

available at www.sciencedirect.comwww.elsevier.com/locate/brainres**BRAIN
RESEARCH****Research Report****Dysmorphic neurons in patients with temporal lobe epilepsy**

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ABSTRACT

We studied morphologic characteristics of dysmorphic neurons in the hippocampus of seven patients with medically intractable TLE and compare histological, clinical, and imaging features with ten TLE patients with classical hippocampal sclerosis without abnormal cells. Such dysmorphic neurons were observed in the hilus of the dentate gyrus and were characterized by giant or misshapen cells with abnormal cytoskeletal structure and atypical dendritic processes that resembled the dysmorphic neurons from cortical dysplasias. Specimens with dysmorphic cells also contained other cytoarchitectural abnormalities including bilamination of the dentate granular cell layer (four out seven cases), and the presence of Cajal–Retzius cells in the dentate gyrus or Ammon's horn (five out seven cases). There were no statistically significant differences regarding the age at onset, duration of epilepsy, and hippocampal asymmetry ratio between patients with or without dysmorphic cells. Nevertheless, it is interesting to note that a higher proportion of patients with dysmorphic neurons continued to present auras after surgery, when compared with patients without those cells.

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1. Introduction

The physiopathogenesis of mesial temporal sclerosis (MTS), the most frequent cause of refractory epilepsy, has been the object of interesting discussion since its description by Sommer (1880). Initial precipitant injury (IPI) before the age of four, one of the most striking facts in the natural history of mesial temporal lobe epilepsy (TLE), to which the possible cause of epilepsy has been attributed, is found in only 40–50% of the cases (Mathern et al., 1995; Blumcke et al., 2002). Nevertheless, the seizure semiology is so typical that the last

Proposal of Classification of Seizures (Engel, 2001) suggested the denomination “seizures with typical automatisms of the temporal lobe” to characterize the behavioral aspects of the syndrome. Magnetic resonance imaging (MRI) findings include volumetric reduction, loss of the internal structure and hypersignal in T2-weighted images of the hippocampus, associated with more discrete impairment of the amygdala and temporal neocortex (Kuzniecky et al., 1987; Jack et al., 1990; Bronen et al., 1991; Meiners et al., 1994, 1999; Mitchell et al., 1999). As only about 10% of these patients achieve seizure control with antiepileptic drugs, cortico-amygdalo-

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hippocampectomy has been considered as the treatment of choice, promoting control (Engel's class I) in at least 75% of patients and significant reduction in seizure frequency (Engel's class II) in another 12% (Blumcke et al., 2002). Despite these facts, up to 35% of patients with epilepsy related to MTS continue presenting auras after surgery (Henkel et al., 2002) and similar results have been observed regardless of the surgical approach (Spencer, 1999).

Histologically, the hippocampus is the most affected structure in MTS and, classically, shows pyramidal cell loss and gliosis in CA1, CA3 and CA4, with preservation of CA2 (Ammon's horn sclerosis, AHS), and granular cells loss or dispersion in the dentate gyrus (Wolf and Blumcke, 1999). Nevertheless, recent molecular neuropathological studies focusing on developmental aspects of hippocampal organization have described anomalies not routinely detected by neuropathological examination and suggest that AHS might be a maldevelopmental disorder (Blumcke et al., 2002).

Such anomalies include focal or extensive bilaminar arrangement of dentate granular neurons, a persistent population of hippocampal Cajal–Retzius cells, clusters of nestin-immunoreactive cells reminiscent of precursors during hippocampal ontogeny and anomalies of the CA1 pyramidal cell/subicular layers with undifferentiated neurons (Blumcke et al., 2002; Sloviter et al., 2004).

In comparing the features of paraffin (5 μm) and vibratome (50 μm) hippocampal sections from TLE patients, we unexpectedly observed that some specimens contained neurons with huge cellular body and abnormal dendritic arborization that resembled the dysmorphic neurons from cortical dysplasias. In the present paper, we report some morphological characteristics of those abnormal “dysmorphic” cells in patients with medically intractable seizures and compare histological, clinical and imaging features with findings in TLE patients with classical hippocampal sclerosis without those cells.

2. Results

2.1. Morphological analysis

The morphologic characterization of the neurons included size (*perimeter* and *area*) and form (*form factor*) of the cellular

body, as well as number, length and tortuosity of the dendrites. In order to better characterize the dendritic trees of each studied cell, first to sixth order ramifications were analyzed, starting from the cellular body. However, since some neurons did not present high-order ramifications within the examined histological section, we included in the present study only data regarding first-order dendrites and total values of each tree for each studied parameter (number of segments, length and tortuosity). Figs. 1 and 2 summarize the results regarding the cellular body and dendritic trees of 39 reconstructed neurons. Briefly, the aberrant aspect of the so called giant or dysmorphic neurons is due to the following characteristics: (1) these neurons present a larger cellular body when compared to the normal-appearing neurons of the hilus; (2) these neurons also present abnormal dendritic trees, characterized by more abundant, longer and more tortuous dendritic segments, when compared to normal cells.

2.2. Clinical correlation

All the patients studied here ($n = 17$) showed typical MTS signs on MRI and routine histopathological examination. Interestingly enough, the dysmorphic neurons described above were identified in only seven out of seventeen specimens. For clinical correlation, patients with typical hippocampal sclerosis (AHS) alone (group 1, $n = 10$) were compared with patients presenting AHS and dysmorphic neurons (group 2, $n = 7$). Clinical data of both groups are shown in Table 1.

In group 1, we observed the typical aspect of hippocampal sclerosis (AHS) including pyramidal cell loss and gliosis in CA1, CA3 and CA4 (*hilus*), with preservation of CA2, in addition to dentate granular cell loss and/or dispersion. The age at surgery ranged from 33 to 53 years (mean 39.1; SD 7.2), the duration of epilepsy from 11 to 39 (mean 23.8; SD 8.8) and IPI occurred in 8 out of 10 cases, being febrile seizures in two patients. The volumetric study on pre-surgical MRI showed an asymmetry ratio ranging between 6.40% and 72.41% (mean 43.59%, SD 19.32, $n = 10$). One year after surgery, 50% of patients in this group were completely seizure-free (Engel class IA) and 10% still had auras (Engel class IB).

In group 2, dysmorphic neurons were mainly observed in the hilus of the dentate gyrus and were characterized by misshapen cells with abnormal orientation, size, cytoskeletal

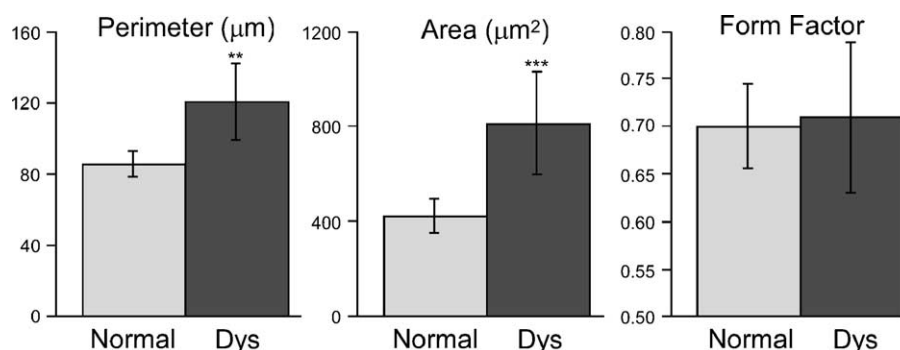


Fig. 1 – Morphological characteristics of the reconstructed neuronal cell bodies. Dys: dysmorphic cells; * $P < 0.001$; ** $P < 0.005$; * $P < 0.05$; none: $P > 0.05$.**

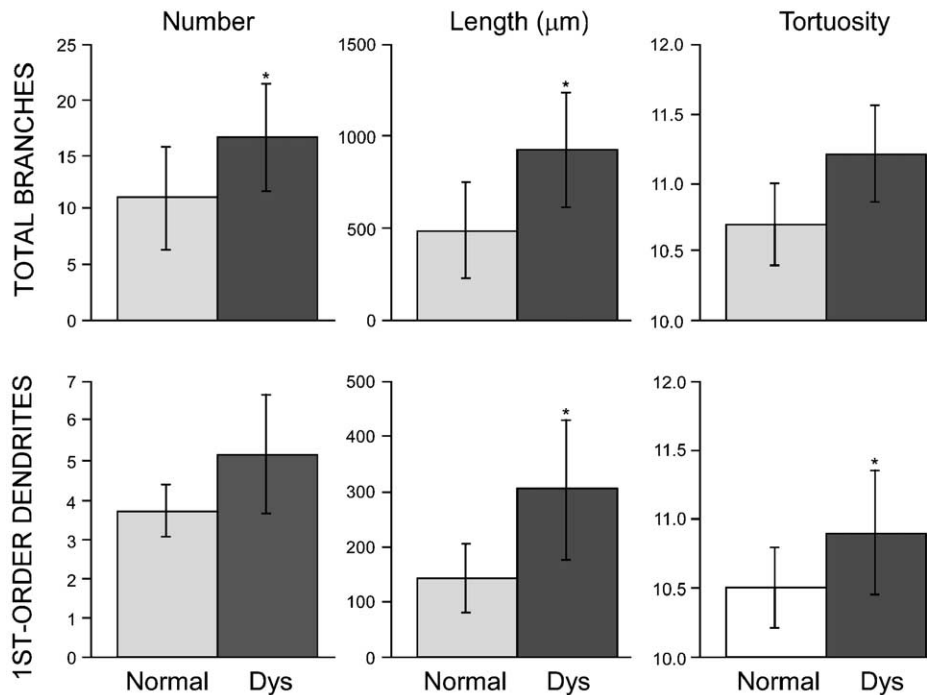


Fig. 2 – Morphological characteristics of the reconstructed neuronal dendrites. Dys: dysmorphic cells; * $P < 0.001$; ** $P < 0.005$; * $P < 0.05$; none: $P > 0.05$.**

structure and atypical dendritic processes (Fig. 3). In this group, we also observed other cytoarchitectural abnormalities including bilamination of the dentate granular cell layer and the presence of Cajal–Retzius cells in the dentate gyrus or Ammon’s horn (Fig. 3). Bilamination of dentate granular layer was observed in four patients and was characterized by double layered granular cells separated by a thin white matter band (Fig. 3g). Cajal–Retzius cells were observed in five patients and exhibited typical fusiform or ovoid shapes with a single horizontal dendrite in subpial location (Fig. 3h). These features were not observed in group 1 specimens. Clinically, the age at the time of the surgery in this group ranged between 21 and 50 years (mean = 36.4; SD = 10.5). Four presented IPI before the age of four although none had febrile seizures. Four had the typical clinical profile of MTS syndrome defined by the presence of IPI, silent (latent) period between 8 and 11 years and seizure onset, with typical temporal lobe automatisms, between 10 and 14 years of age. The volumetric study on MRI showed an asymmetry ratio ranging between 20.24% and 84.95% (mean = 54.64%, SD = 22.42). One year after surgery, only 28.5% of patients in this group were completely seizure free (Engel class IA), and 42.8% still had auras (Engel class IB).

There was no statistically significant differences regarding the age at onset ($P = 0.922$, $n = 17$), duration of epilepsy ($P = 0.922$; $n = 17$) and hippocampal asymmetry ratio ($P = 0.304$, $n = 16$) between the two groups. Although small number of cases limit our analysis, it is interesting to note that a higher proportion of group 2 patients (42.8%) continued to present auras after surgery, when compared to group 1 (10%).

3. Discussion

MTS is a lesion observed in approximately 65% of patients with TLE (Babb and Brown, 1987). One of the widely discussed questions in epileptology is whether MTS/AHS represents the cause or the consequence of repeated seizures. Some data suggest that subtle, pre-existing hippocampal malformation may contribute to the development of subsequent AHS (Fernandez et al., 1998; Sloviter and Pedley, 1998; Sloviter et al., 2004), and recent molecular neuropathological studies focusing on developmental aspects of hippocampal organization suggested that AHS itself might be a maldevelopmental disorder (for review, see Blumcke et al., 2002). Accordingly, in our series, the presence of dysmorphic neurons associated with Cajal–Retzius cells and bilamination of the dentate gyrus points at a malformation of cortical development (MCD) involving the hippocampal formation.

Dysmorphic neurons have been observed in different types of MCD, and their morphological and neurochemical characteristics indicate a disturbance of neuronal proliferation or migration (Spreafico et al., 1999). Dysmorphic features have also been recognized in hilar neurons in AHS, including abnormal dendritic ramifications and accumulation of neurofilaments (Blumcke et al., 1999a,b; Thom et al., 1999). Their resemblance to the dysplastic neurons of cortical dysplasia raises the possibility that they represent a hippocampal malformation. Thom et al. (2002) identified such dysmorphic hilar cells in 55% of AHS cases and found a positive correlation

Table 1 – Clinical data of patients

Case	Age at surgery (years)	Duration of TLE (years)	IPI	Age of epilepsy onset (years)	CPS with present characteristics (age and frequency)	Seizures between IPI and TLE onset	Surgical outcome (Engel)
1	33	19	Afebrile seizure at 3 years	8	14 y (1–2/month)	Yes (subtle CPS)	IIB
2	33	18	–	15	15 y (4/month)	–	IB
3	49	38	SE at 1 year	1	11 y (4–5/month)	Yes. GTCS (1/month)	IB
4	29	19	Neonatal seizures	10	10 y (4/month)	No	IA
5	50	14	–	32	36 y (12/month)	–	IIB
6	21	9	Focal seizure at 4 years	12	12 y (15/month)	No	IB
7	40	15	–	25	25 y (3/month)	–	IA
8	33	16	–	12	17 y (3–5/month)	–	IA
9	53	39	2 seizures at 18 months	14	14 y (6–10/month)	No	ID
10	40	25	–	15	15 y (2/month)	–	IIB
11	48	30	Afebrile seizure at 3 years	18	18 y (1–2 /month)	No	IIB
12	37	34.5	Febrile seizure at 2 years	2.5	2.5 y (6–8 /month)	No	IA
13	43	33	Seizure at 4 years	10	10 y (8–12/month)	No	IA
14	33	23	HT at 8 years	10	10 y (15/month)	No	IA
15	37	18	Afebrile seizure at 3 years	4	19 y (8–10/month)	Yes. GTCS	IB
16	29	11	Febrile seizure at 7 month	18	18 y (4/month)	No	IA
17	38	20	–	18	18 y (4/month)	No	IIB

Cases 1 to 7 presented hippocampal dysmorphic neurons. CPS: complex partial seizures; GTCS: generalized tonic–clonic seizures; HT: head trauma; IPI: initial precipitant insult; SE: status epilepticus; TLE: temporal lobe epilepsy; NC: neurocysticercosis; y: year.

between their presence and the extent of granule cell dispersion. Since granular cell disorganization has been considered to most likely represent a neuronal migration disorder (Stanfield and Cowan, 1979; Houser, 1990; Houser et al., 1992; Harding and Thom, 2001), it could reinforce the hypothesis that the presence of dysmorphic hilar cells represent a disturbance of hippocampal development. Although the role of these cells in AHS-related epilepsy remains to be identified, recent electrophysiological data from MCD cases suggest the participation of dysplastic cells in human epileptogenesis (Mathern et al., 2000; Cepeda et al., 2003, 2005). Under experimental conditions, sampled abnormal-appearing cells (“giant neurons”) generated large Ca^{2+} currents and influx when depolarized (Cepeda et al., 2003). When the cells were acutely dissociated, peak Ca^{2+} currents and densities were greater in abnormal compared with normal-appearing pyramidal neurons. Indeed, it appears reasonable to postulate that hilar dysmorphic cells might also play an important role in AHS-related epilepsy.

Dentate gyrus alterations in AHS have been largely debated (Houser, 1990; Lurton et al., 1998), with the dispersion of granule cells as the most prominent finding (Houser, 1990; Lurton et al., 1998; El Bahh et al., 1999; Blumcke et al., 2002). It is interesting to note that there is a positive correlation between the presence of granule cell dispersion and the severity of hippocampal neuronal loss (Houser, 1990; El Bahh et al., 1999; Thom et al., 2002), suggesting a post-lesional origin. Nevertheless, the occasional observation of granule cell dispersion in the absence of hippocampal cell loss but in the presence of widespread cortical malforma-

tions would rather suggest a malformative origin (Harding and Thom, 2001). In our series, five out seven patients presented granular cell dispersion associated with dysmorphic neurons. The bilamination of dentate gyrus has been also observed in surgical specimens from TLE patients (Blumcke et al., 2002; Thom et al., 2002; Rougier et al., 2003) and, in our series, the presence of this abnormality was always associated with dysmorphic neurons. Although the mechanisms that underlie granule cell disorganization are not completely understood, it seems that development-related proteins, such as neurotrophins, reelin and p35, could play a role (Blumcke et al., 1996, 1999a,b; Lurton et al., 1997, 1998; Thom et al., 2002).

Recent studies have shown an abnormal persistence of Cajal–Retzius cells in human AHS (Blumcke et al., 1996, 1999a, b; Thom et al., 2002), including an excess of cells in the molecular layer of the dentate gyrus. During development, these cells synthesize reelin, an extracellular matrix protein that plays an important role in the basic organization of the cerebral cortex. Mutant mice with a deficiency in reelin expression present cortical malformations and epileptic seizures (Spreato et al., 1999). As increased numbers of reelin-positive cells have been identified in MCD cases such as focal cortical dysplasia (Garbelli et al., 2001) and polymicrogyria (Eriksson et al., 2001), the most likely explanation for the persistence of Cajal–Retzius cells in AHS cases would be that it represents a hippocampal malformation. Although Cajal–Retzius cells and reelin could play a role in the architectural abnormalities of the granular layer in AHS, some authors have failed to demonstrate a relationship between the number of

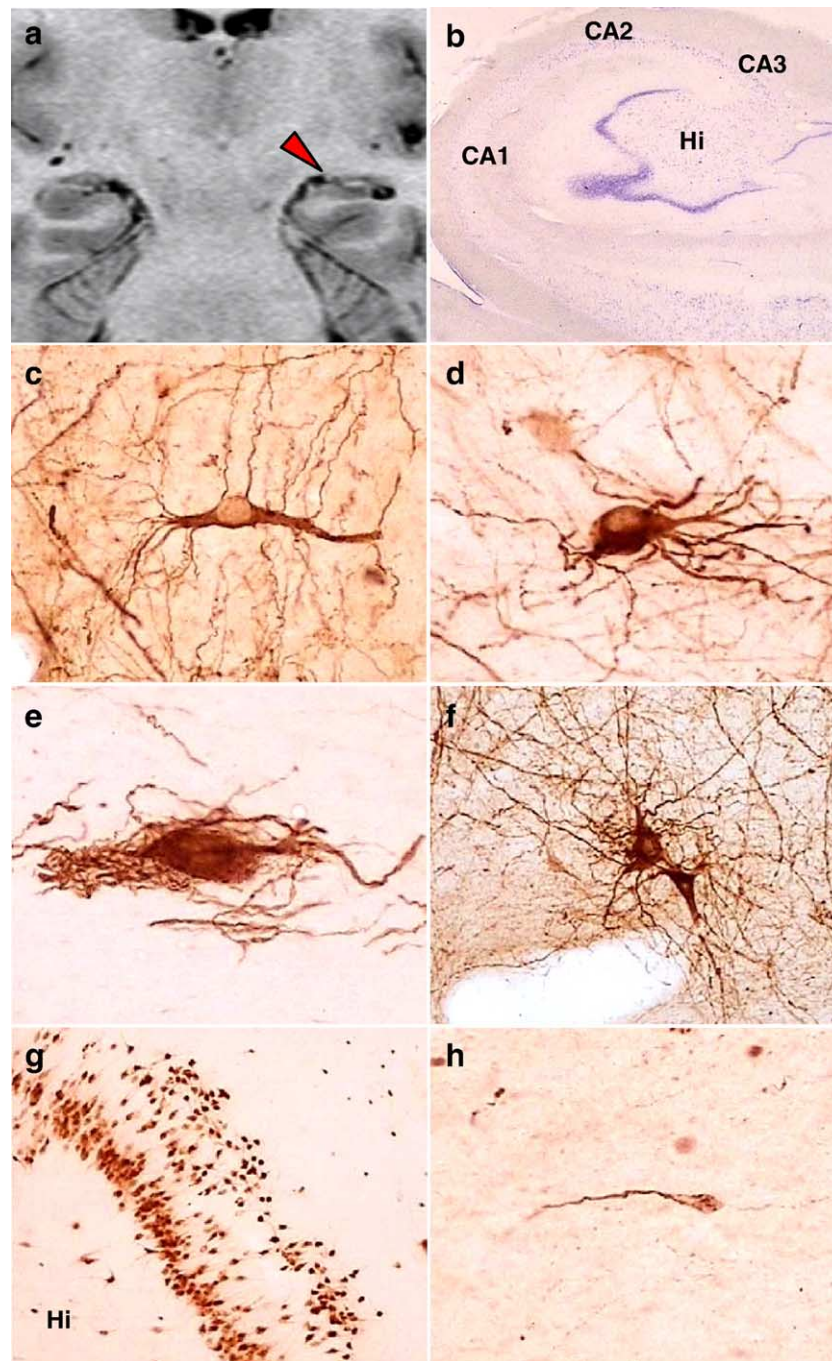


Fig. 3 – Hippocampal abnormalities observed in group 2 patients. (a) MRI aspect of the hippocampal sclerosis (arrowhead); (b) Ammon's horn sclerosis observed at routine neuropathological examination (20× magnification); (c–f) dysmorphic neurons immunostained with SMI-311 antibody (400× magnification); (g) bilamination of the dentate gyrus (Neu-N immunostaining; 100× magnification); (h) hippocampal Cajal-Retzius cell (SMI-311 immunostaining; 400× magnification). Abbreviations: CA1-3 = subfields of the Ammon's horn; Hi = Hilus of the dentate gyrus.

reelin-positive cells and the presence of severe granular cell dispersion (Thom et al., 2002). Nevertheless, since AHS-associated findings generally represent the final picture of a long lasting pathological condition, we cannot exclude the possibility that Cajal-Retzius cells play a role in the disorganization of hippocampal architecture in an earlier period of the disease.

Finally, a remarkable observation in our series was that patients with dysmorphic cells tend to maintain auras after surgery. More than 40% of these patients still had auras after 1 year, while only 10% of patients without dysmorphic neurons presented auras in the same period. Based on these data, it is possible to suggest that these patients may have a more diffuse involvement of the temporal lobe when

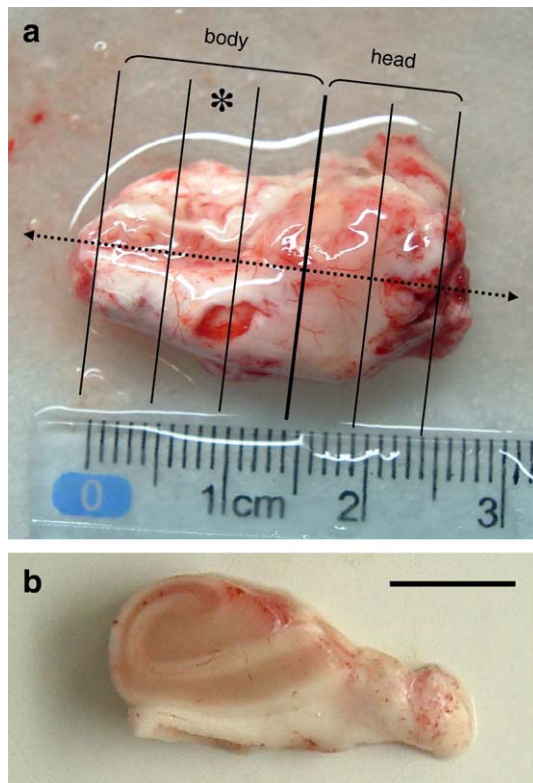


Fig. 4 – Macroscopic aspect of the surgical specimen. Parallel lines in panel a indicate sectioning plans perpendicular to the main hippocampal axis. The coronal slab in panel b corresponds to the hippocampal region signed with an asterisk in panel a. Scale bar in panel b = 5 mm.

compared to typical AHS cases. The occurrence of neocortical changes in a significant proportion of our patients, particularly in cases with dysmorphic cells (data not shown), led to the hypothesis that their vulnerability to seizures could be the consequence of a dysgenetic disturbance of the whole temporal lobe.

4. Experimental procedure

Surgical specimens from TLE patients with mesial temporal sclerosis (MTS) on pre-surgical MRI and routine histopathological examination were studied. Only patients in which all the subfields of the hippocampus were present and adequately oriented were included in the present investigation. All included patients ($n = 17$) were submitted to standard anterior temporal lobectomy (cortico-amygdalo-hippocampectomy) after detailed anamnesis, video-EEG recordings and MRI studies. Clinical data included patient's age at epilepsy onset, age at surgery, seizure frequency, history of IPI, epilepsy duration and surgical outcome according to Engel's classification 1 year after surgery. Pre-surgical MRI protocol included the following: (a) sagittal T1-weighted and axial T2-weighted acquisitions; (b) fluid-attenuated inversion-recovery (FLAIR) and T1-weighted inversion-recovery acquisitions in coronal plans perpendicular to the long axis of the hippocampus; (c) three-dimensional T1-weighted fast field acquisition in coronal plans. To assess the degree of asymmetry in the volumes between sides, an asymmetry ratio was calculated according to [Bernasconi](#)

[et al. \(1999\)](#): $\text{asymmetry (\%)} = [100 \times (R - L)] / [(R + L) / 2]$ where R refers to the volume of the right hippocampus and L that of the left hippocampus.

4.1. Neuropathology

Brain specimens were fixed in 4% paraformaldehyde for 36–48 h at 4 °C. Each hippocampus (25–30 mm length) was carefully oriented, trimmed and sectioned in the plane perpendicular to its longitudinal axis. The pès hippocampus was identified, and only the body of the hippocampus (10 mm length) was used in the present investigation (5–6 sections/patient). Because sections cut tangentially to the principal cell layers or at inconsistent angles from the longitudinal axis of the hippocampus can produce unusual histological features, considerable care was taken to ensure that all hippocampal sections were cut in a plane strictly perpendicular to the longitudinal axis of the hippocampus ([Fig. 4](#)). Five micrometer-thick paraffin sections were processed for routine hematoxylin–eosin examination. Fifty micrometer-thick vibratome sections were processed for immunocytochemistry as described by [Silva et al. \(2002\)](#). Briefly, free-floating sections were treated with H_2O_2 3% by 10 min, washed in phosphate-buffered saline (PBS), incubated with normal horse serum (NHS) 10% in PBS with Triton X-100 0.4% for 45 min and then incubated overnight with primary antibody at 4 °C. Monoclonal antibodies anti-non-phosphorylated neurofilament (SMI-311, monoclonal, 1:1000, Sternberger Monoclonals Incorporated) and anti-NeuN (1:1000, Chemicon) were used to observe the cytoarchitectural organization of the tissue. Particularly, the SMI-311 antibody was used because it provides a Golgi-like staining that allows a good neuronal reconstruction by *NeuroLucida*. Sections were then washed in PBS, incubated at room temperature with biotinylated anti-mouse IgG (Vector, 1:200 in NHS 1%) for 1 h, washed in PBS, incubated in avidin–biotin complex peroxidase (ABC, Vectastain, Vector) for 1 h, washed several times in PBS and revealed with diaminobenzidine (DAB, Sigma) 0.075% in H_2O_2 0.002%. Sections were finally washed in PBS, mounted in gelatin coated slides, dehydrated, covered and observed at light microscopy. All slides were reviewed, blinded to clinical data, by three observers (AVS, HHM and JNS).

4.2. Morphological analysis

The histological pattern described in the [Duvernoy and Vannson \(1988\)](#) atlas was used to identify the normal cytoarchitectural features in every hippocampal section. Dysmorphic neurons were identified according to the morphological characteristics described in dysplastic human tissue by several authors ([Tassi et al., 2002](#); [Najm et al., 2004](#); [Palmini et al., 2004](#); [Cepeda et al., 2005](#)). Advanced microscopical imaging techniques were used to characterize quantitatively the morphology of thirty-nine hilar SMI-positive neurons randomly selected from the seventeen patients. At least twenty of those neurons have been formerly considered abnormal, giant or “dysmorphic” by our neuropathological team (A.V.S., J.N.S.). Three-dimensional reconstruction of SMI-labeled neurons was achieved using the *NeuroLucida* System (MicroBrightField, USA), in order to characterize anomalies of the somato-dendritic complex. The system consists of a microscope equipped with a high-resolution display monitor coupled to the drawing tube and a high resolution motorized stage, allowing for a perfect merging and a continuous alignment of the image of the histological section with the digital drawing, as the latter proceeds across the section. In such system, geometrical properties of all structures are recorded in the actual 3D space of the section, and branching processes are linked in a logical tree such that, in addition to topographical aspects, morphological features can be efficiently analyzed from the data files. After somato-dendritic reconstruction, quantitative analysis of the somatic perimeter, area and form factor

(non-paired *t* test with Welch correction), and dendritic length and tortuosity (Mann–Whitney test) was performed.

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