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CLINICO-PATHOLOGICAL SUBTYPES OF HIPPOCAMPAL SCLEROSIS IN TEMPORAL LOBE EPILEPSY AND THEIR DIFFERENTIAL IMPACT ON MEMORY IMPAIRMENT

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Abstract—Hippocampal anatomy and network organization are capable to generate drug-resistant temporal lobe epilepsy (TLE) in humans and particularly vulnerable to segmental neuronal cell loss. Surgical hippocampectomy has been proven successful in treatment and available human tissue specimens allow systematic clinico-pathological examination. Different patterns of hippocampal cell loss have been identified in TLE patients and are recently classified by the International League against Epilepsy (ILAE) into four distinct subtypes in order to stratify the heterogenous group of TLE patients also with respect to postsurgical outcome. Another important aim of the international consensus classification system of hippocampal sclerosis (HS) is to gain further insights into the morpho-functional organization of human memory frequently compromised in TLE patients.

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Key words: brain, hippocampus, dentate gyrus, epilepsy, seizure, neuropathology.

THE ANATOMICAL ORGANIZATION OF THE HUMAN HIPPOCAMPUS

The anatomical term hippocampus was coined by Julius Caesar Arantius in 1587 by comparison of elevations at the inferior horn of the lateral ventricles with a seahorse's (hippocampus) head pointing to the third ventricle (Lewis, 1923). This characteristic morphology also raised another term introduced by de Garengoet in 1742. He compared the mesial view of the hippocampus with an Ammon's horn adopted from the Egyptian god Ammun Kneph (Lewis, 1923; Walther, 2002). It is the pyramidal cell layer of the various hippocampal subregions that is microscopically recognized as cornu ammonis (CA) sectors. The anatomical classification of hippocampal subfields follows, however, different terminologies as the result of differences in rodent and human anatomy. The classification introduced by Lorente de Nó in 1934 is most widely used for the human brain in recognizing four hippocampal sectors, namely CA1–CA4 (Lorente de Nó, 1934). The transition areas between CA1 and subiculum or between the CA3 and CA4 regions remain, however, difficult to clarify using routine histologic staining techniques and are also difficult to distinguish with currently available imaging technologies (Coras et al., 2014a).

The hippocampus is a constituent of the three-layered allocortex (Braak, 1980), 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 anatomically distinguished: the dentate gyrus (DG) (or fascia dentata) with its molecular, granular, and polymorphic layers, the cornu ammonis (stratum oriens, stratum pyramidale and stratum moleculare) and the subiculum. The DG consists of small nerve cells usually referred to as "granule cells". The perikarya of granule cells assemble tightly together into 4–6 layers. Their axons form the mossy fiber system projecting to pyramids of the third and the forth CA sectors. The apical dendrites ramify within the molecular layer and receive topographically organized afferents from the ipsilateral tractus perforans and contralateral hippocampus. The granule cell layer is functionally regarded as "gate keeper" of the hippocampus (Heinemann et al., 1992), as it receives major hippocampal input. A helpful and interactive overview of the parahippocampal–hippocampal network is presented in (van Strien et al., 2009). The major neuronal component of sectors CA3, CA2 and CA1 are pyramidal cells in stratum pyramidale, receiving their input from intrahippocampal projections within the stratum lacunosum-moleculare (stratum lucidum in CA3) and projecting via stratum oriens and alveus into remote limbic regions (Fig. 1).

HIPPOCAMPAL SCLEROSIS (HS) IN HUMAN TEMPORAL LOBE EPILEPSY (TLE)

The human hippocampus is particularly prone to generate seizures and to perpetuate temporal lobe epilepsy (TLE). The end stage of the disease often results in pathomorphological patterns summarized as hippocampal sclerosis (HS; syn. Ammon's horn

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Abbreviations: DG, dentate gyrus; GCD, granule cell dispersion; HS, hippocampal sclerosis; ILAE, International League against Epilepsy; TLE, temporal lobe epilepsy.

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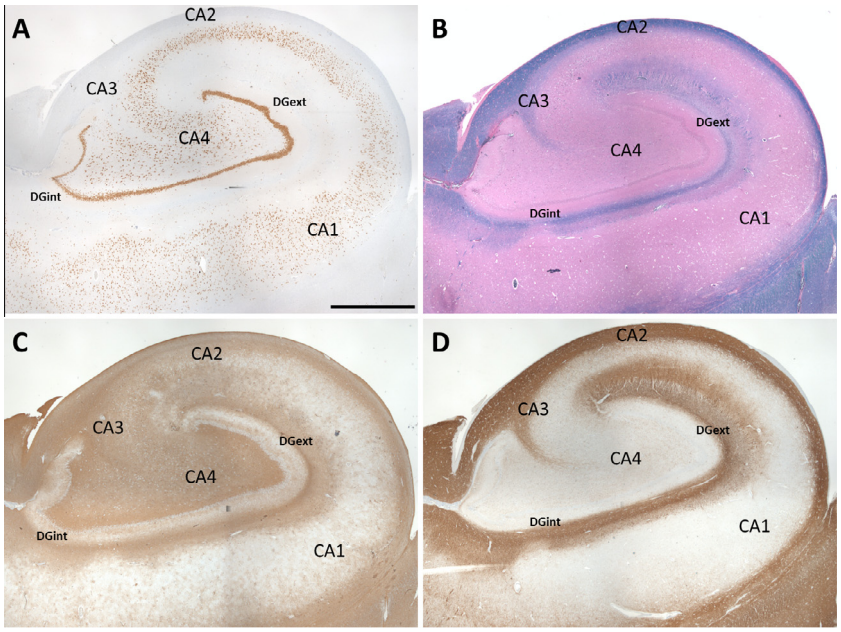

Fig. 1. Anatomy of the human hippocampus (Nissl-LFB, NeuN, MBP, GFAP). Serial sections from the mid-body level of a surgical human hippocampus obtained from a TLE-patient. (A) NeuN immunoreactivity for neuronal subpopulations (labeled in brown color) indicates no segmental neuronal cell loss (no-HS according to ILAE classification). DG – dentate gyrus with its internal and external limbs (DGint, DGext, respectively). Scale bar = 2 mm, applies also to (B–D). (B) Hematoxylin-Eosin-Luxol-Fast-blue histochemistry distinguishing areas of gray from white matter (blue color; same myeloarchitecture is also visualized in (D) = immunoreactivity for myelin basic proteins). (C) Immunoreactivity for glial fibrillary acidic protein. Reactive gliosis is prominent in sectors CA4 and CA3, but does not indicate neuronal cell loss (no-HS, gliosis only, ILAE classification).

sclerosis). In HS patients, diagnostic MRI protocols (T2, FLAIR) recognize severe atrophy of the affected hippocampus and histopathological examination of surgical resections identifies segmental neuronal cell loss in the pyramidal cell layer of the cornu ammonis (CA), most dramatically affecting CA1 and CA4 (Blumcke et al., 2002; Thom et al., 2005b; Blumcke et al., 2012, 2013b; Cendes et al., 2014). HS can be identified in 48% of our large series of 3311 patients suffering from TLE. Within the entire cohort of 4512 epilepsy patients submitted to surgical treatment, HS is recognized in 35.2%, with 5% presenting as dual pathology, i.e. combination with tumours or scars (Table 1).

Although the pathogenesis of HS remains to be identified, clinical histories follow a characteristic schedule in most patients. Approx. 50% of patients suffered from an "initial precipitating injury" before the age of 4 years (Mathern et al., 1995b; Blumcke et al., 2002). In this cohort, complex febrile seizures are the most frequently noted events (Shinnar et al., 2012; Lewis et al., 2014). Birth trauma, head injury or meningitis are other early childhood lesions observed in TLE patients. The mean age at onset of spontaneous complex partial seizures is 11.5 years. Structural, molecular or functional analyses were usually not obtained at this early period. Diagnosis of HS is confirmed after a long period of unsuccessful antiepileptic medication (Kwan et al., 2010), with a mean age at time of surgery of 34.6 years and a history of epileptic seizures of 23.3 years. As in most other series reported so far, both genders were equally

Table 1. Surgical specimens collected at the German Neuropathology Reference Centre for Epilepsy Surgery

ENTITY	Number pts.	Age OP	Hemisphere	Gender	Onset	Duration
HS	1591	34.6	659 L / 611 R	786M / 805 F	11.5	23.3
DUAL	218	24.8	78 L / 112 R	127M / 91 F	9.7	14.6
LEAT	1236	28.5	407 L / 397 R	638M / 565 F	16.5	12.8
MCD	577	18.5	228 L / 242 R	299M / 276 F	5.6	12.4
VASCULAR	271	36.4	91 L / 108 R	157M / 114 F	23.5	13.4
SCARS	239	25.2	92 L / 91 R	147M / 90 F	10.3	14.8
ENCEPHALITIS	73	22.0	26 L / 29 R	43M / 29 F	13.9	9.4
NO LESION	307	29.2	117 L / 58 R	161M / 146 F	12.7	16.1

All data were obtained from the German Neuropathology Reference Centre for Epilepsy Surgery in Erlangen, Germany. Histopathological evaluation and clinical histories are as follows: HS: hippocampal sclerosis; DUAL: dual pathologies (including HS); LEAT: long-term epilepsy associated tumours, including Gangliogliomas and Dysembryoplastic Neuroepithelial Tumours; MCD: Malformations of Cortical Development, including Focal Cortical Dysplasias. Number of patients included. Age OP = Age of patients at surgery (in years); Hemisphere: L (left), R (right); Gender: F = Female, M = Male; Onset = Age at onset of spontaneous seizure activity (in years); Duration = Duration of seizure disorder before surgical treatment (in years).