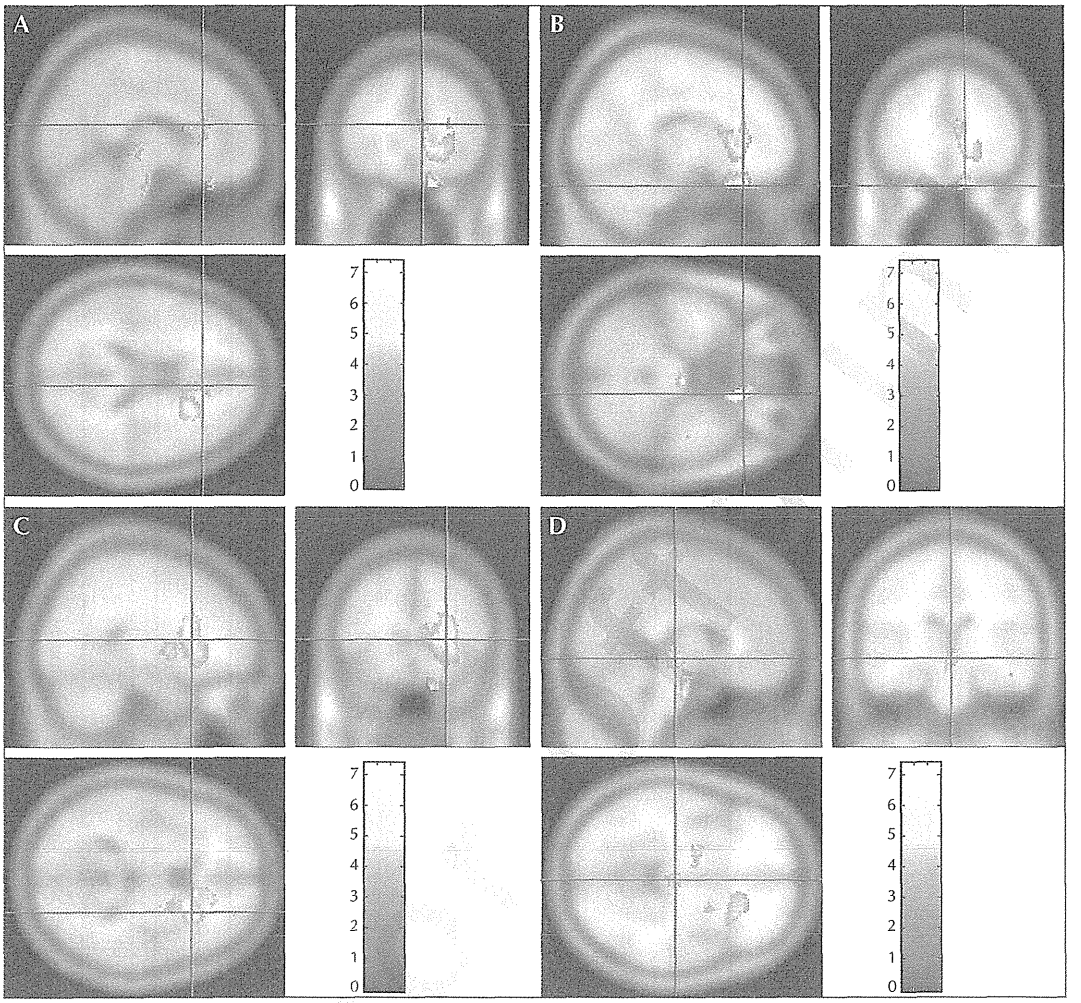

Figure 1. Statistical parametric mapping shows dominant hyperperfusion in the right anterior cingulate cortex (BA24, 32). (A) at t-value of 4.65 at SPM coordinates (x, y, z), (mm) equal (8, 28, 18); right orbito-frontal gyrus (B) at t-value of 7.38 at SPM coordinates (x, y, z), (mm) equal (14, 32, -28); lentiform nucleus (C) at t-value of 4.19 at SPM coordinates (x, y, z), (mm) equal (22, 4, 0); and midbrain (D) at t-value of 4.69 at SPM coordinates (x, y, z), (mm) equal (2, -22, -6).
The coloured stripe represents t-values at a threshold of 10.21, $p<0.002$.

(2008) reported two types of HMS. One includes marked agitation with either body rocking, kicking or boxing, along with associated facial expressions of fear and stereoelectroencephalographic (SEEG) ictal changes mainly centred on the ventro-mesial frontal cortex. The other type of HMS consists of mild agitation and includes either horizontal movements or rotation of the trunk and pelvis, which is usually associated with tonic/dystonic posturing and changes localised within the mesial premotor cortex and dorsal anterior cingulate. These reported electrical changes overlap with the regions of hyperperfusion seen in the present study. The brainstem hyperperfusion seen in the present study is a new finding in HMS. Shin *et al.* (2002) examined the ictal SPECT in patients with a mesial temporal lobe seizure and documented that ictal hyperperfusion patterns were related to the semiologic progression of seizures. Moreover, they reported that automatism was commonly associated with the hippocampal-amygdala complex and, infrequently, the mesial and orbital frontal lobe, cingulate cortex and subcortical regions (Shin *et al.*, 2002).

Tassinari *et al.* (2005a) described the role of central pattern generators (CPGs) in the motor expression of epileptic seizures as well as parasomnias. CPG, which was defined as a *"network of nerve cells that contain the information that is necessary to activate different motor neurons in the appropriate sequence and intensity to generate motor patterns"*, is genetically

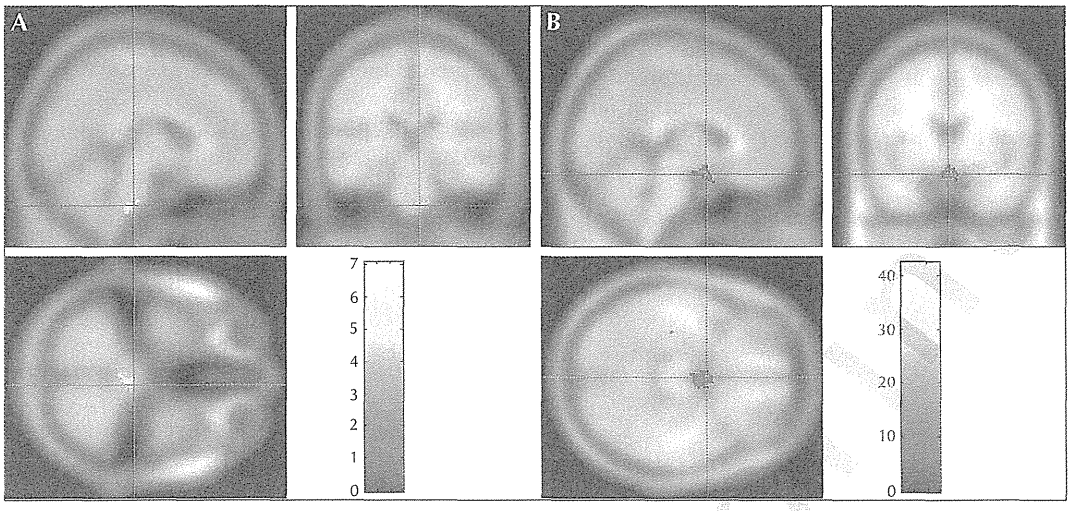

Figure 2. (A) HMS-1: statistical parametric mapping shows a dominant hyperperfusion in the right brainstem including medulla. (B) HMS-2: statistical parametric mapping shows a dominant hyperperfusion in the subcallosal gyrus, Brodmann area 25 at t-value of 5.32 at SPM coordinates (x, y, z), (mm), equal (0, 2, -18).
The coloured stripe represents t-value at a threshold of 10.21, $p<0.003$.

determined in the mesencephalon, pons, and spinal cord. They suggested that in some seizures (mainly fronto-nocturnal hypermotor and temporal-limbic), the epileptic discharge acts as a trigger for the appearance of behaviours which are the expression of inborn motor patterns, related to the CPG. They also concluded that these behaviours could be related to an epileptic event as well as non-epileptic behaviour during sleep and that these are an indirect effect of the cortical discharges on the CPG, located in the brainstem. This correlates with our results, that certain areas in the brainstem are involved in the pathogenesis of HMS which could be referred to as CPGs.

A study by Wong *et al.* (2010) documented two clusters of significant hyperperfusion: one involving the fronto-mesial regions bilaterally, cingulated gyri and caudate nuclei, and another involving the ipsilateral temporal pole, mesial temporal structures, fronto-orbital region, insula and basal ganglia. In patients with sleep-related HMS of temporal lobe origin, hypermotor manifestations started when discharges spread to the cingulate and frontal cortices (Nobili *et al.*, 2004). This is in agreement with the present findings, however, the mechanisms by which epileptic seizures may induce violent motor phenomenon remain unclear and mostly speculative. Based on experimental and clinical data, it has been suggested that an inhibitory effect from the orbito-frontal cortex to the amygdale is one mechanism underlying the control of negative emotion and related behaviour (Davidson *et al.*, 2000). It is speculated, as for ictal fear (Bartolomei *et al.*, 2005) or ictal biting behaviour (Tassinari *et al.*, 2005b), that a transient alteration of the above inhibitory network (Davidson *et al.*, 2000) could result in release of otherwise physiologically suppressed violent behaviour. Violent behaviours may be provoked by a dysfunction of basal ganglia, since they resemble previously described movement disorders (Demirkiran and Jankovic, 1995). Ictal fear represented as frightened facial expression was a common symptom in the patients in the present study and was found to correlate with discharge involving the ACC, OFG and temporal neocortex (Biraben *et al.*, 2001).

Involvement of the ascending cholinergic pathway in the brainstem has been documented in autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) patients (Picard *et al.*, 2006). However, its involvement in HMS is a new discovery that may open new windows to our understanding of the pathogenesis of HMS. In the present study, SPM showed no areas of hyperperfusion in frontal or temporal lobes, including the epileptic foci. These results could be attributed to the rapid propagation of seizure activity originating in other parts of the cortex to the ACC, OFG, midbrain and basal ganglia. Direct projections from the dorsal ACC to the dorso-lateral striatum (Devinsky *et al.*, 1995) and prefrontal cortical projections to the midbrain in primates (Frankle *et al.*, 2006) are well established and could subserve the propagation of epileptic discharge within that network.

It is concluded that HMS may originate from mesial or lateral frontal as well as extrafrontal regions, although the symptomatogenic zone involved in the process of discharge propagation may be the OFG, ACC, midbrain, pons, LFN, or all of these. This may suggest, in agreement with other studies, that a network

including the frontal and possibly extrafrontal brainstem and limbic structures are involved in the genesis of these complex epileptic manifestations. These findings, which remain to be confirmed in larger studies, may help to clarify the pathophysiology of HMS. □

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References

Bartolomei F, Guye M, Wendling F, Gavaret M, Regis J, Chauvel P. Fear, anger and compulsive behavior during seizure: involvement of large scale fronto-temporal neural networks. *Epileptic Disord* 2002; 4: 235-41.

Bartolomei F, Trebuchon A, Gavaret M, Regis J, Wendling F, Chauvel P. Acute alteration of emotional behavior in epileptic seizures is related to transient desynchrony in emotion-regulation networks. *Clin Neurophysiol* 2005; 116: 2473-9.

Biraben A, Taussig D, Thomas P, *et al.* Fear as the main feature of epileptic seizures. *J Neurol Neurosurg Psychiatry* 2001; 70: 186-91.

Blume WT, Lüders HO, Mizrahi E, Tassinari C, van Emde Boas W, Engel J Jr. Glossary of descriptive terminology for ictal semiology: report of the ILAE task force on classification and terminology. *Epilepsia* 2001; 42: 1212-8.

Chassagnon S, Namer IJ, Armspach JP, *et al.* SPM analysis of ictal-interictal SPECT in mesial temporal lobe epilepsy: relationships between ictal semiology and perfusion changes. *Epilepsy Res* 2009; 85: 252-60.

Chee MW, Kotagal P, Van Ness PC, Gragg L, Murphy D, Lüders HO. Lateralizing signs in intractable partial epilepsy: blinded multiple-observer analysis. *Neurology* 1993; 43: 2519-25.

Davidson RJ, Putnam KM, Larson CL. Dysfunction in the neural circuitry of emotion regulation-a possible prelude to violence. *Science* 2000; 289: 591-4.

Demirkiran M, Jankovic J. Paroxysmal dyskinesias: clinical features and classification. *Ann Neurol* 1995; 38: 571-9.

Devinsky O, Morrell MJ, Vogt BA. Contribution of anterior cingulated cortex to behavior. *Brain* 1995; 118: 279-306.

Frankle WG, Laruelle M, Haber SN. Prefrontal cortical projections to the midbrain in primates: evidence for a sparse connection. *Neuropsychopharmacology* 2006; 31: 1627-36.

Holthausen H, Hoppe M. Hypermotor seizures: pathophysiology and clinical semiology. In: Lüders HO, Noachtar S. *Epileptic seizures*. Philadelphia: Churchill Livingstone, 2000: 439-48.

Knowlton RC, Lawn ND, Mountz JM, *et al.* Ictal Single-Photon Emission Computed Tomography imaging in Extratemporal lobe epilepsy using Statistical Parametric Mapping. *J Neuroimaging* 2004; 14: 324-30.

Kotagal P, Lüders HO, Williams G, Nichols TR, McPherson J. Psychomotor seizures of temporal lobe onset: analysis of symptom clusters and sequences. *Epilepsy Res* 1995; 20: 49-67.

Lancaster JL, Woldorff MG, Parsons LM, *et al.* Automated Talairach atlas labels for functional brain mapping. *Hum Brain Map* 2000; 10: 120-31.

Lee SK, Lee SY, Kim KK, Hong KS, Lee DS, Chung CK. Surgical outcome and prognostic factors of cryptogenic neocortical epilepsy. *Ann Neurol* 2005; 58: 525-32.

Lüders HO, Acharya J, Baumgartner C, *et al.* Semiological seizure classification. *Epilepsia* 1998; 39: 1006-13.

Marks WJ, Laxer KD. Semiology of temporal lobe seizures: value in lateralizing the seizure focus. *Epilepsia* 1998; 39: 721-6.

McNally KA, Paige AL, Varghese G, *et al.* Localizing value of ictal-interictal SPECT analyzed SPM (ISAS). *Epilepsia* 2005; 46: 1450-60.

Nobili L, Cossu M, Mai R, *et al.* Sleep-related hyperkinetic seizures of temporal lobe origin. *Neurology* 2004; 62: 482-5.

Picard F, Bruel D, Servent D, *et al.* Alteration of in vivo nicotinic receptor density in ADNFLE patients: a PET study. *Brain* 2006; 129: 2047-60.

Rheims S, Ryvlin P, Scherer C, *et al.* Analysis of clinical patterns and underlying epileptogenic zones of hypermotor seizures. *Epilepsia* 2008; 49: 2030-40.

San Pedro EC, Mountz JM, Ojha B, Khan AA, Liu HG, Kuzniecky RI. Anterior cingulated gyrus epilepsy: the role of ictal rCBF SPECT in seizure localization. *Epilepsia* 2000; 41: 594-600.

Shin WC, Hong SB, Tae WS, Kim SE. Ictal hyperperfusion patterns according to the progression of temporal lobe seizures. *Neurology* 2002; 58: 373-80.

Spencer SS. Neural networks in human epilepsy: evidence of and implications for treatment. *Epilepsia* 2002; 43: 219-27.

Tao Y, Guojun Z, Yuping W, Lixin C, Wei D, Yongjie L. Surgical treatment of patients with drug-resistant hypermotor seizure. *Epilepsia* 2010; 51: 2124-30.

Tassinari CA, Rubboli G, Gardella E, *et al.* Central pattern generators for a common semiology in fronto-limbic seizures and in parasomnias. A neuroethologic approach. *Neurol Sci* 2005a; 26: 225-32.

Tassinari CA, Tassi L, Calandra-Buonaura G, *et al.* Biting behavior, aggression, and seizures. *Epilepsia* 2005b; 46: 654-63.

Van Paesschen W, Dupont P, Sunaert S, Goffin K, Van Laere K. The use of SPECT and PET in routine clinical practice in epilepsy. *Curr Opin Neurol* 2007; 20: 194-202.

Waterman K, Purves SJ, Kosaka B, Strauss E, Wada JA. An epileptic syndrome caused by mesial frontal lobe seizure foci. *Neurology* 1987; 37: 577-82.

Williamson PD, Spencer DD, Spencer SS, Novelly RA, Mattson RH. Complex partial seizures of frontal lobe origin. *Ann Neurol* 1985; 18: 497-504.

Wong CH, Mohamed A, Larcos G, McCredie R, Somerville E, Bleasel A. Brain activation patterns of versive, hypermotor, and bilateral asymmetric tonic seizures. *Epilepsia* 2010; 51: 2131-9.