

# Motor cortex and hippocampus are the two main cortical targets in LGI1-antibody encephalitis

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Encephalitis associated with antibodies against leucine-rich glioma-inactivated 1 (LGI1) protein is increasingly recognized as an auto-immune disorder associated with characteristic tonic-dystonic seizures. The cortical or subcortical origin of these motor events is not clear. Some patients also present with different epileptic seizures and with cognitive impairment. The frequency of these features and their timing during the natural history of this encephalitis have not been fully described. We therefore reviewed data from 34 patients harbouring antibodies against LGI1 protein (21–81 years, median age 64) referred to the French Reference Centre for Neurological Paraneoplastic Syndrome. Three types of evidence suggested tonic-dystonic seizures were of cortical origin: (i) a slow, unilateral, frontal electroencephalographic wave, of duration ~580 ms and amplitude ~71  $\mu$ V, preceded the contralateral tonic-dystonic seizures in simultaneous electroencephalographic and myographic records from seven of seven patients tested; (ii) 18-Fluorodeoxyglucose imaging revealed a strong hypermetabolism in primary motor cortex, contralateral to the affected limb, during encephalitis for five patients tested, as compared with data from the same patients after remission or from 16 control subjects; and (iii) features of polymyographic records of tonic-dystonic seizure events pointed to a cortical origin. Myoclonic patterns with brief, rhythmic bursts were present in three of five patients tested and a premyoclonic potential was identified in the cortex of one patient. Initially during encephalitis, 11 of 34 patients exhibited tonic-dystonic seizures (32%). Distinct epileptic syndromes were evident in 13 patients (38%). They were typically simple, focal seizures from the temporal lobe, consisting of vegetative symptoms or fear. At later stages, 22 of 32 patients displayed tonic-dystonic seizures (68%) and 29 patients presented frequent seizures (91%) including status epilepticus. Cognitive impairment, either anterograde amnesia or confusion was evident in 30 of 34 patients (88%). Brain imaging was normal in patients with isolated tonic-dystonic seizures; in patients with limbic symptoms it revealed initially a hippocampal hyperintensity in 8 of 19 patients (42%) and 17 of 24 patients (70%) at later stages. Our data suggest that the major signs of LGI1-antibody encephalitis can be linked to involvement of motor cortex and hippocampus. They occur in parallel with striatum involvement. One of these cortical targets is involved, often unilaterally at disease onset. As the encephalitis progresses, in the absence of immunomodulatory treatment, the second cortical target is affected and effects become bilateral. Progression to the second cortical target occurs with a variable delay of days to several months.

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**Abbreviations:** T = tonic; TDS = tonic-dystonic seizure; T-M = tonic-myoclonic; VGKC = voltage-gated potassium channel

## Introduction

Encephalitis associated with antibodies directed against the LGI1 protein (LGI1-antibodies) is a recently described autoimmune syndrome. Initial diagnoses were based on the presence of antibodies against voltage-gated potassium channel-complexes (VGKC-antibodies) (Vincent *et al.*, 2004). It has become clear that the antibodies target other proteins including LGI1 and contactin-associated protein-like 2 (Caspr2, encoded by *CNTNAP2*), which are associated within a complex regulating VGKCs (Irani *et al.*, 2010; Lai *et al.*, 2010). LGI1 is mainly expressed in the CNS, and patients with LGI1 antibodies exhibit limbic encephalitis and seizures. Caspr2 is also expressed in the peripheral nervous system, and patients with Caspr2 antibodies exhibit neuromyotonia or Morvan's syndrome as well as a limbic encephalitis (Irani *et al.*, 2010; Klein *et al.*, 2013).

Mutations in the *LGI1* gene have also been identified in patients with an autosomal dominant temporal lobe epilepsy with auditory features (Gu *et al.*, 2002; Kalachikov *et al.*, 2002; Morante-Redolat *et al.*, 2002). The *LGI1* gene encodes a secreted protein, not an ion channel, in contrast to many other genes involved in autosomal dominant epilepsy. This protein may regulate presynaptic VGKCs and so affect transmitter release (Fukata *et al.*, 2010). Post-synaptically, LGI1 interactions with ADAM22 protein are thought to maintain AMPA receptors at synaptic sites (Fukata *et al.*, 2006). Finally, LGI1 may also play a role in the development of glutamatergic synapses (Zhou *et al.*, 2009). Maximal immunostaining with CSF samples from patients with LGI1-antibody-related encephalitis, is detected in dendritic regions with high density of glutamatergic synapses. Autoimmune syndromes linked to antibodies targeting synaptic proteins such as LGI1 and Caspr2

respond well to immunomodulatory treatment, and often have non-paraneoplastic origins (Vincent *et al.*, 2011; Linnoila *et al.*, 2014).

The diversity of symptoms associated with LGI1-antibody encephalitis and the natural history of the syndrome have not yet been completely described. 'Faciobrachial dystonic' motor seizures have been shown to precede the onset of limbic encephalitis (Irani *et al.*, 2011). The origin of motor seizures has been discussed: some authors suspect a subcortical (Striano *et al.*, 2011), others a cortical origin (Andrade *et al.*, 2011; Irani *et al.*, 2011) and others contributions from both sites (Boesebeck *et al.*, 2013). Improved knowledge on early symptoms and investigations should aid diagnosis and permit rapid immunomodulatory treatment, which could help prevent irreversible lesions, such as hippocampal atrophy. A better understanding on the origin of motor seizures may aid the choice of adjunctive treatment. For these reasons, we describe here a large series of patients with LGI1-antibody encephalitis focusing on early manifestations of the syndrome and on the apparently cortical origin of associated motor seizures.

## Materials and methods

### Patients with LGI1-antibody encephalitis

Patients with LGI1-antibody-linked encephalitis were retrospectively selected from the database of the French Reference Centre for Neurological Paraneoplastic syndrome. Demographic, clinical, biological, imaging and electrophysiological data were reviewed from patients with clinical onset of the syndrome before January 2015. We then subdivided the population according to the estimation of the cortical origin of

their initial symptoms. The subdivision was made *a posteriori* using clinical and paraclinical data from each patient.

In a subset of these patients, further studies were performed as described below.

## LGII-antibody detection

The presence of LGII-antibodies in serum or CSF was measured using a cell-based assay with human embryonic kidney cells (HEK293) overexpressing the LGII protein fused to the green fluorescent protein (GFP) and the ADAM22 protein. HEK293 cells were grown on glass coverslips in Dulbecco's modified Eagle medium with 10% foetal calf serum. They were co-transfected with plasmids coding for *LGII*-GFP and *ADAM22* using Lipofectamine® LTX (Life Technologies). Cells were grown for 48 h and then incubated with the patient's serum (1:20) or CSF (1:10) in a dilution buffer [phosphate-buffered saline (PBS) containing 1% bovine serum albumin and 5% normal goat serum] for 2 h. Cells were then washed in dilution buffer, fixed in 1% paraformaldehyde for 15 min, washed in PBS and incubated with Alexa Fluor® 555 anti-human IgG (Life Technologies) and DAPI. Bound antibodies were visualized with a fluorescence microscope (Axiophot, Zeiss). Negative controls consisted of serum or CSF from patients without encephalitis.

## EEG analysis

EEG signals were recorded with 21–27 scalp electrodes placed according to the 10–20 system. In some patients, one or two bipolar electromyographic signals were recorded in parallel from major muscles activated during motor seizures. Patient behaviour was captured with a simultaneous video recording. Data from several recording systems (Medatec, Micromed, Nicolet) were reviewed in an average reference montage.

## Brain MRI

Standard procedures for brain MRI included T<sub>1</sub>, T<sub>2</sub>, T<sub>2</sub>\* and FLAIR (fluid attenuated inversion recovery) sequences. In some patients, MRI was performed with an 'epilepsy protocol' where coronal sections orthogonal to the main axis of the hippocampus were used to better visualize hippocampal structures.

## Brain <sup>18</sup>F-FDG-PET studies

### PET procedure

A subgroup of patients underwent 18-fluoro-deoxyglucose (18-FDG) PET scans during initial clinical evaluations at diagnosis and after remission of symptoms. Brain PET/CT images were acquired with a hybrid PET/CT system (Gemini XLS, Philips Medical Systems) 30 min after intravenous injection of <sup>18</sup>F-FDG (2.5 MBq/kg). During <sup>18</sup>F-FDG injection and until image acquisition, patients rested in a quiet environment with eyes closed. A CT scan was recorded to provide an attenuation-correction map. It was followed by a 15-min emission scan consisting of three 5-min frames. <sup>18</sup>F-FDG-PET images were reconstructed using iterative reconstruction and corrected for gamma-ray attenuation and scatter. Procedures were identical for baseline and post-treatment studies.

## PET data analysis

Metabolic data were analysed using SPM5 software (Wellcome Department of Cognitive Neurology, University College, London) implemented in MATLAB (Mathworks, Sherborn, MA). PET frames were realigned, summed, co-registered to individual T<sub>1</sub>-weighted MRI, spatially normalized in Montreal Neurological Institute (MNI) space, and normalized to global intensity with SPM5.

A z-score mapping implemented in BrainVisa software (<http://brainvisa.info>) was used to extract areas with differences in metabolism during encephalitis and remission. Values from identified image areas in PET data were subtracted between conditions for each patient. Relative differences were computed into z-scores as described (Huberfeld *et al.*, 2006). Clusters of <100 voxels (8 ml) and voxels with absolute values of <1.5 z-score were extracted before displaying z-score maps onto anatomical MRI.

Regions of metabolic change in patients were compared to the same areas of brain scans from 16 healthy volunteers (mean age 55.2 ± 11.5 years, range 36–75) using the general linear model with linear contrasts in SPM5. Images were smoothed and proportional scaling was used to adjust global values for metabolism. Contrast was first used to estimate major effects of the pathology by comparing values from patients during acute encephalitis to values from control in order to identify cortical or subcortical regions of altered glucose metabolism. Age was entered as a confounding variable. Secondly, changes within patients were assessed by comparing values from patients during acute encephalitis with those obtained after remission using a paired *t*-test. As sample sizes were small, SPM(T) maps were thresholded at *P* < 0.05 corrected for multiple tests using the false discovery rate (FDR) method to compare patients with controls. An uncorrected threshold of *P* < 0.005 was used to compare encephalitis and remission states in patients. Only clusters of more than 50 voxels were considered. The MarsBaR software (<http://marsbar.sourceforge.net>) was used to search for correlations in metabolic changes at cortical and subcortical sites.

## Polymyography of spasms and myoclonus

Polymyography was performed in five patients with a Neuropack (Nihon Kohden) in the Saint-Antoine Hospital Neurophysiology Unit (EA). EMG signals were recorded with pairs of 9-mm diameter silver/silver chloride electrodes (Medtronic) placed 2-cm apart over muscle bellies. We recorded from several muscles chosen according to the site of movement disorders. They included: (i) orbicularis oris; (ii) deltoid, biceps brachii, extensor carpi radialis and palmaris for upper limbs; and (iii) vastus lateralis, tibialis posterior and flexor hallucis brevis for lower limbs. EMG signals were band-pass filtered at 20–500 Hz. Patients were recorded during rest, posture and action/intention. We attempted to initiate stimulus-sensitive myoclonus with light distal touch, pinprick or passive limb mobilization and brisk sounds. Myoclonus frequency as well as the duration and temporospatial organization of myoclonus or spasm were measured. Polymyographic data were completed with cortical tests including EEG-Jerk-Locked Back-Averaging (JLBA) and C-reflex studies, performed as previously described (Aparis *et al.*, 2008).

## Ethics

We obtained the agreement of our local ethics committee (CCP-Ile de France Paris VI and University Claude Bernard Lyon 1) for retrospective data analysis.

## Statistical analysis

Nominal variables were compared using the exact test of Fisher and quantitative variables with the Mann-Whitney or Kruskal-Wallis test. Differences were significant for  $P$ -values  $<0.05$  (two-sided), except for multiple comparisons where the Bonferroni correction was used. Statistical analyses were performed with Statview software (SAS institute, version 5.0).

## Results

### Clinical presentation of the LGII-antibody encephalitis

We studied 34 patients with encephalitis and LGI1-antibodies detected in serum or CSF. They were identified by the French Reference Centre for Neurological paraneoplastic syndromes between January 2010 and January 2015. Table 1 provides clinical details for the patients (19 male and 15 female, median age 64 and range 21–81 years). The median delay from the onset of the encephalitis and the diagnosis was 4.4 months (range: 0.2 to 13). Prodromal signs, other than weight loss in a young patient, were not identified.

#### Tonic-dystonic seizures

Tonic-dystonic seizures (TDS) could be identified in 22 of 32 patients with available data. They consisted of a sudden, short and predominantly distal tonic contraction of the upper limb of duration  $\sim 1$  s (19/19 patients). In some patients the hemiface (14/19) and the lower limb (11/20) were involved (Supplementary Fig. 1). The end of the movement was accompanied by a dystonic posture, with the fingers of the hand moving apart and a few brief automatisms. Movements varied from moderate to hemiballistic. Some patients (7/18) groaned during seizures, others (3/18) showed a brief anarthria. When lower limbs were involved in TDS patients often fell (12/20) inducing traumas (7/20), including subdural haematoma. TDS were often initially unilateral (12/17 patients). They evolved with time into bilateral, asynchronous TDS (10 of 17 patients), occurring either independently or with a short delay (*à bascule*). TDS occurred during wakefulness (20/20) and sleep (5/6 patients). They were provoked in some patients (6/13) by motor triggers, such as change of position or orthostatism, by surprise, such as an unexpected sound, or by emotion and stress. An aura, sensed more proximally in the same hemibody (shoulder, ear or hemithorax), was reported to precede TDS by a few

seconds by three of nine patients. Frequency of TDS increased with time from about one every second day to a median value of  $\sim 35$  per day (range: 10 TDS during 1 month to one per 5 min). Consciousness was always maintained during isolated TDS (12/19 patients). It was lost in all patients where TDS evolved rapidly into temporal or frontal lobe seizures (7/19).

#### Temporal lobe seizures

In most patients (29/32) distinct epileptic seizures, either focal or generalized, emerged with time. These seizures typically originated from the temporal lobe (24/29). In 14 patients with simple focal seizures, subjective symptoms suggesting a mesial temporal origin included sensation of fear ( $n = 6$ ) or vegetative symptoms ( $n = 13$  patients), such as ascending epigastric or hot and cold feeling, blockpnea, falling sensations and pilo-erection. They initially lasted a few seconds, occurred during waking and sleep, at a frequency of 10–40 per day close to a status epilepticus. Consciousness was not lost. Some of these seizures were initially misdiagnosed as psychogenic non-epileptic events. Dismnesic symptoms, such as *déjà vu*, *déjà vécu*, and reminiscences were reported at first in two patients, or were reported after immunomodulatory treatment by three of six patients. These late onset dysmnesic seizures occurred at most twice per day and could usually be controlled by antiepileptic drugs.

Seventeen patients presented with loss of consciousness and seven with automatisms suggesting a temporal lobe origin (gestural, oral and speech, including coprolalia and cough). Their frequency and intensity increased with time to a maximum of 24 seizures per day. Focal seizures were preceded by TDS ( $n = 5$ ), followed by TDS ( $n = 1$ ) or associated with a slow and prolonged dystonia of the right hand ( $n = 1$ ). Eighteen patients presented generalized convulsive seizures and a generalized convulsive status epilepticus was observed in six patients.

#### Cognitive impairment

Cognitive impairments were diagnosed in 30 of 34 patients, based on neurological examination at admission. Anterograde memory deficits were frequent (29/34). Such deficits worsened without immunotherapy, and could lead to amnesic syndromes. Patients progressively showed temporal and spatial disorientation (21/33) and permanent confusion (20/33 patients). Patients with cognitive impairment progressively scored low on the Mini-Mental State Examination (median of the minimum score: 23/30; range 11/30 to 28/30). A dysexecutive syndrome was diagnosed in 13/32 patients. Fast scoring for frontal evaluation (Dubois *et al.*, 2000) showed a mild impairment (median of minimum value: 15/18; range 3–17/18). Frontal syndrome, such as disinhibition, gluttony or self-neglect, were rarely evident. Language was perturbed in 12 of 32 patients and behaviour problems were observed in 16/32 patients.



**Table 1 Clinical features and tests of the patients with LGII antibodies encephalitis**

	Total cohort	Subdivision in three groups according to suspected cortical origin of the initial symptoms during the first month of encephalitis				
		Mesial temporal lobe involvement		Motor cortex involvement		P-value
					Early involvement of both structures	
<b>Demography</b>						
Number of patients	34	15/32	46.7%	7/32	21.8%	31.2%
Gender M/F	19/15	8/7	53.3% M	3/4	42.9% M	70% M
Age at onset, years, median (range)	64.1 (21–81.2)		65.4 (21–77.9)		65.0 (59.3–79.6)	55.8 (24.6–81.2)
		Number of patients/ number of patients with available data	%	Number of patients/ number of patients with available data	%	Number of patients/ number of patients with available data
<b>Initial symptom</b>						
Cognitive impairment	19/34	11/15	55.8	0/7	0	6/10
Seizures	13/34	7/15	38.2	1/7	14.3	5/10
Motor tonic/dystonic seizures	11/34	0/15	32.3	7/7	100	4/10
<b>Cumulative symptoms</b>						
Cognitive impairment	30/34	15/15	88.2	5/7	71.4	8/10
Seizures	29/34	14/15	85.2	5/7	71.4	10/10
Motor tonic/dystonic seizures	22/32	5/15	68.7	7/7	100	10/10
Mood disorders	15/34	8/15	44.1	3/7	42.9	3/10
Sleep disorders	12/32	7/15	37.5	2/7	28.6	3/10
Motor disorders <sup>a</sup>	7/32	4/15	21.8	2/7	28.6	1/10
<b>Sodium level</b>						
Hyponatremia during evolution <sup>c</sup>	20/29	8/11	68.9	5/7	71.4	6/10
<b>MRI</b>						
Abnormal MRI at the time of initial symptoms	8/23	5/10	34.7	0/4	0	2/7
Unilateral hippocampal hypersignal	6/8	4/5	75	0/4	0	2/2
Bilateral hippocampal hypersignal	2/8	1/5	25	0/4	0	0/2
Subsequent abnormal MRI	21/31 <sup>b</sup>	12/15	67.7	2/6 <sup>b</sup>	33.3	7/10
Unilateral hippocampal hypersignal	7/21	2/12	30.0	1/2	50	3/7
Bilateral hippocampal hypersignal	13/21	10/12	61.9	0/2	0	3/7
Hippocampal sclerosis	6/21	4/12	28.5	0/2	0	2/7
<b>CSF</b>						
Abnormal	3/30	1/15	10	1/7	14.3	1/8
Hypercellularity	3/3	1/15	100	1/7	14.3	1/8
<b>EEG</b>						
Abnormal	24/32	12/13	75	5/7	71.4	6/10
Focal or diffuse slowing	20/24	11/12	83	4/5	80	4/6
Seizure activity	17/24	9/12	70.8	4/5	80	4/6
<b>Cancer</b>						
Present	2/32	1/15	6.2	1/6	16.7; lung	0

<sup>a</sup>Cerebellar ataxia, apraxia or tremor.<sup>b</sup>One patient had a brain vascular lesion, not related to the encephalitis.<sup>c</sup>Hyponatremia was defined as serum sodium concentration of less than 134 mM.\*Mesial/motor  $P = 0.005$ , mesial/both  $P = 0.001$ , motor/both  $P < 0.999$ ; \*\*mesial/motor  $P = 0.048$ , mesial/both  $P = 1$ , motor/both  $P = 0.067$ ; \*\*\*mesial/motor  $P = 0.066$ , mesial/both  $P = 0.129$ , motor/both  $P = 0.5$  (no significant difference due to Bonferroni correction). F = female; M = male.

### Other impairments

Twelve of 32 patients reported sleep disturbances, sometimes major and leading to agrypnia. Fifteen of 34 patients reported mood changes, although antiepileptic drugs and steroid therapy may have contributed. Two patients reported autonomic system disturbances, in one case orthostatic hypotension and excessive sweating and cardiac arrest during anaesthesia in the other.

### Natural history of the disease

Table 1 presents three distinct clinical symptoms that were evident in 34 patients during the first month of the encephalitis. Firstly, TDS were detected in 11 patients. Secondly, a distinct pattern of epileptic seizure, mainly of temporal lobe origin, was present in 13 patients. Thirdly, 19 patients exhibited various forms of cognitive impairment. Some patients shared several of these symptoms. We estimated the cortical origin of these initial symptoms for 32 patients. Evidence from this group suggested the motor cortex alone was involved for eight patients, the mesial temporal lobe was involved for 21 patients and a shared motor and temporal cortex involvement for three patients.

As the LGI1-antibody encephalitis evolved, and before immunosuppressive treatment was initiated, associated cortical regions also changed. In five of eight patients with a pure initial motor cortex component, mesial temporal cortex became secondarily involved with a median delay of 6 months (range 0.6–6). For 11 of 21 patients in whom a pure mesial temporal lobe involvement was first observed, motor cortex symptoms became evident with a median delay of 1 month (range 0.2–10). These latencies to secondary involvement were not significantly different ( $P = 0.171$ , Mann Whitney test). Kaplan-Meier curves constructed to determine changes with time after the onset of the disease, of the fraction of patients with only a single cortex involved also showed no significant difference between patients with initial temporal or motor cortex involvement (Supplementary Fig. 3). Finally, a comparison of the main clinical and investigation findings at follow-up (Table 1), according to the identified cortical regions during the first month of the encephalitis (both hippocampus and motor cortex,  $n = 10$ ; hippocampus alone,  $n = 15$ ; motor cortex alone,  $n = 7$  patients), revealed no significant differences.

### Biological investigations

While the CSF was typically normal, a moderate pleocytosis ( $8\text{--}14$  white cells/ $\text{mm}^3$ ) was detected in 3 of 30 patients. Intrathecal immunoglobulin synthesis was never detected. Twenty of 29 patients presented hyponatremia (median 128; range 113–133 mmol/l). Sodium levels were normal in 7 of 9 patients with no major cognitive impairment, experiencing TDS, sometimes with temporal lobe seizures. The other two patients

with hyponatremia received furosemide and carbamazepine. In contrast, hyponatremia was present in 18 of 20 patients with major cognitive impairment, with or without TDS. This difference was statistically significant ( $P = 0.0007$ , Fisher's exact test). Tumours, one affecting the lung the other the kidney, were present in 2 of 32 patients.

### Different EEG changes related to motor or temporal seizures

EEG abnormalities were detected in 24 of 32 patients. They consisted of a focal, diffuse slowing ( $n = 20$ ) and ictal activity ( $n = 17$  patients). Further analysis of EEG records was done in nine of these patients (Table 2).

#### A focal contralateral EEG wave precedes tonic-dystonic seizures

We analysed EEGs from seven patients with isolated TDS in detail. Background EEG activity was normal in the three patients without other symptoms. Stereotyped brief tonic contractions of duration  $0.9 \pm 0.4$  s ( $n = 87$  events) were recorded from the major muscle group implicated in the TDS by EMG electrodes. Concomitant muscle artefacts, of irregular frequency, were detected on some EEG records. A focal EEG wave (Fig. 1) was detected from frontal cortex electrodes of all patients with isolated TDS ( $n = 7$ ). It preceded muscle artefacts, and was recorded from two or more adjacent fronto-polar, frontal or central electrodes. It was better detected on average reference montage than on bipolar montages. The mean duration was  $577 \pm 320$  ms and mean amplitude was  $71 \pm 34$   $\mu\text{V}$  ( $n = 99$  events). The EEG transient was typically unilateral and contralateral to TDS muscle contractions. In one patient the wave was only detected on median frontal electrodes (Fz, Cz). It always preceded TDS in some patients, but was less consistently detected in others. In three patients with bilateral asynchronous TDS, distinct unilateral slow waves were generated independently for each side. These EEG transients were consistently associated with TDS and disappeared with remission.

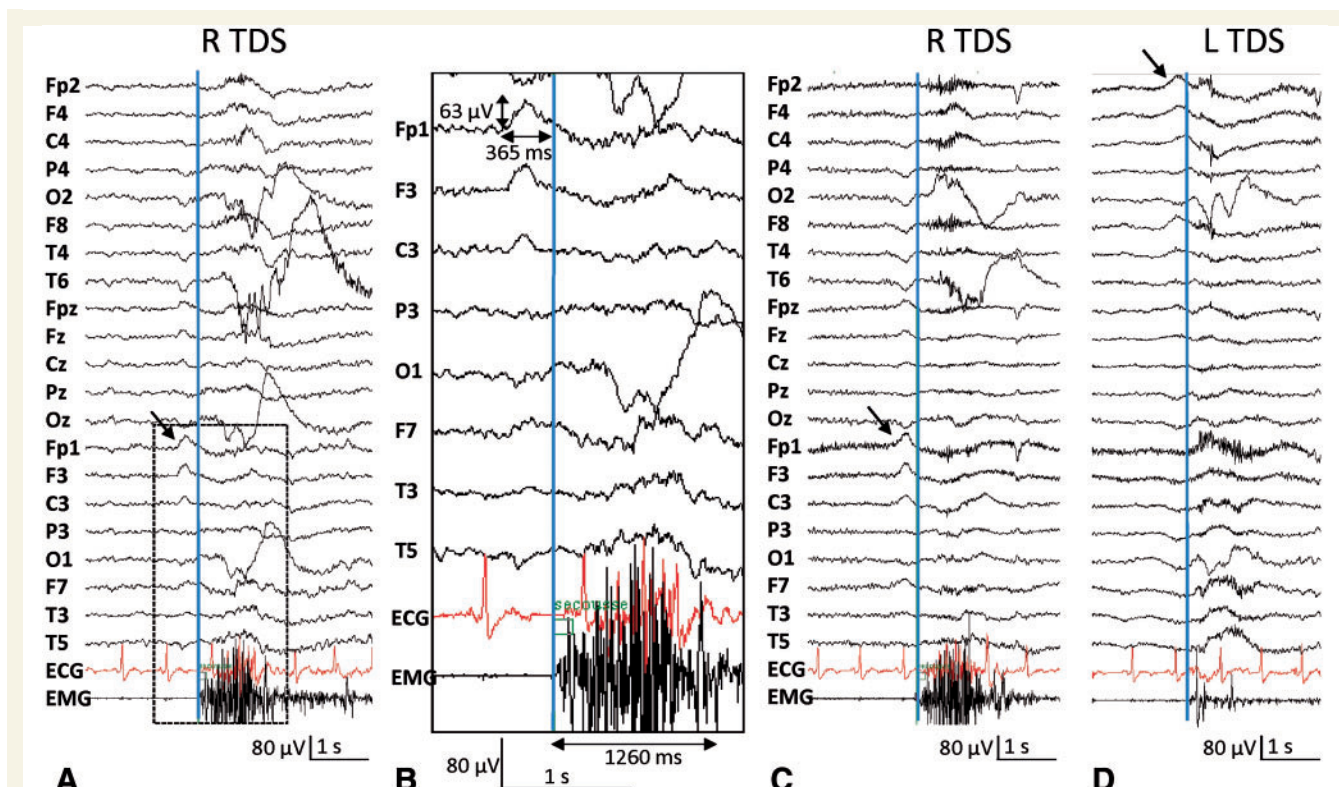
#### Classical EEG epileptic activities during temporal seizures

In five patients with limbic encephalitis and cognitive impairment, a slowing of background EEG activity was frequently observed. Interictal epileptic events, including spikes and sharp waves, were preferentially generated by the temporal or frontal lobes during sleep or drowsiness. Seizures recorded from four of these five patients began with a unilateral or bilateral flattening of EEG background over several seconds and in one patient with a similar focal slow wave as those associated with TDS (duration 575 ms; amplitude  $81 \pm 5$   $\mu\text{V}$ ;  $n = 3$  seizures). In another patient, a tonic-dystonic seizure was systematically observed 10 to 30 s before the seizure. After irregular muscular artefacts,

**Table 2** Main clinical and paraclinical characteristics of the LGII encephalitis patients with multimodal evaluation

Patient	Age/sex	TDS	TLE	Cognitive deficit	LGII ab	CSF	Na <sup>+</sup>	EEG changes before TDS	EEG slowing/epileptic activity	Brain MRI	FDG-PET Hyper-metabolism	Poly-myography
1	56/M	R and L	Vegetative status, then rare and late dysmnesic Sz	Moderate	CSF	N	N	Focal wave before R and L TDS	Moderate slowing of the background activity	Increase T <sub>2</sub> and FLAIR signal and oedema in the R hippocampus then HS	PUT > CAU; Mot C bil; Sen C	T-M
2	64/M	R and L (some preceded by sensory aura)	Vegetative status, then rare dysmnesic Sz	No	Serum and not CSF	N	N	Focal wave before R and L TDS	Slow waves on the Fp lobes during sleep	Increase FLAIR signal in the R hippocampus, then N	CAU > PUT; Mot C bil; Sen C; MTL	T-M
3	64/F	L	No	No	Serum and not CSF	N	N	Focal wave before L TDS	N	N	PUT; Mot C uni; Sen C	T
4	63/F	R and L	CPS	Yes	CSF	N	130	Focal wave before L TDS	Interictal and ictal activity on R Te lobe	N	ND	ND
5	22/F	R (dystonic posture during CPS)	CPS; then late dysmnesic Sz when recovery	Yes	CSF	N	129	No	Interictal and ictal activity on R or L Te lobe	N, then increase FLAIR signal and oedema in both hippocampi	CAU > PUT; Mot C uni; Sen C; MTL	T
6	79/M	R and L	CPS (including vegetative and emotional symptoms)	Yes	CSF	Moderate pleocytosis (14 white cells/mm <sup>3</sup> ; control: 5/mm <sup>3</sup> ); protein 0.4 g/l	133	Focal wave before R TDS	Slowing of the background activity	N (except vascular leucopathy)	CAU > PUT; Mot C bil; PreM C; MTL	ND
7	63/M	R	No	No	Serum and not CSF	N	N	Focal wave before R TDS	N	N	ND	T-M
8	21/F	R and L	CPS near status (vegetative, gustatory and dysmnesic)	Yes	CSF	N	131	Focal wave before R and L TDS	Fp and R Te lobe interictal activities; Fp ictal activity Slowing of the background activity	Increase FLAIR signal in the R hippocampus, then atrophy	ND	ND
9	44/M	L	Vegetative Sz	No	Serum and not CSF	N	N	Focal wave before L TDS	N	N	ND	ND

M = male; F = female; TLE = temporal lobe epilepsy; ab = antibody; Na<sup>+</sup> = natremia; R = right; L = left; N = normal; ND = not determined; CPS = complex partial seizure; Sz = seizure; Te = temporal; Fp = fronto-polar; HS = hippocampal sclerosis; PUT = putamen; CAU = caudate nucleus; Mot C = motor cortex; bil = bilateral; uni = unilateral; Sen C = sensorimotor cortex; PreM C = premotor cortex; MTL = mesial temporal lobe. PUT > CAU: striatal FDG hypermetabolism that was predominant in the putamen.



**Figure 1 EEG records of isolated TDS.** EEG traces from Patient 1 show brief, isolated TDS affecting right (R) or left (L) limbs. Scalp EEG records with an average reference montage, EMG records from a bipolar electrode over the right deltoid. A focal slow wave on frontal EEG electrodes (arrow) consistently preceded EMG activity. Before the TDS involving the right limb (**A–C**), the EEG transient was recorded by left frontal electrodes (Fp1, F3, C3, Fpz, Fz). Before the left limb TDS (**D**), it was detected on right frontal electrodes (Fp2, F4, F8, C4, Fpz). **B** shows expanded traces from **A**. The contralateral cortical wave had a duration of 365 ms and amplitude of 63  $\mu$ V. EMG activity duration was 1260 ms, and amplitude increased and then decreased, as rhombus-shaped EEG traces from infantile epileptic spasms (Vigevano et al., 2001).

a rhythmic EEG activity, generally irregular distributed bilaterally over frontal and temporal lobes was detected. A secondary unilateral temporal or frontal organization was sometimes evident (Supplementary Fig. 4). Total seizure duration was  $43 \pm 16$  s ( $n = 18$  seizures).

## Brain MRI changes only detectable during temporal involvement

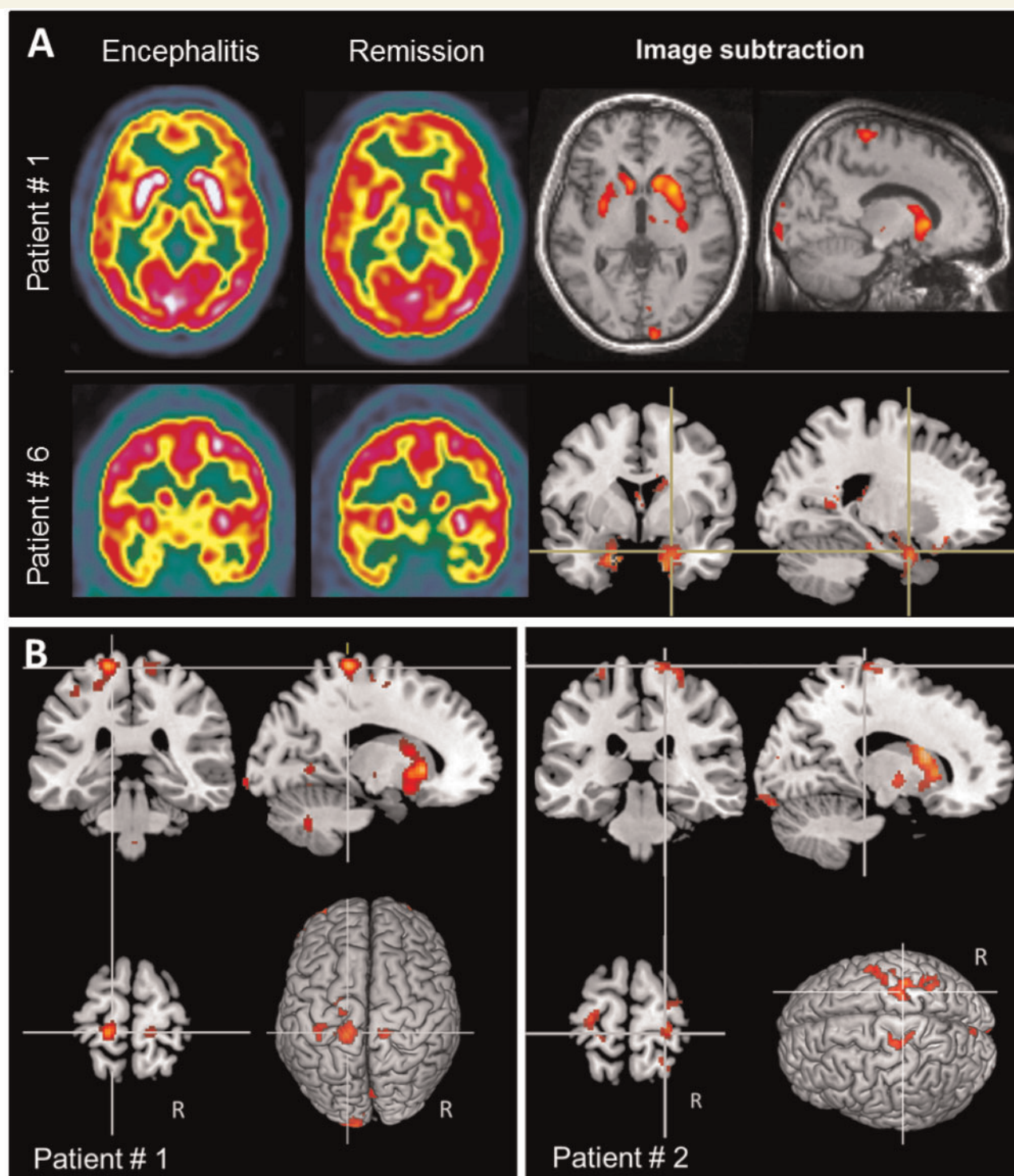
Brain MRI scans made at the time of the first symptoms showed abnormal FLAIR hyperintensity in the hippocampus for 8 of 23 patients. It was unilateral in six patients and bilateral in two. Later scans revealed hippocampal FLAIR hyperintensity in 20 of 31 patients, unilateral for seven and bilateral for 13 of them. An initial swelling, suggestive of an oedema, was evident at first in some cases and later disappeared. In six patients a hippocampal atrophy suggestive of sclerosis followed the swelling. It was unilateral in four patients and bilateral in two. Initial MRI scans were normal in five of five patients with isolated TDS. When the mesial temporal lobe was clinically involved, initial MRI scans showed hippocampal FLAIR hyperintensity in 8 of 19 patients and later scans showed a hyperintensity in 17 of 24 patients (Supplementary Fig. 2).

## Frontal, temporal cortical and subcortical hypermetabolism

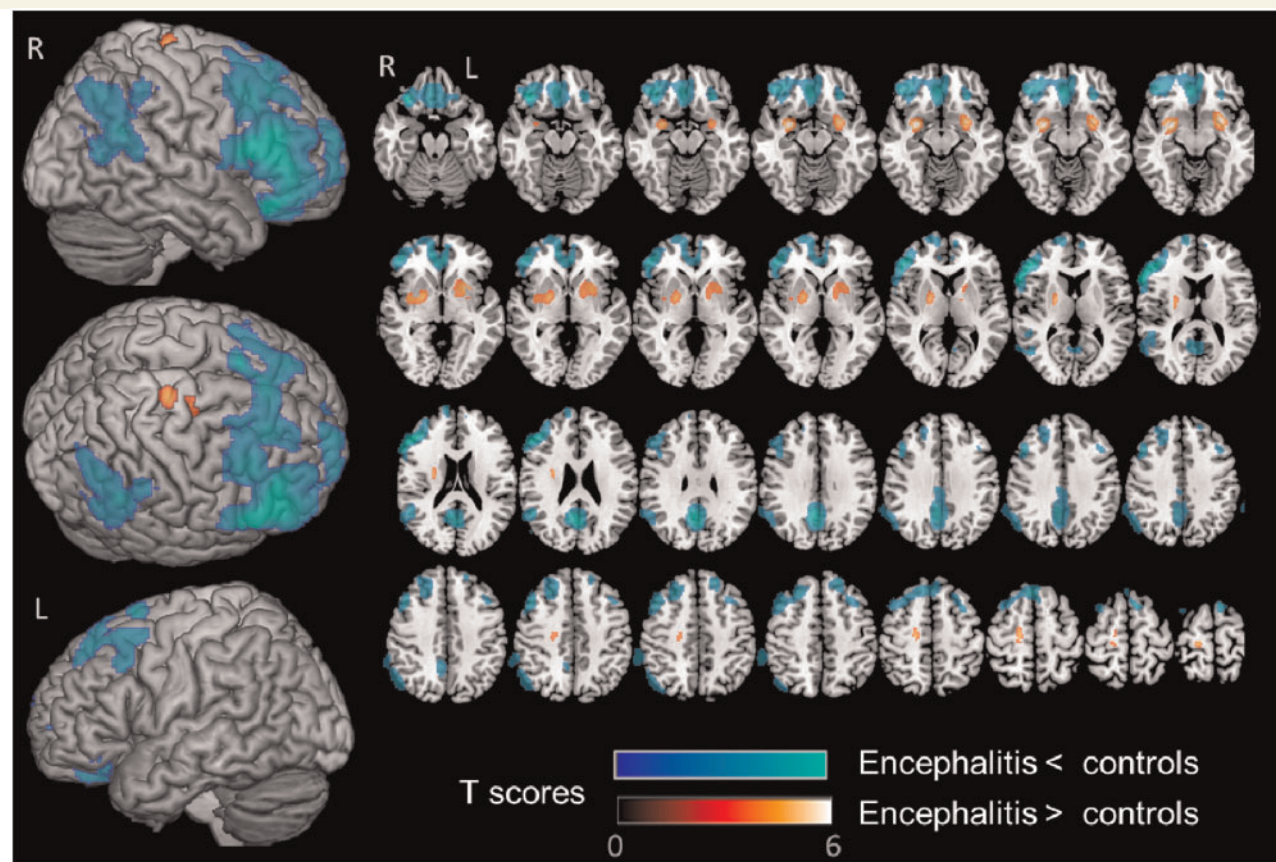
$^{18}$ F-FDG-PET brain scans were made for a group of five patients both during initial clinical evaluation and after immunotherapy and remission of symptoms. The median age of these patients was 64 years (range: 25.8–80.0, Patients 1–3, 5 and 6; Table 2). Initial PET scans were done at a median interval of 4.1 months (range 1.6–14.4) after onset of the encephalitis (symptoms at the time of the PET are indicated in Table 2). Post-treatment imaging was performed after a median interval of 8.5 months (range 4–14.9 months).

$^{18}$ F-FDG signals revealed a strong bilateral increase in metabolism in the striatum during the encephalitis in all patients ( $n = 5$ ). It predominantly involved the putamen in two patients (Patients 1 and 3; Table 2), and the caudate nucleus in the others (Fig. 2A). A strong hypermetabolism was also evident in the primary motor cortex [Brodmann area (BA) 4], especially in regions linked to upper limb movements. Cortical hypermetabolism was located contralateral to the affected limb (Patients 3 and 5), and for bilateral TDS was stronger contralateral to the most affected limb (Fig. 2B). The zone of increased metabolism extended to premotor cortex and supplementary motor areas in one patient (BA 6) (Patient 6), and to sensorimotor cortex in





**Figure 2 Hypermetabolism in the striatum, mesiotemporal and motor cortex.** (A) FDG PET scans reveal striatal and mesiotemporal hypermetabolism during encephalitis. *Top:* Bilateral striatal hypermetabolism of Patient 1 during encephalitis disappeared during remission after treatment. *Bottom:* Mesiotemporal hypermetabolism of Patient 6 during encephalitis, associated with mesial temporal seizures, disappeared during remission. Axial slices are coloured with a French scale. Subtracted images (encephalitis – remission) superimposed on T<sub>1</sub>-weighted MRI with hot colour scale showing only differences > 1.5 standard deviations (SD). (B) Hypermetabolism in primary motor cortex during encephalitis. Patients 1 and 2, with TDS affecting upper limbs bilaterally, exhibited a bilateral hypermetabolism in primary motor cortex. Metabolic changes in Patient 2 also affected the left premotor and sensorimotor cortices. The coronal views reveal bilateral striatal hypermetabolism in both patients. Regions of significant metabolic changes (z-score > 1.5) shown on three orthogonal views and on 3D volume renderings made with MRICro software.



**Figure 3 Between groups' analyses of brain FDG-PET: SPM results.** Comparison of metabolism from FDG-PET scans for patients with encephalitis and healthy controls. T-maps show hypo- (cold) and hyper-metabolism (hot colours). Glucose metabolism was increased in the striatum, amygdala, and right motor primary cortex of patients and decreased in prefrontal cortex, anterior cingulate, precuneus and right parietal associative areas. SPM T-maps are projected onto a surface rendering and axial views of a customized MRI template. Axial slices are shown according to radiological convention (right is left). All  $P < 0.05$  corrected. R = right; L = left.

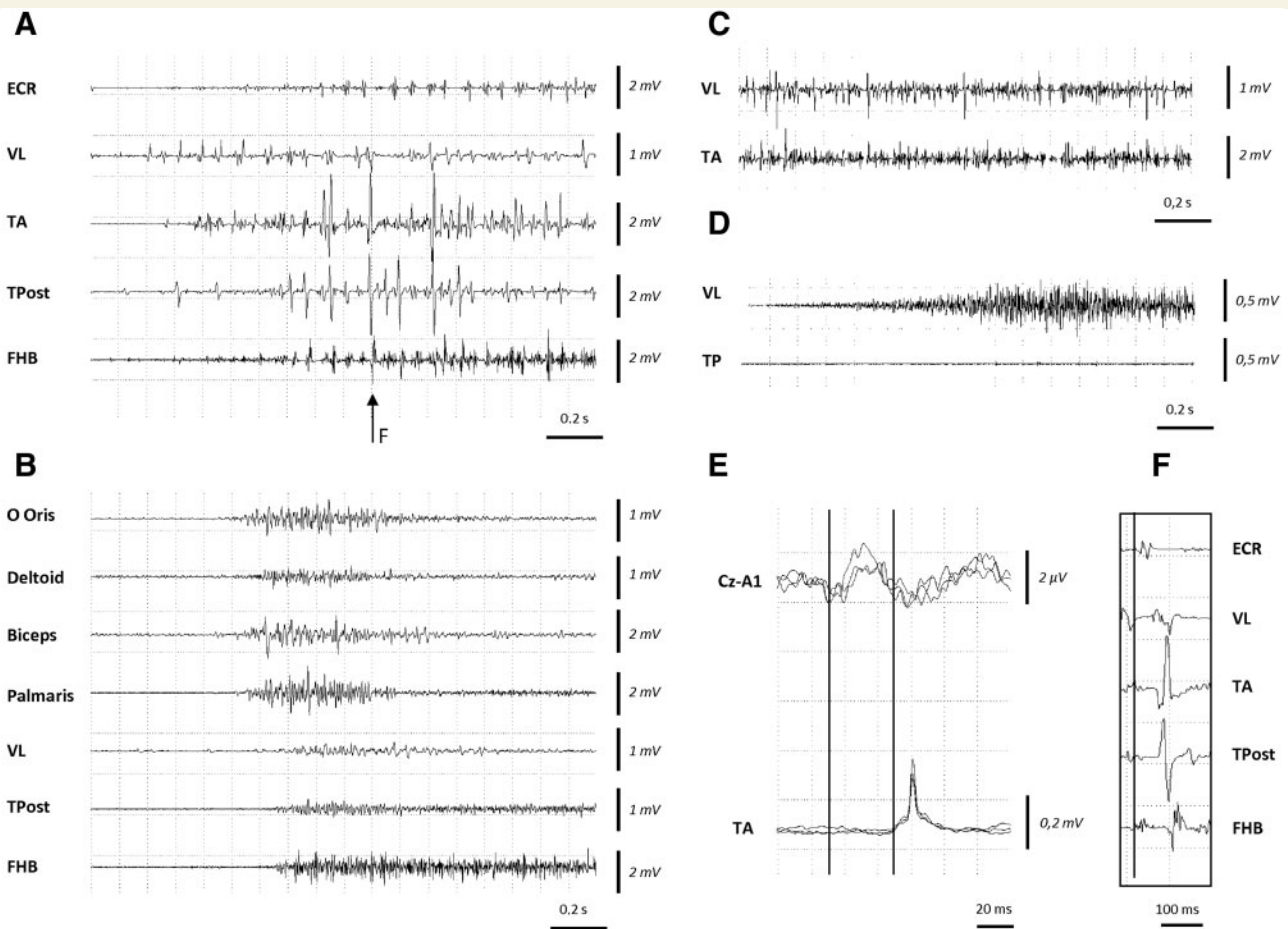
four of five patients (Table 2). We also detected a mesio-temporal hypermetabolism in patients with mesial temporal lobe epilepsy (Patients 2, 5 and 6) (Fig. 2A). In a patient with major cognitive impairment (Patient 6) a strong hypometabolism was evident in prefrontal and parieto-temporo-occipital associative cortices.

We also compared  $^{18}\text{F}$ -FDG-PET signals from patients with encephalitis with those from controls. Glucose metabolism was higher for the patients in the striatum bilaterally, the amygdala, and the right motor primary cortex (BA 4). It was lower for orbitofrontal, right basal dorsolateral area, anterior cingulate, precuneus and right parietal associative cortices (all  $P < 0.05$  corrected) (Fig. 3 and Supplementary Table 1). A direct comparison between encephalitis and remission states for the five patients revealed increased metabolism in the right motor primary cortex, and striatum bilaterally during encephalitis ( $P < 0.001$  voxel-level, Supplementary Table 1). The metabolic increase in striatum and amygdala was significantly correlated with prefrontal hypometabolism during encephalitis ( $\rho = -0.90$  all  $P < 0.05$ ). No significant metabolic differences were evident between patients in remission and controls.

## Cortical myoclonia are associated with some motor seizures

Polymyographic records revealed two different EMG patterns associated with TDS (Fig. 4, Tables 2 and 3). In two patients, we recorded a continuous EMG pattern corresponding to a purely tonic spasm (T). The EMG was normal during voluntary contraction, with no interictal myoclonus. In three patients a distinct myoclonic EMG pattern was composed of brief, 20–40 ms, rhythmic, 10–20 Hz, bursts, corresponding to a tonic spasm with superimposed myoclonus (T-M). Temporal and spatial organization of T-M jerks (Fig. 4F) was compatible with a fast pyramidal conduction along the corticospinal pathway as for a cortical myoclonus. Brief, 30–60 ms, mild, irregular interictal myoclonia were recorded during voluntary contraction in all T-M patients. Agonists and antagonist muscles were synchronously active. These characteristics may point to a cortical generation of the jerks. There were no reflex jerks and no trans-cortical C-wave. EEG-jerk-locked-back-averaging (JLBA) revealed a low amplitude EEG cortical transient from the Cz electrode





**Figure 4** EMG activity during TDS in LGII encephalitis. Two EMG patterns associated with TDS. (A, C, E and F) In Patient 1, brief EMG bursts of duration 20–25 ms and frequency 10 Hz reflect a tonic spasm with superimposed myoclonus. (B and D) In Patient 3, continuous EMG activity corresponds to a purely tonic spasm. During voluntary contraction, brief (30–48 ms) irregular myoclonus were recorded from Patient 1 (C; vastus lateralis and tibialis anterior muscles, knee and foot extension) but EEG activity was normal in Patient 3 (D, vastus lateralis muscle, knee extension). (F) The temporo-spatial organization of the tonic spasm with superimposed myoclonus. It is compatible with a fast pyramidal conduction along the corticospinal pathway as for cortical myoclonus. (E) The cortical origin of the jerks is further suggested by a cortical EEG transient from the Cz electrode which precedes the tibialis anterior muscle signal by 35 ms. Transient revealed with EEG-JLBA method. ECR = extensor carpi radialis; VL = vastus lateralis; TA = tibialis anterior; Tpost = tibialis posterior; FHB = flexor hallucis brevis.

**Table 3** Polymyographic analyses of patients with tonic-dystonic seizures during LGII encephalitis

Patient	Spasms/tonic-dystonic seizures			Interictal myoclonus				
	Type	Total spasm duration (ms)	Jerks inside the spasm duration (ms); frequency, pattern	Activation mode; Rhythmicity	Severity	Duration (ms); synchrony	Reflex jerks/ C-wave	JLBA latency (ms); amplitude ( $\mu$ V); studied limb
1 <sup>a</sup>	T-M	1200–1600	20–25; 10 Hz, P	p, a; arrhythmic	+	30–48 ms, Sy	—/—	Positive; –35 ms; 3 $\mu$ V; LL
2	T-M	900–4000	30 ms; 15 Hz, P	p, arrhythmic	Subclinical	46–58, Sy	—/—	NA
3 <sup>a</sup>	T	700–1600	no	no	0	NA	—/nd	NA
5	T	500–700	no	no	0	NA	—/—	NA
7	T-M	500–600	30–40; 20 Hz, S	p, arrhythmic	Subclinical	32–38, Sy	—/—	Negative; UL

<sup>a</sup>Neurophysiological recordings are illustrated in Fig. 4.

P = pyramidal conduction pattern; p = posture; a = action; JLBA = Jerk-Locked Back-Averaging; S = diffuse synchronous pattern; Sy = synchrony between agonists and antagonists muscles; LL = lower limbs; UL = upper limbs; nd = not determined; NA = not applicable; + = mild.

preceding tibialis anterior muscle jerks by 35 ms. These data demonstrate a cortical origin of interictal jerks.

## Discussion

This study on LGI1-antibody encephalitis provides new insights on the nature and origin of motor events in this syndrome. First reports mainly described patients with features of limbic encephalitis (Vincent *et al.*, 2004). We show that motor cortex is another major target. The encephalitis may initially affect either of these two regions independently. Frequently both cortical targets are involved in later stages of LGI1-antibody encephalitis.

Several of our findings suggest that tonic-dystonic seizures originate in motor cortex: (i) they are preceded by a focal EEG slow wave in fronto-central cortex, contralateral to the movement; (ii) they are associated with a hypermetabolism in the motor cortex on FDG-PET scans; and (iii) they are associated with two patterns of EMG signal: one tonic, and the other with a myoclonic element for which we were able to isolate a premyoclonic cortical transient.

We confirmed several pathognomonic features of tonic-dystonic seizures previously associated with LGI1-antibody encephalitis (Sen *et al.*, 2014). Motor events are usually of short duration, often triggered by an external stimulus. Their frequency typically increases as the syndrome progresses reaching several tens of events per day. TDS are initially unilateral and evolve into bilateral, often alternating events. We found upper limbs, but not the face, were invariably involved in TDS and so prefer this term to ‘faciobrachial dystonic seizures’ (Irani *et al.*, 2011). In our population, the initial motor event was typically tonic, like an epileptic spasm. Motor events typically ended in a dystonic posture, possibly associated with the striatal activation observed in FDG-PET. TDS related to LGI1-antibodies differ from the slow dystonic posture that may be observed late during seizure initiated in the mesial temporal lobe, possibly related to propagation of discharges to the putamen (Mizobuchi *et al.*, 2004). Simultaneous EEG and EMG records let us identify isolated TDS, of duration 0.5–2 s linked to a specific slow EEG wave. This deflection of duration ~700 ms occurred contralaterally on fronto-polar, frontal or central electrodes and preceded the TDS. These linked EEG and EMG activities resemble the pattern sometimes described during infantile epileptic spasms where a slow wave transient, maximal in the vertex, is associated with a rhombus-shaped EMG activity (Vigevano *et al.*, 2001). One difference is that infantile spasms are usually bilateral, whereas isolated TDS may be strictly unilateral. In three LGI1-antibody patients studied by Andrade *et al.* (2011) a ‘generalized EEG electrodecremental event’ precedes the TDS by 500 ms. A closer look (Andrade *et al.*, 2011) may suggest the existence of an EEG transient in frontal electrodes, as the one describe here.

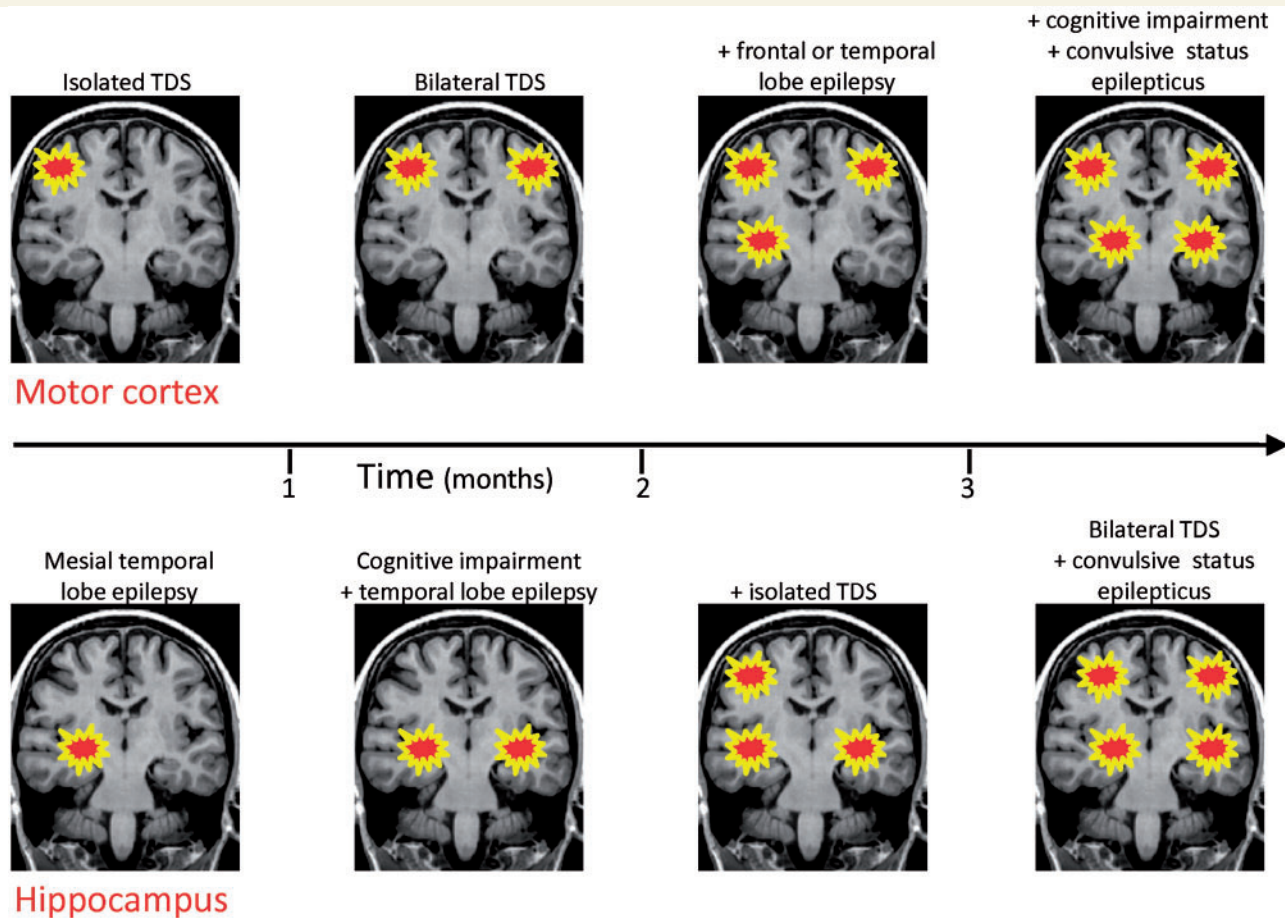
TDS in LGI1-antibody encephalitis were also associated with frontal or temporal lobe seizures, of longer duration

and classical spatiotemporal ictal EEG organization. TDS mostly preceded these seizures, but could also occur during or after focal seizures. It seems likely that motor cortex and hippocampus, hyperexcitable due to autoimmune effects on LGI1, are recruited in various sequences initiated by activity in one of these areas: (i) TDS initiated in one hemisphere are followed by contralateral TDS after few seconds; and (ii) TDS are followed by a frontal or temporal lobe seizures. Cortical areas may be recruited by subcortical hyperactivity of the basal ganglia. This latter possibility differs from classical cortical ictal spread where firing propagates to adjacent areas continuously. EEG abnormalities specifically linked to TDS have not been reported previously (Boesebeck *et al.*, 2013; Sen *et al.*, 2014) although variable EEG activities related to cortical seizures have been described (Irani *et al.*, 2011, 2013; Shin *et al.*, 2013). We thus identified a novel EEG marker for isolated TDS. This transient wave, best detected with an average EEG reference montage, may then assist rapid diagnosis of patients with LGI1-antibody encephalitis presenting with isolated TDS, when the other classical investigations are unremarkable. Our data and that of others (Irani *et al.*, 2011, 2013) showed that brain MRI, as well as biological tests including CSF and natremia, are normal in these patients.

Comparing FDG-PET during encephalitis and after remission revealed hypermetabolism of the basal ganglia in all patients, as previously reported (Irani *et al.*, 2011; Boesebeck *et al.*, 2013; Shin *et al.*, 2013; Renard *et al.*, 2015). This striatal hypermetabolism may be a useful marker in early stages of the encephalitis when patients may present with isolated TDS but EEG, MRI or CSF abnormalities are not yet apparent (Irani *et al.*, 2011; Shin *et al.*, 2013). It is unclear whether the basal ganglia hypermetabolism is the result of a direct activation by the LGI1-antibodies, or the consequence of the cortical hyperactivation. Hypermetabolism was also evident in the primary motor cortex involved in the upper limb movements in patients with TDS. It was located contralateral to the affected limb or the most affected limb in bilateral TDS. This novel motor cortex hypermetabolism was evident in comparisons of PET data from each patient during the encephalitis and then remission and also when patient data were compared to those from healthy volunteers. These findings, and the slow EEG potential recorded from the frontal lobe, strongly suggest a motor cortical origin for TDS. Some patients reported a sensory aura preceding the TDS and in those cases we could identify an associated hypermetabolism in the postcentral cortex. We note that EEG records were made in the days before or after the FDG-PET, limiting the precision of data on the condition of the patients at this time point.

Polymyographic records provided useful insights on the cortical origin and the patterns of tonic-dystonic seizure events. Two patterns of motor event were evident. One was a continuous EMG pattern corresponding to a purely tonic spasm. The other was a myoclonic EMG pattern, composed of brief rhythmic bursts, corresponding to a





**Figure 5 Natural history of LGII-antibody encephalitis.** Clinical symptoms vary according to the cortical regions involved. The top row shows a typical progression of symptoms when the motor cortex is the initial target. When the hippocampus is the initial target, the progression differs as shown in the bottom row. Without immunomodulatory treatment, symptoms become bilateral and spread to involve the other cortical target. Timing is schematic.

tonic spasm with superimposed myoclonus. Several properties pointed to a cortical origin for the second pattern: (i) the temporo-spatial organization of the jerks was compatible with a fast pyramidal conduction along the cortico-spinal pathway as expected for cortical myoclonus; (ii) the existence of brief irregular interictal myoclonus, during voluntary contraction; (iii) the synchronous involvement of agonists and antagonists muscles; and (iv) the identification of a low amplitude EEG cortical transient in the frontal lobe preceding the jerks, by EEG-jerk-locked-back-averaging.

The hippocampus and nearby limbic areas are the second major target of LGII-antibody encephalitis (Vincent *et al.*, 2004). Associated cognitive deficits mainly affected memory processes. In the patients studied, a deficit of anterograde memory was apparent at late stages of the encephalitis together with confusion and Mini-Mental State Examination scores reaching a median of 24/30, before immunosuppressive treatment. We confirmed a previously reported (Irani *et al.*, 2011) link between hyponatremia and a severe, permanent limbic involvement. In some patients

frontal cortical dysfunction was also identified. FDG-PET in patients with cognitive impairment interestingly revealed hypometabolism in the bilateral prefrontal and parieto-temporo-occipital associative cortex, which was associated with an increased metabolism in striatum and amygdala. Thus the cognitive impairment may result in part from basal ganglia actions on associative cortex rather than a direct LGII-antibody-mediated hyperexcitability. Intense activation of the striatum by neocortical or limbic inputs could tend to inhibit cortical areas by the thalamo-cortical projections.

Temporal lobe seizures also reflect that limbic area is a target of LGII-antibodies in this encephalitis. They have been reported in about half of patients (Irani *et al.*, 2011) and mainly after the occurrence of TDS. In this study they were noted in 82% of patients, often before the occurrence of TDS. About half of reported temporal lobe seizures were simple focal seizures, with vegetative symptoms or feelings of fear suggestive of a mesial temporal origin. Seizures were typically brief, very frequent near status epilepticus, drug-resistant, and consciousness was usually not lost. We

emphasize mesial temporal lobe epilepsy as an initial presentation in patients with no TDS or permanent cognitive deficit. As initial scalp EEG may reveal no epileptic activity and MRI may be normal, possible misdiagnosis as psychogenic non-epileptic event should be avoided. Dysmnestic symptoms were rarely detected at onset, but after immunotherapy, possibly reflecting that specific neuronal populations are targeted initially by the LGI1-antibodies. Complex focal seizures with temporal symptoms occurred usually at later stages and were often associated with permanent limbic involvement. In patients with clinical temporal lobe involvement, MRI revealed a hippocampal hyperintensity in initial scans of 39% of patients and in 70% of patients in later scans, similar to previous reports (Lai *et al.*, 2010; Irani *et al.*, 2011, 2013; Shin *et al.*, 2013). The delayed hippocampal hyperintensity remained unilateral in one-third of the cases. The MRI hyperintensity was well correlated with a mesiotemporal hypermetabolism in FDG-PET scans of patients with mesial temporal lobe epilepsy.

Finally, as patient recruitment was based on the presence of the LGI1 antibody rather than specific symptoms, we can present an unbiased natural history of this encephalitis. Initial symptoms were TDS, temporal lobe seizures and cognitive impairments in approximately equal proportions. These initial signs can be related to the temporal lobe or motor cortex—the two main cortical targets. Our data suggest LGI1-antibody encephalitis initially involves one of these targets unilaterally. The disease progresses, before immunomodulatory treatment, to bilateral effects and then reaches the second cortical target (Fig. 5). Our data suggest the delay to involvement of the second target may vary from days to several months. We found no differences in clinical outcomes between patients with an initial hippocampal or motor cortical involvement.

Early recognition of TDS in LGI1-antibody encephalitis, and initiation of immunotherapy have been shown to accelerate recovery and prevent secondary limbic involvement (Irani *et al.*, 2011, 2013). Our data add to this picture, an initial limbic involvement, before the emergence of TDS. Identification of an initial temporal lobe involvement from *de novo* temporal lobe seizure or specific cognitive deficits would permit a rapid diagnosis of LGI1-antibody encephalitis and initiation of immunotherapy. Our data also suggest that LGI1-antibody involvement might be considered in patients presenting with generalized convulsive seizures, as observed in about half the patients of our cohort with a generalized convulsive status epilepticus in 18% of the patients.

We have extended the age of onset of LGI-antibody encephalitis to the youngest, 21-year-old, patient of our series. We, and others, have shown that inactivation of the *LGI1* gene elicits seizures. They are early-onset and rapidly lethal with clinical and EEG evidence for a hippocampal origin (Chabrol *et al.*, 2010) or myoclonic seizures suggestive of TDS (Fukata *et al.*, 2010; Yu *et al.*, 2010). Selective late postnatal inactivation of the *LGI1* gene in

glutamatergic pyramidal neurons showed a less severe phenotype (Boillot *et al.*, 2014).

As this study was retrospective, we did not examine all subjects with comparative brain FDG-PET, polymyography and coupled EEG-EMG analyses. Prospective studies could improve our vision of the syndrome, but data may be difficult to obtain. This encephalitis may be quickly and reliably diagnosed from symptoms including pathognomonic TDS. The rapid initiation of immunosuppressive treatment then precludes lengthy further analyses.

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## Supplementary material

Supplementary material is available at *Brain* online.

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## Appendix I

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