International consensus classification of hippocampal sclerosis in temporal lobe epilepsy: A Task Force report from the ILAE Commission on Diagnostic Methods

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SUMMARY

Hippocampal sclerosis (HS) is the most frequent histopathology encountered in patients with drug-resistant temporal lobe epilepsy (TLE). Over the past decades, various attempts have been made to classify specific patterns of hippocampal neuronal cell loss and correlate subtypes with postsurgical outcome. However, no international consensus about definitions and terminology has been achieved. A task force reviewed previous classification schemes and proposes a system based on semiquantitative hippocampal cell loss patterns that can be applied in any histopathology laboratory. Interobserver and intraobserver agreement studies reached consensus to classify three types in anatomically well-preserved hippocampal specimens: HS International League Against Epilepsy (ILAE) type 1 refers always to severe neuronal cell loss and gliosis predominantly in CA1 and CA4 regions, compared to CA1 predominant neuronal cell loss and gliosis (HS ILAE type 2), or CA4 predominant neuronal cell loss and gliosis (HS ILAE type 3). Surgical hippocampus specimens obtained from patients with TLE may also show normal content of neurons with reactive gliosis only (no-HS). HS ILAE type 1 is more often associated with a history of initial precipitating injuries before age 5 years, with early seizure onset, and favorable postsurgical seizure control. CA1 predominant HS ILAE type 2 and CA4 predominant HS ILAE type 3 have been studied less systematically so far, but some reports point to less favorable outcome, and to differences regarding epilepsy history, including age of seizure onset. The proposed international consensus classification will aid in the characterization of specific clinicopathologic syndromes, and explore variability in imaging and electrophysiology findings, and in postsurgical seizure control.

KEY WORDS: Brain, Hippocampus, Neurology, Epileptology, Neuropathology, Seizures.

Hippocampal sclerosis (HS) is the most common histopathologic abnormality found in adults with drug-resistant temporal lobe epilepsy (TLE; Cavanagh & Meyer, 1956; Bruton, 1988; Blumcke et al., 2002; de Lanerolle et al., 2003; Blumcke et al., 2012). In a European series of 5,392 patients with epilepsy who were undergoing surgical resection for various etiologies, HS was identified in 33.6%, with an additional 5.1% showing dual pathology, that is, HS in combination with cortical malformations, tumors, vascular lesions, and scars (Blumcke & Spreafico, 2012). However, no reliable information is available on the prevalence of TLE. In a hospital-based study of 2,200 adult outpatients, 25% of patients with TLE were reported to have findings on magnetic resonance imaging (MRI) indicative of hippocampal atrophy (Semah et al., 1998). The proportion of patients with hippocampal atrophy increases to approximately 70% when considering patients referred to tertiary epilepsy centers for presurgical evaluation of drug-resistant TLE (Cendes et al., 1997; Bernasconi, 2006). Familial cases of HS have been described (Cendes et al., 1998), without gender or affected side predominance (Briellmann et al., 1999). HS-like patterns of cell damage have also been reported in nonepileptic elderly populations and related to anoxic or ischemic injury and neurodegeneration (Zarow et al., 2008; Nelson et al., 2011; Montine et al., 2012).

Surgical resection offers postoperative seizure freedom at 2 years in 60–80% of patients with drug-resistant TLE (Engel et al., 1993; Arruda et al., 1996; Bien et al., 2001; Wiebe et al., 2001; Wieser et al., 2003; Janszky et al., 2005; von Lehe et al., 2006). Longer-term follow-up studies present less favorable results (Jehi et al., 2010; de Tisi et al., 2011; Bien et al., 2013), supporting the notion that TLE is a heterogeneous condition in terms of network properties and prognostic features (Stefan & Pauli, 2002; Wieser, 2004; Kahane & Bartolomei, 2010; Thom et al., 2010b; Bonilha et al., 2012), as well as degree and pattern of MRI structural anomalies within the ipsilateral temporal lobe (Bernasconi et al., 2003; Townsend et al., 2004; Sankar et al., 2008) or outside the temporal lobe (Bernasconi et al., 2004; Bernhardt et al., 2010).

In fact, neuropathologic investigations have described different patterns of neuronal cell loss within hippocampal subfields and adjacent temporal lobe structures in surgical specimens (Sagar & Oxbury, 1987; Bruton, 1988; Wyler et al., 1992; Mathern et al., 1995d; Proper et al., 2001; de Lanerolle et al., 2003) or autopsy brains from patients with epilepsy (Sommer, 1880; Margerison & Corsellis, 1966; Meencke & Veith, 1991; Meencke et al., 1996; Thom et al., 2005). Time-related factors such as epilepsy duration (Janszky et al., 2005), age at epilepsy onset, and the presence of an early preceding event, especially complex and prolonged febrile seizures (Sagar & Oxbury, 1987; Mathern et al., 1995b,c; Davies et al., 1996; Blumcke et al., 1999; von Lehe et al., 2006), are likely to influence the degree of HS. Seizure frequency and severity, as well as genetic

susceptibility, could also affect the development of HS. A reliable neuropathologic classification system could be highly valuable to differentiate histopathologic subgroups and improve prediction of postsurgical outcome.

With this background in mind, the Task Force for Neuropathology of the International League Against Epilepsy (ILAE) Commission on Diagnostic Methods was tasked to evaluate previously published data (for review see also Blumcke et al., 2012), and to develop a consensus classification system based on qualitative histopathologic assessments that could be utilized by neuropathologists in most hospitals. The ILAE classification system, which was validated by interobserver and intraobserver agreement studies using a virtual slide microscopy platform, is based on a well-defined anatomic subfield definition (Fig. 1). It is hoped that this system will prove useful in predicting individual responses to treatment as well as to related comorbidities, such as memory impairment and mood disorders.

THE ILAE CLASSIFICATION OF HS IN PATIENTS WITH TLE

The histopathologic hallmark of HS is segmental pyramidal cell loss, which can affect any sector of the Ammon's horn. Hippocampal neuronal cell loss is always associated
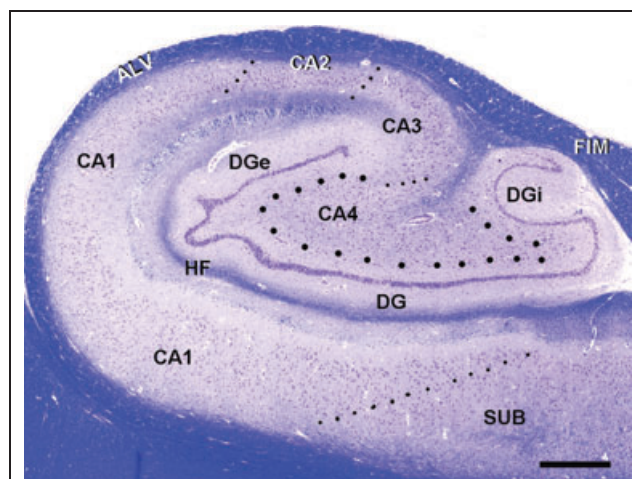

Figure 1.
Microscopic anatomy of the human hippocampus. Cresyl-violet and Luxol-Fast-Blue staining of a postmortem human hippocampus illustrating the ILAE classification use of terminology: SUB, subiculum; CA1–CA4, sectors of the Cornu ammonis; DG, dentate gyrus with external (DGe) and internal limbs (DGi); HF, remnant of hippocampal fissure; ALV, alveus; FIM, fimbria. Dotted lines circumscribe anatomic boundaries between CA sectors, and cell quantification (see Table 1) should be always performed at the center of these regions. See also Appendix 2 for a more detailed description. Scale bar = 1,000 μm.
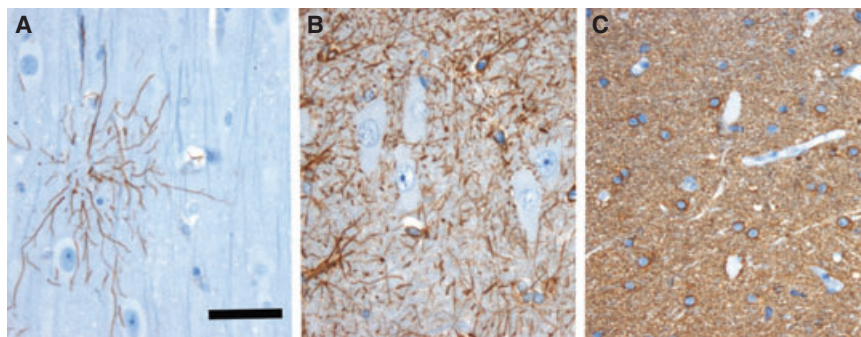*Epilepsia* © ILAE

Figure 2.
Different microscopic patterns of reactive astrogliosis. Brightfield GFAP-immunoreactivity patterns counterstained with hematoxylin in human epilepsy hippocampus specimens. (**A**) A single reactive astrocyte was immunolabeled in this CA1 region of a no-HS specimen, whereas many other astrocytes did not express detectable levels of GFAP. (**B**) A pattern of moderate reactive astrogliosis can often be observed in epileptic human brain. Depicted from a CA1 region of ILAE HS type 1 with only slight decrease of neuronal density. (**C**) Severe fibrillary astrogliosis with a dense meshwork of GFAP-labeled fine processes in a sclerotic CA1 region of ILAE HS type 1. Scale bar = 20 μm, applies also to **B** and **C**.
Epilepsia © ILAE

with a severe pattern of astrogliosis, defined by a dense meshwork of intensely immunostained glial fibrillary acidic protein (GFAP)–positive processes (Fig. 2C). This atrophic and hardened tissue consistency led to early introduction of the term "Ammon's horn sclerosis" (Sommer, 1880). We will refer only to this pattern of severe astrogliosis when referring to HS, acknowledging the fact that reactive astrogliosis can show a continuum of changes in pathologic brain specimens ranging from reversible cell hypertrophy with preservation of cellular domains to long-lasting scar formation with rearrangement of tissue structure (Sofroniew & Vinters, 2010).

In the present article, the ILAE Task Force proposes a classification system that allows reliable recognition of three types of HS by visual histopathologic examination of en bloc resected surgical specimens (Table 1, Fig. 3). This classification showed good interobserver and intraobserver agreement among 10 neuropathologists using a virtual slide microscopy system (Coras et al., 2012), and two evaluation rounds with 20 and 30 surgical tissue samples (see below).

HS ILAE Type 1

This is the most common type of HS (approximately 60–80% of all TLE-HS cases in reported series; Bruton, 1988; Davies et al., 1996; Blumcke et al., 2002, 2007; de Lanerolle et al., 2003; Thom et al., 2010a). The CA1 segment is most severely affected (with >80% cell loss; Blumcke et al., 2012). Other segments also show significant neuronal cell loss (Fig. 3A), affecting 30–50% of pyramidal neurons in CA2, 30–90% of neurons in CA3, and 40–90% of neurons in CA4. The dentate gyrus (DG) is usually affected by 50–60% granule cell loss. The distribution of cell loss within segments of the hippocampus follows that described in the late 1800s (Bratz, 1899), and associated

Table 1. ILAE consensus classification of hippocampal sclerosis

Class.[a]	Subfield pathology patterns of neuronal cell loss and gliosis (in *en bloc* resected samples)			
	HS ILAE Type 1	HS ILAE Type 2 "CA1 Predominant"	HS ILAE Type 3 "CA4 Predominant"	No-HS / Gliosis only
CA1[b]	2	1 - 2	0 - 1	0
CA2[b]	0 - 2	0 - 1	0 - 1	0
CA3[b]	0 - 2	0 - 1	0 - 1	0
CA4[b]	2	0 - 1	1 - 2	0
DG[c]	0 - 2	0 - 1	0 - 2	0 - 1

Semiquantitative microscopic examination based on formalin-fixed, paraffin-embedded surgical specimen (4–7 μm section thickness), hematoxylin and eosin staining, Cresyl-violet combined with Luxol-fast blue staining (CV/LFB; Fig. 1), GFAP immunohistochemistry (Fig. 2) and NeuN immunohistochemistry (recommended; Fig. 3). The scoring system refers to neuronal cell loss (NeuN staining) and is defined for CA1–CA4 as following: 0 = no obvious neuronal loss or moderate astrogliosis only; 1 = moderate neuronal loss and gliosis (GFAP); 2 = severe neuronal loss (majority of neurons lost) and fibrillary astrogliosis.
[a]This classification applies to anatomically intact hippocampal specimen where all subfields are represented (en bloc resection recommended). Arrows indicate a transition of neuronal cell loss toward predominant CA1 loss in ILAE HS type 2 and predominant CA4 loss in ILAE HS type 3.
[b]Note that the limitations of visual inspection alone indicate that first detectable neuronal loss corresponds to approximately 30–40% cell loss (in H&E stains, shown by quantified neuronal density measurements). Quantitative methods will be more reliable for scoring.
[c]Scores for the dentate gyrus (DG): granule cell layer is normal (score 0), dispersed (score 1; can be focal) or shows severe granule cell loss (score 2; can be focal).

with the cell loss, are signs of synaptic reorganization of excitatory and inhibitory axons (Mathern et al., 1995a,d). Cell loss is sometimes focal in the DG and accompanied by
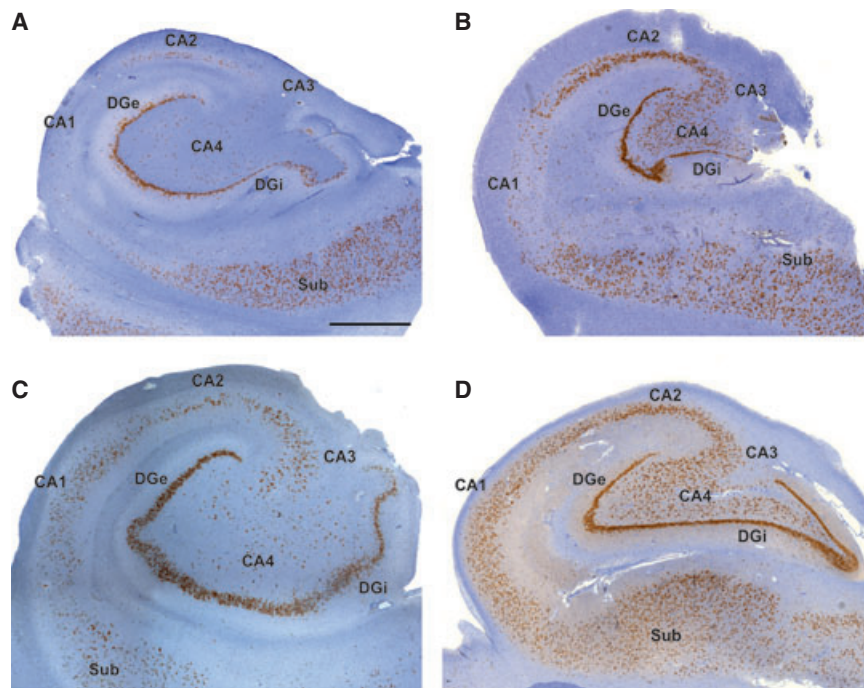
Figure 3.
Histopathologic subtypes of hippocampal sclerosis in patients with TLE. (**A**) ILAE hippocampal sclerosis type 1 shows pronounced preferential pyramidal cell loss in both CA4 and CA1 sectors. Damage to sectors CA3 and CA2 is more variable, but frequently visible. Note variable cell loss also in the dentate gyrus, with abundant granule cell loss in the internal limb (DGi) in this sample, and a transition with preservation of cells in the subiculum (SUB). (**B**) ILAE hippocampal sclerosis type 2 (CA1 predominant neuronal cell loss and gliosis): This is a rarer and atypical HS pattern characterized by neuronal loss primarily involving CA1 compared with other subfields where damage is often not really detectable by visual inspection (Table 1). (**C**) ILAE hippocampal sclerosis type 3 (CA4 predominant neuronal cell loss and gliosis): This is characterized by restricted cell loss mostly in CA4. This surgical specimen is obtained from a patient with limbic encephalitis and late onset of her TLE. (**D**) No hippocampal sclerosis, gliosis only: Microscopic inspection does not reveal significant cell loss in any of the hippocampal subregions (no-HS). All stainings represent NeuN immunohistochemistry with hematoxylin counterstaining using 4-μm–thin paraffin embedded sections. DGe/DGI, external/internal limbs of dentate gyrus; Sub, subiculum. Scale bar in **A** = 1,000 μm (applies also to **B**–**D**).
Epilepsia © ILAE

granule cell dispersion (GCD; Houser, 1990). GCD is defined by broadening of the granule cell layer above 10 layers (Wieser, 2004), an ill-defined boundary with the molecular layer, and ectopic granule cells (either isolated, clustered, or bilayered) separated from the main layer by intervening neuropil. It is important to note that GCD can only be reliably assessed with certainty in regions without curvature of the DG. Due to the large variability in granule cell pathology without a clear association with clinical outcome (Blumcke et al., 2009; Stefan et al., 2009), it was agreed that any type of granule cell pathology (graded as 0–2) could be present in HS ILAE type 1. The Task Force also acknowledged the longstanding discussion about so-called classic and severe/total cell loss patterns in HS (Wyler et al., 1992; Blumcke et al., 2007; Thom et al., 2010a). However, it became apparent after the evaluation that distinguishing the two groups was not always reliable even

among experts. Hence, the group felt it was too difficult to reliably differentiate between these patterns using a qualitative scoring system, and clinical features were also not significantly different between classical and severe variants. The scoring system, therefore, refers to classic and total HS as hippocampal sclerosis ILAE Type 1.

Hippocampal sclerosis ILAE type 2 (CA1 predominant neuronal cell loss and gliosis)

This type presents histopathologically with predominant neuronal loss in CA1 (Fig. 3B), affecting almost 80% of pyramidal cells. All other sectors show mild cell loss barely visible by qualitative microscopic inspection, that is, in CA2 < 20%, in CA3 < 20%, and in CA4 < 25% of principal cells. This pattern is uncommon, being seen in approximately 5–10% of all TLE surgical cases. Due to the pathology pattern largely restricted to CA1, the Task Force

considered this an atypical type similar to that described earlier (de Lanerolle et al., 2003). DG pathology patterns may include granule cell dispersion, but usually lack severe granule cell loss (Blumcke et al., 2007).

Hippocampal sclerosis ILAE type 3 (CA4 predominant neuronal cell loss and gliosis)

ILAE type 3 shows predominant cell loss in CA4 (approximately 50% cell loss) and the dentate gyrus (35% cell loss), whereas CA3 (<30%), CA2 (<25%), and CA1 (<20%) are only moderately affected (Table 1; Fig. 3C) (Blumcke et al., 2012). It is also a rare HS variant detectable in approximately 4–7.4% of all TLE surgical cases (Bruton, 1988; Blumcke et al., 2007; Thom et al., 2010a). This type is probably similar to that described in 1966 by Margerison and Corsellis as end folium sclerosis. Consensus terminology will call this HS ILAE type 3 (CA4 predominant sclerosis). It is likely, that HS type 3 will be more often associated with a dual pathology such as Rasmussen's encephalitis or other lesions (Mathern et al., 1997).

No hippocampal sclerosis, gliosis only (no-HS)

Despite electrophysiologic evidence for generation of seizures in the mesial temporal lobe using intracranial electrodes, histopathologically about 20% of TLE cases do not show significant neuronal cell loss with only reactive gliosis (Blumcke et al., 2007), and it has been shown that cell density measurements are not different from age-matched autopsy controls (Bruton, 1988; de Lanerolle et al., 2003; Blumcke et al., 2007; Thom et al., 2010a). This observation has been noted in neuropathologic surveys of TLE series at surgery and postmortem (Blumcke et al., 2002; Thom et al., 2005). We designated this group, therefore, as "no hippocampal sclerosis with gliosis only (no-HS)" (Fig. 3D). This contrasts with the Wyler classification, in which 10% difference in neuronal cell densities already classify as HS Wyler grade 1 (see Appendix 4). Noteworthy, no-HS often presents with various degrees of gliosis. As evidence grows for glia-mediated excitation and inflammation in modulating or triggering seizures (Devinsky et al., 2013), isolated gliosis may play a pivotal role in the pathophysiology of hippocampal damage, particularly in TLE patients with no-HS. Future studies should aim at clarifying the complex interplay between glia and neurons and their impact on hippocampal morphology.

Granule cell dispersion

Granule cell dispersion (GCD) was first described by Carolyn Houser (Houser, 1990) and occurs in approximately 50% of all TLE cases (Blumcke et al., 2002, 2009). However, clinicopathologic correlation studies did not prove evidence for any predictive value of GCD for postsurgical outcome (Blumcke et al., 2007, 2009; Stefan et al., 2009; Thom et al., 2010a; da Costa Neves et al., 2013). In addition, GCD is variably described in ILAE HS types 1, 2,

and 3 (Blumcke et al., 2007; Thom et al., 2010a), and may also occur in patients without hippocampal neuronal cell loss (Blumcke et al., 2007). Evidence currently suggests GCD as result of Reelin deficiency in the DG (Haas et al., 2002; Haas & Frotscher, 2009; Kobow et al., 2009), and that the presence of GCD is associated with greater cell loss in the hilus, an older age at epilepsy surgery, and longer epilepsy duration (Blumcke et al., 2009; Neves et al., 2012). The involvement of granule cells in the mechanisms of plasticity and memory formation also suggests that depletion of granule cells, in particular within the internal limb (Altman & Bayer, 1990), could be related to memory impairment in patients with TLE (Pauli et al., 2006; Blumcke et al., 2009; Coras et al., 2010; Neves et al., 2012). Further prospective studies are required, however, to confirm such correlation between GCD and clinical variables.

INTEROBSERVER AND INTRAOBSERVER AGREEMENT FOR THE ILAE CONSENSUS HS CLASSIFICATION SYSTEM

Methodology

Fifty cases were selected by two neuropathologists from the European Epilepsy Brain Bank (IB and RC). They were considered to comprise a broad spectrum of histopathology changes in patients with TLE. All tissue specimens were fixed overnight in 4% formaldehyde and routinely processed in liquid paraffin according to standardized histopathology protocols. Sections were cut at 4 μm with a microtome (Microm, Heidelberg, Germany), and mounted on positively charged slides (Menzel, Braunschweig, Germany). Hematoxylin and eosin (H&E) staining and histochemical reactions (cresyl-violet combined with Luxol-Fast-Blue [CV/LFB]) were performed from one representative tissue sample of each surgical case and fully digitalized using the DotSlide Virtual Slide System (Olympus, Tokyo, Japan) equipped with a 20× microscope objective. In addition, immunohistochemical staining using antibodies directed against glial fibrillary acidic protein (GFAP, mouse monoclonal; Dako, Glostrup, Denmark), neuronal nuclear antigen (NeuN, mouse monoclonal; Merck Millipore, Billerica, MA, U.S.A.), were performed with a semiautomated staining apparatus (Ventana Benchmark; Roche Diagnostics, Mannheim, Germany). Short summaries of clinical data including gender, age at surgery, seizure onset, and side of resection were provided for each case. There was no access to preoperative imaging or imaging reports. Personalized results were visible and statistically analyzed only by the system administrator, who is a senior assistant professor at the pathology department of Amsterdam neither experienced in epilepsy surgery nor enrolled in this survey or any other epilepsy-related scientific study. Interobserver agreement was calculated by kappa-coefficient analysis. The

kappa-coefficient was also used to determine intraobserver reproducibility (Sim & Wright, 2005).

For case evaluation, 10 experienced neuropathologists/experimentalists from seven different countries (England, Germany, Italy, Japan, The Netherlands, Turkey, and U.S.A.) gained online access to the virtual slide system Digital Slidebox 4.5 (Slidepath; Leica Microsystems, Dublin, Ireland), and were asked to classify at first 20 anatomically well-preserved cases (obtained from en bloc resections) within a 28-day period using an earlier version of HS classification scheme (not shown). For each case, raters chose between predefined diagnosis (for example HS Type 2, no-HS), and also evaluated each anatomic subfield (DG, CA4, CA3, CA2, CA1, and Sub) according to the proposed scoring system (0–1–2, see Table 1 for definitions). During the first two agreement rounds, we have also separated HS type 1 into 1a (so called "classic" pattern with CA3 being more preserved) and 1b (so called "severe HS" with CA3 being strongly affected). All diagnostic reports were submitted and retrieved from the Digital Slidebox system. Ten raters submitted their reports within the given time limit. None of the raters had access to results of other reviewers. The same 10 participants re-reviewed the slide series after a 2-month interval. The website was not accessible during the interim period. The cases were provided in different order of appearance at the second evaluation round. Following discussion of the initial set of results, the Task Force decided to open a third and fourth evaluation round, presenting 30 new cases with a similar study design.

Results

As shown in Table 2, overall interobserver agreement increased consistently over the four evaluation series. The Task Force considered the results from the first and second round not sufficiently reliable, because very good agreement was achieved only for the diagnosis of no-HS, and good agreement for ILAE type 1b and type 3. The scoring system for subfield analysis was, therefore, adopted for those areas in which interobserver agreement was fair or moderate (data not shown). This process generated the present scoring system shown in Table 1. In the third and fourth rounds, when raters used the revised scoring system, a reliable differentiation was achieved for all HS types as well

as no-HS with an overall kappa agreement value of 0.7483. Differentiation between HS types 1a and 1b remained, however, challenging (data not shown), and the Task Force decided to merge these subtypes into ILAE type 1. Intraobserver reliability was also good at the fourth round and reached a kappa value of 0.7056.

This latter series included also 10 fragmented surgical specimens to evaluate the classification of probable HS (with CA1 available) and possible HS (with CA4 available) diagnosis. The raters reached only fair to moderate agreement scores for these specimens, and the Task Force decided not to introduce this terminology for fragmented specimens into the consensus classification.

All raters favored NeuN (Wolf et al., 1996) as the most valuable immunostaining for the assessment of neuronal cell loss in surgical TLE specimens. GFAP as well as CV/LFB were helpful to judge anatomic hallmarks and extent of gliosis, but were not considered mandatory for the proposed semiquantitative classification. NeuN staining correlates very well with neuronal cell counts obtained from H&E or CV/LFB stains, but this has to be tested in each individual laboratory by comparing semiquantitative analysis from both stains on consecutive sections (Blumcke et al., 2007). This knowledge will be helpful when surgical artifacts (for example bleeding) compromise NeuN immunostaining, or if postmortem specimens will be included for research purpose.

ASSESSMENT OF FRAGMENTED SURGICAL SPECIMENS (ANATOMICALLY INCOMPLETE SAMPLES)

The Task Force recognized that the proposed classification scheme requires en bloc resected hippocampal tissue specimens with complete anatomic representation of all subfields. The group is aware, however, that different approaches to hippocampectomy may not always provide anatomically well-preserved hippocampus specimens for histopathologic examination or for further research. Working with these limitations, it is recommended, therefore, that microscopic assessment should include at least the CA1 and

	HS Type 1a (classic)	HS Type 1b (severe)	HS Type 2 "CA1 predominant"	HS Type 3 "CA4 predominant"	No-HS/gliosis only	Mean
Table 2. Interobserver agreement study for the classification of HS types						
1st round	0.3983[a]	0.5665[b]	0.1133[c]	0.6051[d]	0.6954[d]	0.4891[b]
2nd round	0.4901[b]	0.6144[d]	0.1295[c]	0.6296[d]	0.8870[e]	0.5760[b]
3rd round	0.6595[d]		0.4965[b]	0.7956[d]	0.8437[e]	0.6875[d]
4th round	0.7074[d]		0.6317[d]	0.7836[d]	0.9064[e]	0.7483[d]

Kappa values are always ≤ 1. In our study, *kappa* was interpreted as follows: [a]0.2–<0.4, fair agreement; [b]0.4–<0.6, moderate agreement; [c]<0.2, poor agreement; [d]0.6–<0.8, good agreement; [e]0.8–1.0, very good agreement.

CA4 regions where possible. In the context of electroclinical and neuroimaging findings of TLE, this would allow the diagnosis of "probable HS." With more anatomic regions available (showing cell loss scores 1–2), the diagnosis of HS becomes more confident, and the ILAE scoring system may become applicable. If less tissue is available for microscopic examination (i.e., neither CA1 or CA4 or only one of these), neuropathology cannot neither confirm nor support the clinical diagnosis of any ILAE defined HS type. This should be documented as such in the diagnostic report or scientific manuscripts.

Hippocampal Sclerosis and Other Pathologies Including Associated Focal Cortical Dysplasia (FCD Type IIIa)

An intriguing issue remains the association between TLE and focal cortical dysplasia (FCD). Despite the many published results, neither a distinct etiology nor a clinicopathologic phenotype for TLE with FCD has been identified, which elicits continuous debate (Spreafico & Blumcke, 2010). Notwithstanding, HS is frequently associated with other pathologies (Blumcke et al., 2002), and electroclinical as well as imaging abnormalities in TLE-HS patients often extend beyond the hippocampus, suggesting a more widespread substrate for the generation or persistence of seizures (Chassoux et al., 2000; Chabardes et al., 2005; Fauser & Schulze-Bonhage, 2006; Barba et al., 2007; Bartolomei et al., 2010). Another Task Force of the ILAE Diagnostic Commission has classified, therefore, distinct histopathologic patterns in TLE patients with HS as FCD type IIIa (Blumcke et al., 2011). It has not yet been clarified whether FCD type IIIa is an acquired pathology with accompanying reorganizational dysplasia resulting from some initial injury that has also produced HS, or a distinct developmental entity. The latter would favor the hypothesis that HS is the consequence of chronic epileptogenicity of the temporal lobe due to the dysplasia. Several aspects argue, however, for a common etiology between HS and FCD type IIIa. Patients from both groups have a similar age at onset and a similar history of febrile seizures as an initial precipitating injury (Marusic et al., 2007); no other clinical differences have yet been identified between HS and HS/FCD type IIIa cases (Thom et al., 2009). Accordingly, postsurgical outcome is similar in patients with HS only compared to HS with FCD type IIIa (Tassi et al., 2010).

Another well-recognized clinical challenge is that of ipsilateral temporal atrophy with temporopolar gray/white matter blurring, visible on MRI in up to 70% of TLE-HS patients (Choi et al., 1999; Meiners et al., 1999; Mitchell et al., 1999). It is often regarded as a sensitive radiologic FCD marker, but a recent correlation between 7T MRI and histopathology including electron microscopy showed severe and patchy myelin loss in temporal white matter as underlying substrate, rather than any kind of cortical/subcortical dysplasia (Garbelli et al., 2012). Whether these temporopolar histologic changes might relate with the electroclinical temporopolar type of TLE-HS (Chabardes et al., 2005) remains another interesting issue.

Histopathologically proven cortical abnormalities in TLE-HS patients are less frequent and usually present in two variants. In approximately 10% of temporal lobe surgical specimens from HS patients, an abnormal band of small and clustered "granular" neurons can be observed in the outer part of neocortical layer 2 (Garbelli et al., 2006; Thom et al., 2009). This pattern is likely to present with severe neuronal cell loss in layers 2 and 3 with associated laminar gliosis (GFAP-positive astrogliosis) and cortical reorganization, and has been described so far only in the temporal lobe of patients with TLE-HS. However, there is no correlation between this FCD type IIIa variant and MRI findings (Thom et al., 2009; Garbelli et al., 2011). Small "lentiform" nodular heterotopia can be identified as another structural abnormality in the temporal lobe of patients with TLE-HS. They also remain undetected by MRI (Meroni et al., 2009). Lentiform heterotopia should be separated from the frequent observation of "isolated" heterotopic neurons either at the gray–white matter junction or in deep subcortical white matter location. Both findings are often encountered in surgical specimens obtained from patients with epilepsy, although their pathogenic or epileptogenic significance remains undetermined (Rojiani et al., 1996; Emery et al., 1997; Thom et al., 2001; Arai et al., 2003; Muhlebner et al., 2012). Increased numbers of heterotopic neurons in white matter location should, therefore, still be diagnosed, as a mild malformation of cortical development (mMCD type II) using Palmini's classification system (Palmini et al., 2004), if occurring as isolated finding without HS, tumors, or other principal lesions (Blumcke et al., 2011).

Correlation between Histopathology and MRI

During recent decades, MRI has led to increased rates of successful resective surgery in drug-resistant TLE by allowing in vivo identification of HS (Bernasconi, 2005; Tellez-Zenteno et al., 2007). On visual inspection, classical signs consist of noticeable hippocampal atrophy and increased signal intensity on T_2-weighted images. Visual inspection of the hippocampus may not be able to clearly differentiate ILAE-HS subgroups (Fig. 4). Nevertheless, hippocampal volumetry is more sensitive than visual evaluation and has been long recognized as a reliable surrogate marker of HS (Bernasconi, 2006). Indeed, the degree of atrophy has been shown to correlate with the severity of neuronal loss within hippocampal subfields as determined by various pathologic gradings, including Wyler's classification (Cascino et al.,

Figure 4.
3T MRI findings in histopathologically verified types of TLE-HS. Presurgical $T_2 -$ MRI findings at three Tesla in TLE patients with histopathologically classified hippocampal sclerosis on the right side (left on panel). (**A**) ILAE HS type 1. (**B**) ILAE HS type 2. (**C**) ILAE HS type 3. In these specific examples, volumetric loss is severe in ILAE HS type 1, moderate in ILAE HS type 2, but virtually not detectable in ILAE HS type 3.
Epilepsia © ILAE
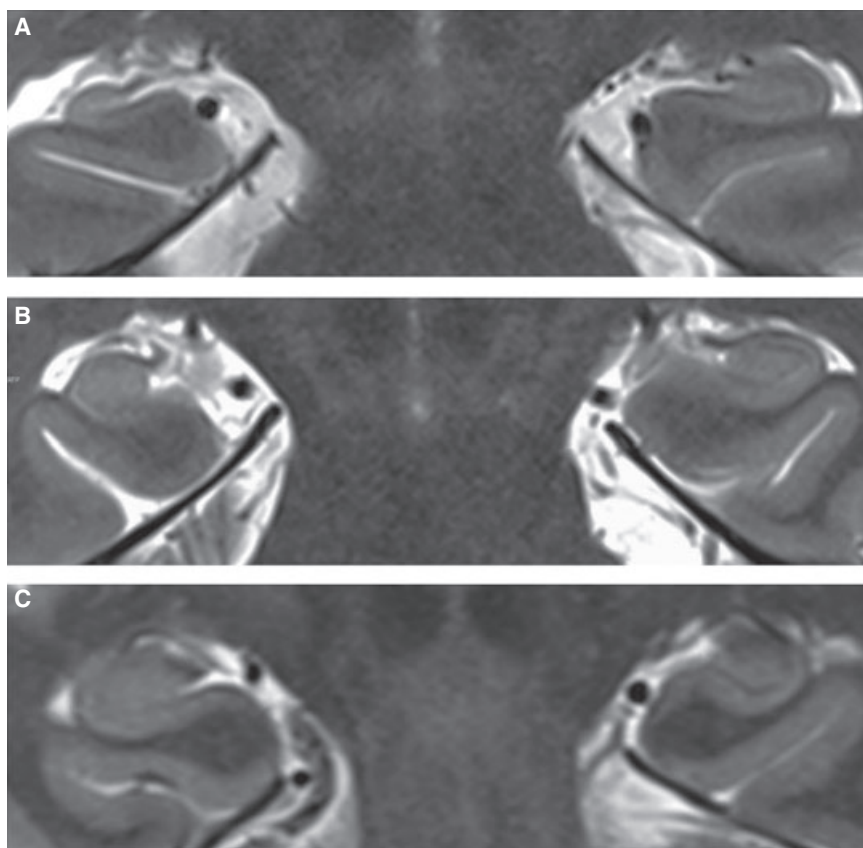
1991; Watson et al., 1996). Notably, mild degrees of hippocampal atrophy were associated with Wyler grades I and II, which represent neuronal cell density loss of approximately 10–50%. Similar to electroclinical and pathologic spectrum, there are significant variations in the degree, pattern, and regional distribution of MRI anomalies among patients, including anteroposterior gradient of atrophy within the hippocampus (Bernasconi et al., 2003), atrophy of the entorhinal cortex (Bernasconi et al., 1999), amygdala (Cendes et al., 1993), and temporopolar region (Sankar et al., 2008). Moreover, structural changes affecting the neocortex of the frontocentral, temporal, and parietal regions (Bernhardt et al., 2009, 2010) as well as the axonal fiber bundles that link them (Concha et al., 2012), suggest widespread abnormalities of brain organization, which may negatively affect outcome after surgery. The limited resolution of current clinical protocols precludes a direct visualization of hippocampal subfields on MRI. Nevertheless, techniques such as shape analysis quantifying submillimetric changes along the surface manifold may circumvent limitations imposed by voxel-resolution of the MRI and allow an approximation of subfield pathology (Kim et al., 2008; Bernhardt et al., 2012). These advances together with the increasing sophistication of acquisition protocols at ultra-high field are likely to further refine the imaging correlates of HS.

Conclusions

A Task Force of the ILAE Commission on Diagnostic Methods proposes a classification of hippocampal sclerosis assessed by semiquantitative histopathologic subfield analysis of en bloc hippocampal resections in patients with TLE. The classification includes patients with ILAE HS type 1 (classic or complete patterns), ILAE HS type 2 (CA1 predominant sclerosis), ILAE HS type 3 (CA4 predominant sclerosis), previously also termed end folium sclerosis, and no-HS. Hippocampal resections that are incomplete may be classified as "probable HS," if there is sufficient material including the CA4 and CA1 regions. It is hoped that this classification system can be used to uniformly diagnose surgical specimens of patients with TLE and provide a vehicle for collaborative studies across surgical epilepsy centers.

Disclosure

All coauthors declare no conflict of interest. We further confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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APPENDIX 1

DEFINITIONS AND TERMINOLOGY ISSUES

1 The term "hippocampal sclerosis" (HS) is used to histopathologically define the pattern of selective neuronal cell loss with concomitant astrogliosis in the hippocampal formation (including the dentate gyrus). This current scheme applies to *patients with temporal lobe epilepsy (TLE)*. Segmental hippocampal neuron loss can be also observed in other pathologic conditions, including dementia, aging, ischemia, and neurodegeneration, but the patterns of neuronal cell loss may differ and usually also involves the subiculum (Nelson et al., 2011; Montine et al., 2012).

2 HS occurs either isolated or in association with another epileptogenic lesion (dual pathology), for example tumor, malformations of cortical development, vascular malformation, encephalitis, or glial scar in the ipsilateral hemisphere. Familial (hereditary) forms of unilateral or bilateral HS exist.

3 The three ILAE types can be microscopically identified, when an anatomically well-preserved surgical specimen is available. *The optimal sample is derived from en bloc resections*. Histologic patterns may vary along the anterior-posterior axis. Although diagnosis should reflect any variability observed (please mention section level at pathology report according to atlas of Duvernoy, 2005), it should usually refer to the mid-body.

4 Mesial temporal sclerosis (MTS) is herein defined as HS plus changes in other structures of the mesial part of the temporal lobe such as amygdala and entorhinal cortex (as evidenced by imaging findings or histopathology).

5 The term "Ammon's horn sclerosis" first coined by Sommer in 1880 is often used synonymous with HS. This ILAE classification system uses only the term HS to acknowledge that the dentate gyrus is also part of the hippocampus proper.

APPENDIX 2

ANATOMIC TERMINOLOGY OF THE HIPPOCAMPUS PROPER AS USED FOR THE ILAE HS CLASSIFICATION

The anatomy of the human hippocampus has a long and controversial history since its first description by Julius Caesar Arantius, who in 1587 compared the anatomic elevations within the inferior horn of the lateral ventricles with that of a seahorse (hippocampus), with the animal's head pointing either to the third ventricle or the anterior part of the temporal lobe. This controversy was further fueled by another term introduced in 1742 by de Garengoet, who compared the mesial view of the hippocampus with the Ammon's horn adopted from the Egyptian god Amun Kneph (Lewis, 1923; Walther, 2002). It is the pyramidal cell layer of the various hippocampal subregions that is now microscopically recognized as cornu ammonis (CA areas) and, indeed, resembles a ram's horn. The histologic classification of hippocampal subfields is equally controversial, with many classification systems available, partly resulting from differences between rodent and human anatomy. The classification introduced by Lorente de Nó in 1934 is most widely used by neuropathologists and designates four hippocampal sectors, namely, CA1–CA4. The transition areas between CA1 and subiculum (termed prosubiculum) or between the CA3 and CA4 regions remain, however, difficult to delineate in humans using routine staining techniques. These difficulties are reflected by attempts to classify hippocampal subregions in only two (Ramon y Cajal, 1893) or three subregions (Vogt & Vogt, 1937). Of note, prominent books from Gloor (Gloor, 1997) and Insausti (Insausti et al., 2010) promote a three-region nomenclature, not used in this ILAE HS classification proposal.

The hippocampus, a major constituent of the allocortex (Braak, 1980), is located in the mesial temporal lobe, occupying the floor of the inferior horn of the lateral ventricle, from the level of the corpus amygdaloideum up to the splenium of the corpus callosum. Three major parts can be distinguished: the dentate gyrus (or fascia dentata), the cornu ammonis, and the subiculum. The dentate gyrus consists of three laminae: the molecular layer, the granular layer, and the polymorphic layer (an ill-defined area of about 50–100 μm width extending from the granule cell layer to the modified CA4 pyramidal cells). Small granule cells form the major neuronal cell layer in the dentate gyrus, and their perikarya assemble tightly together giving the appearance of a clear-cut band. The basal tip of the granule cell soma shows a distinct axon hillock from which a relatively thick axon is generated, which enters the cornu ammonis and forms synaptic contacts with the pyramidal neurons of CA4 and CA3 (the mossy fiber pathway). The apical dendrites ramify within the molecular layer and receive topographically restricted efferents from the collateral hippocampus and ipsilateral tractus perforans (or perforant pathway). According to Duvernoy (2005), the internal third of the molecular layer receives input from the septal fibers, followed by commissural fibres, whereas the majority of the outer two thirds is occupied by perforant pathway fibers. The granule cell layer is functionally regarded as "gatekeeper" of the hippocampus, as it receives the majority of axonal input into the human hippocampus. A helpful and interactive overview of the

parahippocampal-hippocampal network is provided by van Strien et al. (2009).

The exact anatomic delineation of the hilus (the region embraced by the two blades [or limbs] of the dentate gyrus) is controversial. It is designated as CA4 region by Lorente de Nó, and pigment-architectonical analysis confirmed the notion of an independent hippocampal subfield composed of modified pyramidal cells as well as a large variety of interneurons (Braak, 1980). A particular cellular component of CA4 is represented by mossy cells with thorny excrescences, on which mossy fibers of the dentate gyrus granule cells terminate. Indeed, the border between polymorphic cell layer of the dentate gyrus and true CA4 is ill defined, and may be considered as 50–100 μm rim beneath the granule cell layer. Corsellis coined the term "end folium" (Margerison & Corsellis, 1966) for all cells in the hilar region, whereas Gloor described CA4 as "endblade" of CA3, entering the concavity of the dentate gyrus (Gloor, 1997). For our current system we adopt the nomenclature of Duvernoy in partitioning the subfields CA1–4 from the subiculum and the dentate gyrus as illustrated in Figure 1.

APPENDIX 3

CLINICOPATHOLOGICAL AND PROGNOSTIC CORRELATIONS

The electroclinicopathologic spectrum of TLE-HS indicates that structural and functional disturbances are usually more extensive than just the hippocampus (Wieser, 2004; Thom et al., 2010b; Bonilha et al., 2012). We can clinically define subgroups ranging from very focal mesial to more extensive "temporal plus" types (Kahane & Bartolomei, 2010), which could result from a gradually evolving process (Bartolomei et al., 2008). Indeed, neuropathologic investigations of extrahippocampal resected tissue have detected cell loss in adjacent temporal lobe structures (Wyler et al., 1992; Du et al., 1993; Mathern et al., 1995c; Yilmazer-Hanke et al., 2000; de Lanerolle et al., 2003; Blumcke et al., 2007; Thom et al., 2010a). An intriguing issue will be, therefore, to identify the missing links between clinical and pathology patterns of TLE-HS. A reliable consensus classification system is a step forward to achieve this goal by using a common terminology for any prospective evaluation of clinicopathologic HS types with respect to postsurgical seizure control and amelioration/aggravation of frequent comorbidities, such as memory impairment and mood disorders.

The Task Force addressed if there were initial data to indicate that the proposed ILAE classification system correlates with clinical histories and outcomes in surgically treated patients with TLE. For example, TLE patients with normal appearing hippocampus and ILAE HS type 3 (CA4 predominant sclerosis) had a shorter epilepsy duration compared with ILAE HS types 1 and 2 (Blumcke et al., 2007; Thom et al., 2010a,b). Regarding initial precipitating injuries (IPIs), defined by significant seizure and nonseizure events before age 5 years (Mathern et al., 1995c), overall 40–60% of patients present with an IPI before epilepsy onset, most frequently as prolonged and complex febrile seizures (34–70%; Blumcke et al., 2002). In a prospective study of 199 children with febrile seizures (FS), 11.5% of the infants had evidence for acute hippocampal damage and abnormalities in hippocampal development (Shinnar et al., 2012). Other IPIs include encephalitis, anoxia, head trauma, birth trauma, and intracerebral bleeding. There is some evidence to support that an IPI, in particular early febrile seizures, more often associates with ILAE HS type 1 than HS types 2, 3, or no-HS in patients with TLE (Van Paesschen et al., 1997; Blumcke et al., 2007). However, any retrospective evaluation of early FS in series of adult TLE patients will remain difficult and need confirmation in a prospective approach (Hesdorffer et al., 2012).

In the light of recent reports, the proposed ILAE classification system may facilitate a clearer prediction of postsurgical outcome in patients with TLE (Blumcke et al., 2007; Stefan et al., 2009; Thom et al., 2010a). According to these studies, the best outcome was achieved in patients presenting with ILAE HS type 1 (60–80% seizure freedom 1–2 years after surgery), with current indications that fewer patients with atypical HS patterns (ILAE HS type 2 and ILAE HS type 3) became seizure free. The integration of data from previous studies is confounded by different surgical approaches and completeness of resection (including hippocampus, amygdala, entorhinal cortex, and anterior temporal lobe), the extent of mesial temporal resection, different lengths of follow-up, and the presence of a second pathology, all of which could influence outcome measures. The ILAE HS classification system requires further prospective confirmation in large patient cohorts to confirm its utility in predicting prognosis after surgery.

Regarding the extent of hippocampal pathology and resection, only one randomized controlled surgical trial has been published (Schramm et al., 2011). By comparing 2.5 versus 3.5 cm resections of the hippocampus and parahippocampus in 207 patients with TLE, the authors could detect no differences in outcome with respect to complete seizure control (Engel class I). Postmortem-based neuropathology studies of HS have confirmed variation in the extent and pattern of neuronal loss along the longitudinal axis, raising the possibility that poor outcome may also relate to residual HS in the hippocampal remnant (Thom et al., 2012). Clinical experience and neuroimaging studies also support that sclerosis is not always uniform along the anterior-posterior axis, which may influence surgical planning (Bronen et al., 1994; Bernasconi et al., 2003). The conclusion of the Task Force, in the light of current evidence, is that TLE-HS may represent a group of closely related

syndromes with variable pattern and extent of hippocampal histopathology, rather than a single disorder. This recognition may lead to a refinement in the diagnostic and surgical approaches to improve surgical outcome (Thom et al., 2010b; Bonilha et al., 2012).

APPENDIX 4

PREVIOUS HISTOPATHOLOGIC CLASSIFICATION SYSTEMS FOR HIPPOCAMPAL SCLEROSIS

The earliest neuropathology study in patients with epilepsy dates back to 1825, in which Bouchet and Cazauvielh described a hardened and shrunken hippocampus in autopsy brains from patients with a clinical history of epilepsy. Sommer (1880) first presented a microscopic description of hippocampal sclerosis in an autopsy brain from a patient with temporal lobe epilepsy. He observed loss of pyramidal neurons in a portion of the hippocampus corresponding to the sector CA1 of Lorente de Nó (1934), which was later on termed "Sommer's sector." In 1899, Bratz published a detailed report of a unilaterally atrophic hippocampus, illustrating severe loss of pyramidal neurons and gliosis in Sommer's sector, less severe neuronal loss in the hilus of the dentate gyrus, and adjacent sector CA3, and preservation of neurons in CA2, subiculum, and the granule cell layer of the dentate gyrus. His illustration confirmed the boundary between CA1 and a well-preserved subiculum, which represents the "prosubiculum" of Lorente de Nó. In 1966, Margerison and Corsellis defined two types of hippocampal damage. One was similar to that described by Bratz showing severe to total neuronal loss in CA1 and hilus of the dentate gyrus with sparing of CA2, termed "classical" Ammon's horn sclerosis. Another pattern of hippocampal damage that they described was characterized by neuronal loss confined to the hilus of the dentate gyrus or "end folium," termed "end folium sclerosis." In addition to those two patterns of hippocampal sclerosis, Bruton added, in his monograph published in 1988, the third pattern of hippocampal sclerosis called "total" Ammon's horn sclerosis showing almost complete neuronal loss in all sectors of the hippocampus. However, Bruton found no apparent correlation between any of those specific types of hippocampal sclerosis and the clinical history among 107 patients in his study.

The first systematic attempt to semiquantitatively evaluate the severity of hippocampal neuronal loss for histologic grading of hippocampal sclerosis was proposed by Wyler et al. (1992). Four grades for hippocampal sclerosis along with a diagnosis of no hippocampal sclerosis were provided in Wyler's grading system. Grade I referred to mild mesial temporal damage (MTD) showing gliosis with slight (<10%) or no neuronal cell loss in CA1, CA3, and/or CA4;

grade II presented moderate MTD and was characterized by gliosis with 10–50% neuronal cell loss in CA1, CA3, and/or CA4, and "end folium" sclerosis if the lesion is limited to CA3 and CA4; grade III was classified as moderate to marked MTD equivalent to "classical" Ammon's horn sclerosis defined as gliosis with >50% neuronal dropout in CA1, CA3, and CA4, with sparing of CA2; and grade IV refers to marked MTD that is equivalent to "total" Ammon's horn sclerosis, and defined by gliosis with >50% neuronal cell loss in all sectors of the hippocampus. Dentate gyrus, subiculum, and parahippocampal gyrus can also be involved in this category. Wyler's grading system revealed that classical and total Ammon's horn sclerosis were the most frequent pathologies in mesial temporal lobe epilepsy (mTLE). Inverse clinicopathologic correlation has been reported between Wyler's grade and postsurgical memory impairment (Hermann et al., 1992), as patients having the most postoperative memory loss were the ones with normal or grade I pathology, whereas those patients with high-grade pathology III and IV showed little postoperative memory decline. In 1996, Watson et al. proposed a modification of Wyler's grading system. They introduced a six-tiered system by inserting an additional grade between Wyler's grades II and III; that is, Watson's grade III refers to gliosis with >50% neuronal loss in CA1 and 10–50% neuronal loss in CA3/CA4, with sparing of CA2, and the definitions of grades IV and V are the same as Wyler's grades III and IV, respectively. Watson's grade II is defined as gliosis with 10–50% neuronal cell loss in CA1 and/or CA4, indicating that, although not clearly mentioned in the literature, this category also includes end folium sclerosis and CA1 sclerosis (patient 5 in their 18 cases). In 2007, Blumcke et al. proposed a clinicopathologic classification system for hippocampal sclerosis, based on semiquantitative measurements of neuronal loss in CA1–CA4. Based on the fact that extrahippocampal mesial temporal structures such as parahippocampal gyrus and amygdala may also be involved in pharmacoresistant mTLE (Yilmazer-Hanke et al., 2000), they used the term "mesial temporal sclerosis (MTS)" instead of "hippocampal sclerosis (HS)." A cluster analysis of the semiquantitative measurements revealed five distinct patterns, that is: (1) no MTS refers to a group without histopathologically classifiable hippocampal sclerosis including no or only 10% neuronal loss that is within the first standard deviation of age-matched autopsy controls, corresponding to "no hippocampal sclerosis" and Wyler's grades I; (2/3) MTS types 1a and 1b are equivalent to "classical" and "total" hippocampal sclerosis, respectively; (4) MTS type 2 is identical with CA1 sclerosis; (5) and MTS type 3 refers to "end folium sclerosis." They found that these patterns were associated with specific clinical histories and postsurgical outcome; for example, the age of the initial precipitating injury (IPI) appeared to be an important predictor of hippocampal pathology, as it was younger in patients with MTS types 1a and 1b (<3 years) than in those with MTS types 2

(mean 6 years) and 3 (mean 13 years) as well as no MTS (mean 16 years). Although successful seizure control was associated with MTS types 1a and 1b, MTS type 3 (end folium sclerosis) appears to be a predictor of poorer postsurgical seizure control. By contrast, Thom et al. (2010a) described a better outcome in patients with end folium sclerosis and poorer outcome for their no-HS group.

Such differences in results among previous studies remain a major problem in clarifying any clinicopathologic correlation of TLE-HS, and seem to be associated, at least in part, with differences in terminology use, as anatomic boundaries between CA subfield and regions of interest are not uniformly applied. The current proposal from the Task Force of Neuropathology within the Commission on Diagnostic Methods of the International League Against Epilepsy (ILAE) compiled an international consensus for the clinicopathologic classification of hippocampal sclerosis. It is based on knowledge of available classification systems, and the agreement to define common terminology issues first and on the recognition of the importance to identify distinct morphologic patterns. Future work will then allow the patterns to be reliably correlated with clinical TLE variants. Novel techniques including high field imaging may be suitable to translate the knowledge of specific hippocampal subfield patterns into clinical perspectives and help to predict each patient's response to drug versus surgical treatment as well as to related comorbidities, that is, memory impairment and mood disorders.