

# Clinical patterns and pathophysiology of hypermotor seizures: an ictal SPECT study

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**ABSTRACT** – Hypermotor seizures (HMS) can include different forms of hypermotor behaviour due to various mechanisms associated with generation of ictal automatisms. Despite the varied location of seizure onset, similar semiologic features during seizures may exist. Ictal single-photon emission tomography (SPECT) apparently reflects not only the origin of epileptic discharge but also the spread to adjacent cortical areas. Taking this benefit of SPECT studies into account, preoperative SPECT results from 13 patients with HMS who underwent epilepsy surgery were analysed. The radioisotope <sup>99m</sup>Tc-ECD was injected in all patients within five seconds after seizure onset. Group analysis was performed with statistical parametric mapping (SPM) of paired ictal-interictal SPECTs in order to identify regions of significant ictal hyperperfusion. Hyperperfused regions with a corrected cluster-level significance *p*-value of <0.002 were considered significant. Seizure onset at implanted subdural electrodes was defined as the epileptic focus in 12 of 13 patients. Two patterns were recognized: HMS-1 with marked agitation and HMS-2 with mild agitation. Ictal hyperperfusion images revealed significant hyperperfusion in the anterior cingulate cortex, orbito-frontal gyrus, lentiform nucleus, midbrain and pons. These hyperperfused areas represent the symptomatogenic zone which was different from the epileptogenic zone, as confirmed by the favourable outcomes after surgical resection. The present findings suggest that a network, including frontal and possibly extrafrontal brainstem and limbic structures, is involved in the genesis of the complex epileptic manifestations of HMS. Moreover, ictal SPECT analysed by SPM is a useful method for studying the neural networks of different types of seizures.

**Key words:** anterior cingulate cortex, frontal lobe epilepsy, hypermotor seizures, statistical parametric mapping (SPM), symptomatogenic zone

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Analysis of seizure semiology is an important element of presurgical evaluation and is often used to distinguish temporal versus frontal onset (Holthausen and Hoppe, 2000). Because the clinical features of seizures are produced from activation of certain regions of the brain and spread to certain areas, detailed analysis of ictal semiology can often provide insights into the lateralising information of seizure focus and seizure propagation pathways (Chee *et al.*, 1993; Kotagal *et al.*, 1995; Marks and Laxer, 1998). Intracranial electrodes can provide a more precise localisation of seizure focus (Shin *et al.*, 2002) and are often necessary for localisation of the epileptogenic zone (EZ). However, they record only a small portion of the brain, therefore, electrode placement requires guidance by other evidence. The role of ictal SPECT for localisation of the ictal onset zone has already been established (Knowlton *et al.*, 2004; Lee *et al.*, 2005). SPECT has the unique advantage of mapping brain activity at the time of radiotracer injection (during a seizure) and the actual imaging can be performed up to 60-90 minutes later, when the patient is fully stable (McNally *et al.*, 2005). Even though it is used primarily in the presurgical evaluation of refractory patients to localise the ictal onset zone, ictal SPECT also shows hyperaemic regions which represent propagated ictal activity, because radiopharmaceutical is injected after noting seizure onset (Van Paesschen *et al.*, 2007). Therefore, ictal hyperperfusion topography should reflect activated structures responsible for the evolution of symptomatology during the seizure course.

Hypermotor seizures (HMS) have been studied extensively for identification of the epileptogenic zone (EZ), but studies regarding the symptomatogenic zone responsible for the hypermotor activity are sparse (Wong *et al.*, 2010). Using ictal SPECT and voxel-based analysis, the aim of the present study was to identify the neuronal networks generating specific ictal symptomatology in patients with HMS.

## Methods

### Patient selection and clinical characteristics

A retrospective analysis was conducted with patients selected from a database of 291 patients who had undergone an operation for refractory partial epilepsy at our institution between 1996 and 2008. A total of 13 patients were identified with HMS. HMS was defined as ictal complex motor agitation with proximal movements of the limbs, including body rocking, kicking or boxing movements, and horizontal or rotatory movements of the trunk and pelvis while lying on a bed (Williamson *et al.*, 1985; Waterman *et al.*, 1987; Lüders

*et al.*, 1998; Blume *et al.*, 2001). Inclusion and exclusion criteria were chosen to identify a homogeneous group of patients with HMS. Consecutive patients meeting the following inclusion criteria were included: (a) refractory epilepsy with HMS as the only seizure type; (b) early ictal SPECT injection (defined as being given <5 seconds after the start of a clinical or electrographic seizure or within the first half of a seizure) and ongoing seizure activity monitored under video-EEG during an episode of HMS; (c) interictal SPECT after a seizure-free period of at least 24 hours; and (d) post-surgery follow-up of at least two years. Exclusion criteria were as follows: (a) patients with mixed-type complex partial seizures (CPS) and (b) ictal injection during the postictal state or after the first half of a seizure. A diagnosis of HMS was made based on history obtained from the relatives and review of the video-EEG tapes by three of the authors. These three authors also visually assessed the SPECT findings and reviewed the findings of subtraction ictal SPECT co-registered to MRI (SISCOM) and SPM.

The following aspects were obtained from all patients: clinical characteristics (age at epilepsy surgery, sex, age at seizure onset, epilepsy duration, family history of epilepsy and history of febrile seizures), follow-up period after surgery, surgical outcome, and seizure semiology at the time of the ictal SPECT study.

### Seizure evaluation

The video tapes of all recorded seizures for each patient were reviewed. Three of the authors independently analysed clinical semiology. In the case of differing conclusions among the three investigators, consensus was achieved by common re-analysis of seizures. A total of 120 seizures were recorded in the 13 patients. All patients had HMS. The main ictal manifestations were categorised according to the International League Against Epilepsy (ILAE) classification (Blume *et al.*, 2001) and Rheims' classification (Rheims *et al.*, 2008). They were listed as follows: (1) groaning or shouting; (2) asymmetric tonic or dystonic posturing; (3) bilateral tonic or dystonic posturing; (4) marked agitation including body rocking, kicking or boxing behaviour associated with sitting up; and (5) mild agitation characterised by horizontal movements or rotation of trunk and pelvis.

### SPECT and MRI techniques

Interictal SPECT studies were performed by injection of 99mTc-ethyl cysteinate dimer (ECD) under intravenous sedation with midazolam. Midazolam was only given to patients with frequent seizures (two patients with less frequent seizures were excluded; Cases 12

and 13, who had four seizures in a month). Ictal SPECT studies were performed by intravenous injection of  $^{99m}\text{Tc}$ -ECD. The injection line was flushed thoroughly with saline immediately after seizure onset by personnel well acquainted with the patient's seizures and who were stationed at the bedside. The time of seizure onset was defined as the time of the earliest abnormal movements or behaviour, or the onset of impaired awareness or electrographic changes, whichever came first. The interval between seizure onset and time of injection was no more than five seconds. The administered dose was 600 MBq for adult patients and was determined using a formula  $[600 \times (\text{body weight in kg}/60)^{2/3}]$  MBq for paediatric patients. SPECT imaging was performed by two head cameras (Picker Prism 2000XP, Picker International Inc., Uniontown, OH, USA). The data were acquired in  $128 \times 128$  matrices over 20-minute periods. A total of 128 brain slices were obtained by T1-weighted MRI sequences (3D/SMASH, 1.5 Tesla, Shimadzu, Kyoto, Japan) (repetition time: 9.76 milliseconds; echo time: 4.4 milliseconds; flip angle: 15 degrees; matrix:  $256 \times 256$ ; field of view:  $260 \times 260$ ; width: 1.3 mm; gapless). Reconstructed images were reoriented to axial, sagittal, and coronal slices.

### SPM Study

SPECT analysis was performed using SPM software (version SPM2, Wellcome Department of Cognitive Neurology, London, UK) and was run on a MATLAB 6.1 (The Mathworks, Inc., Natick, MA, USA) platform. Default SPM2 parameters for analysis of SPECT images were used, except where noted. Before analysis, SPECT images of the patients with ictal onset arising from the left side were flipped onto the right side to allow group analysis of ipsilateral and contralateral perfusion changes. For paired ictal-interictal comparisons, interictal SPECT images of each patient were linearly transformed to match the ictal SPECT image. Ictal SPECT images were spatially normalised to the standard SPECT template using a 12-parameter affine and a further non-linear transformation, and the transformation matrix of the ictal SPECT was subsequently adjusted to the interictal SPECT of the same patient. Spatially normalised images were then smoothed using an isotropic Gaussian kernel with a 12-mm full width at half maximum (FWHM) to increase the signal-to-noise ratio. A height threshold (individual voxel-level significance) was set at  $p$ -value  $< 0.002$ . The extent threshold was set to  $KE = 125$ . The coordinates of cluster peak were determined using "Automated Talairach Atlas labels for functional brain mapping" (Lancaster et al., 2000). The results were displayed on the three-dimensional planes of a standard T1-MRI template.

### Electrocorticographic records

In 12 of 13 patients, a variable degree of inconsistency was observed among the anatomo-electro-clinical data as to the localisation of the epileptogenic zone (EZ), indicating the need for an ECoG investigation. For each patient, one recorded seizure was selected which was the same type as, and typical of, the seizure studied during ictal SPECT. Based on this epileptic discharge, sites of onset and propagation were determined. All patients had a post-operative follow-up of at least 36 months (36-144 months).

All but one patient (Case 2) underwent ECoG monitoring. Since one patient (Case 1) underwent two ECoGs, owing to continuing seizures after the first ECoG-based, left frontal FCD resection, 13 procedures were performed. Investigations were right-sided in six patients, left-sided in five patients and bilateral in one patient (Case 6). Inter-hemispheric electrodes were placed in five patients. Additional depth electrodes were placed in three patients.

### Results

Demographic and other key aspects of the study population are summarised in *table 1*. There were 13 patients: 10 male and three female. Age at presentation was 3-58 years, with a mean age of 23.7 years. The age at operation ranged from 9 to 58 years with a mean age of 26.8 years.

All HMS behaviour resulted in complex agitation; however, the intensity of agitation varied among patients, allowing differentiation of two types of HMS, as suggested by Rheims et al. (2008). Vocalisations of shouting and groaning, dystonic posturing, and change in facial expressions were accompanying symptoms. A detailed seizure description is presented in *table 2*.

### SPECT image analysis: visual and SISCOM

Analysis of SPECT images was performed by visual side-by-side analysis using SISCOM and SPM.

For visual analysis, the EZ was correctly localised by ictal SPECT in only five patients (two with FLE [frontal lobe epilepsy] and three with TLE [temporal lobe epilepsy]). In three patients, there were bilateral increased perfusion areas (IPAs) over the frontal lobe, which were more prominent ipsilateral to the lesion. In five patients, SPECT showed midline IPAs with ACC (anterior cingulate cortex) involvement (four with FLE and one with TLE), while in two patients no IPAs were identified on ictal SPECT (both with FLE; Cases 5 and 10).

Interictal SPECT was normal in five patients, showed hypoperfusion of the EZ in five patients (two with FLE

**Table 1.** Patient characteristics.

	Sex	Age at onset (yr)	Age at presentation (yr)	Age at operation (yr)	Duration of epilepsy (yr)	Seizure frequency (times/month)	Epilepsy type	Lesion type	Pathological findings	Outcome (Engel)	Follow-up (months)
1	M	2.3	3	9	6.8	500	FLE	FCD	FCD	I	163
2	M	13	28	33	20	100	FLE	FCD	FCD	I	154
3	F	2	24	24	22	30	FLE	Non-lesional	none	III	112
4	M	10	23	24	14	100	FLE	tuberous sclerosis	TS	I	98
5	M	12	31	34	22	500	FLE	FCD	FCD	I	99
6	M	8	18	18	10	30	FLE	Non-lesional	FCD	I	78
7	M	6	12	20	14	30	FLE	Non-lesional	FCD	III	64
8	F	4	19	20	16	30	FLE	FCD	FCD	I	60
9	M	3	21	28	25	30	FLE	Non-lesional	FCD	I	39
10	F	9	58	58	45	30	FLE	FCD	FCD	I	44
11	M	2.7	11	13	10.3	30	TLE	Non-lesional	FCD	I	38
12	M	2	24	27	25	4	TLE	Non-lesional	none	I	51
13	M	13	36	38	25	4	TLE	Non-lesional	FCD	III	39

FLE: frontal lobe epilepsy; TLE: temporal lobe epilepsy; FCD: focal cortical dysplasia; TS: tuberous sclerosis; yr: year.

and three with TLE), showed bilateral frontal hypoperfusion in one patient with right FLE (Case 4), and showed midline hyperperfusion in two patients (both with FLE).

The EZ was correctly localised by SISCOM in 10 patients; detailed findings are presented in *table 3*.

### SPM analysis

Ictal hyperperfusion images in the SPM group analysis of paired ictal-interictal SPECTs of 13 patients revealed significant hyperperfusion in the ACC, orbitofrontal gyrus (OFG), lentiform nucleus (LFN) and midbrain. *Figure 1* shows the mapped areas of statistically significant increases in blood flow as a fusion image with maximal intensities at the OFG at a t-value of 7.38 at SPM coordinates (x, y, z), (mm) equal (14, 32, -28), and at the right ACC at a t-value of 4.65 with coordinates 8, 28, 18 on the sagittal, coronal, and axial sections, respectively. Other statistically significant areas of increased regional cerebral blood flow (rCBF) obtained were the LFN at a t-value of 4.19 (22, 4, 0), the claustrum at a t-value of 4.80 (26, 20, 8), the midbrain at a t-value of 4.69 (2, -22, -6), and the pons at a t-value of 4.79 (4, -16, -30).

SPM analysis was also performed on each group of patients, which did not reveal any significant results at  $p < 0.002$ . Analysis was then performed at  $p < 0.003$ , which revealed hyperperfusion in the white matter, the closest grey matter in the left frontal lobe, the subcallosal gyrus, Brodmann area 25 in HMS-2, and the right brainstem including the medulla in HMS-1 (*figure 2*).

### Electrocorticography

Subdural electrodes were placed in all patients and additional depth electrodes were placed in three patients. Detailed ECoG findings are presented in *table 3*. The ictal onset zone included the lateral frontal cortex in nine patients, anterior temporal cortex in two patients, parieto-temporal cortex in one patient and the ACC in one patient.

### Surgery and outcome

All 13 patients underwent epilepsy surgery. Surgery involved resection of the frontal lobe in nine patients, the temporal lobe in three patients and the left ACC in one patient. The EZ localised by focal low-amplitude fast activities or rhythmic spikes on a few electrodes

**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

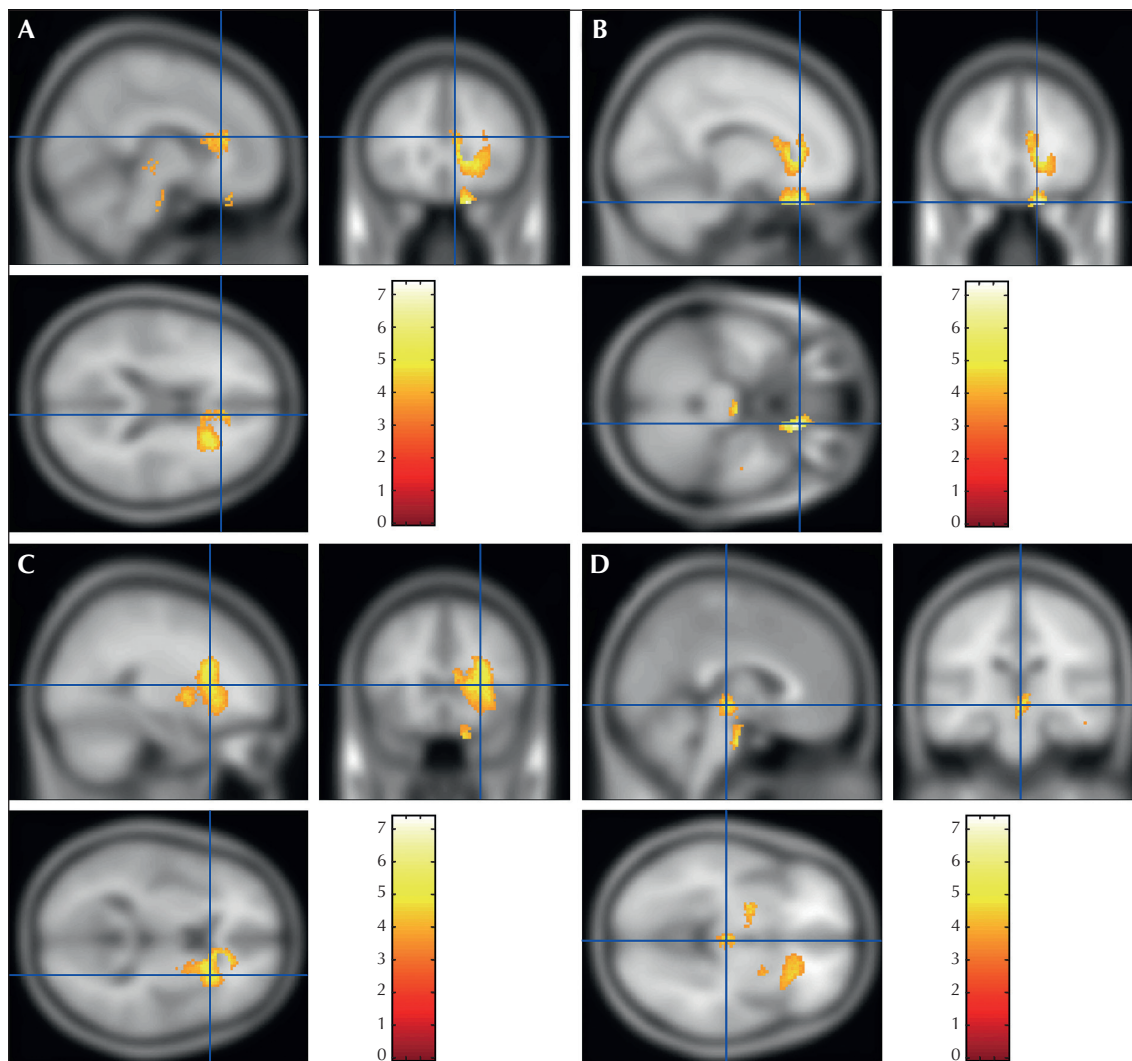
Identifying cerebral mechanisms underlying the clinical manifestation of epileptic seizures can provide insight into the physiological processes underlying non-pathological behaviour in the normal brain. The network structures within the brain are connected functionally, and structurally, it is not surprising 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.



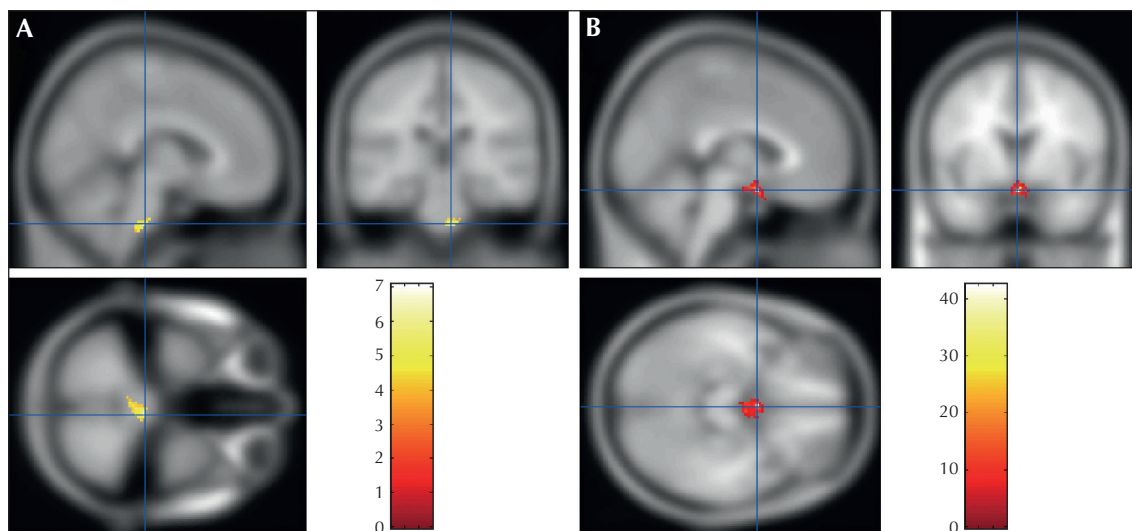
**Figure 1.** Statistical parametric mapping shows dominant hyperperfusion in the right anterior cingulate cortex (BA24, 32). (A) at t-value of 4.65 at SPM coordinates (x, y, z), (mm) equal (8, 28, 18); right orbito-frontal gyrus (B) at t-value of 7.38 at SPM coordinates (x, y, z), (mm) equal (14, 32, -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, cingulate 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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### Disclosures.

None of the authors has any conflict of interest to disclose.

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