Investigation of cortical synchronous activity of neuronal populations, *in vitro*

Theses of the Ph.D dissertation

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1 Introduction

In vitro models of behaviourally relevant oscillations of the brain are useful tools to explore the generation mechanisms of synchronization processes. This is especially valid for human studies, where the examination of *in vivo* mechanisms is obviously limited. This thesis makes an attempt to uncover the cellular and network properties of two behaviour-related cortical oscillations.

1.1 Rodent hippocampal sharp-waves

Hippocampal sharp-waves (SPWs) have been observed in rodents during slow wave sleep and behavioural immobility and are thought to play an important role in memory formation processes [1]. They have been associated with large field potential deflections and high frequency oscillatory ripple activity [2, 3]. Their generation is thought to depend on synchronous firing in a small subset of CA3 pyramidal cells together with an enhanced discharge rate of interneurons [4]. *In vitro* models of SPW activity also consist of rhythmically recurring field potential transients accompanied by high frequency oscillations and increased neuronal firing, showing striking similarities to SPWs occurring *in vivo*. *In vitro* population events are typically initiated in the hippocampal CA3 region, and spread to the DG, the CA1 region and the subiculum [5–10].

Published studies disagree on the neural responses of CA3 pyramidal cells during SPWs *in vitro* [11–15]. Moreover, while it has been demonstrated that a hippocampal SPW is initiated

stochastically when the summed activity of CA3 pyramidal cells surpasses a certain threshold [16], another group has contradicted this finding by showing that a hippocampal SPW can be triggered at monosynaptic delays by inducing firing in a single PC [17]. Therefore, the exact cellular mechanisms involved in SPW generation are still disputed [13].

The role of inhibitory cells in the generation of SPWs *in vitro* seems to be crucial [13, 18]. Hippocampal interneurons can be classified into partially overlapping morphological or functional groups: Perisomatic interneurons (PV^+ axo-axonic and basket cells and $CB1^+$ basket cells) innervate the axon initial segments and the somatic region of PCs, controlling their output, while dendritic inhibitory cells innervate the dendritic region of PCs to influence their inputs. The interneuron-selective interneurons specifically innervate inhibitory cells and are supposed to have a role in network synchronizations [19–21]. GABAergic signalling is generally agreed to regulate the generation of SPWs *in vitro* [5, 7, 9]. One study which examined the firing behavior of different interneuron types during SPWs in mouse hippocampal slices found that parvalbumin-containing basket cells were the most active during SPWs, whereas axo-axonic cells and CB1-positive basket interneurons were recruited to a lesser extent [18].

In this study, we aimed to reveal the cellular and network properties of spontaneously occurring SPWs in rat hippocampal slices. The use of laminar multielectrodes allowed detailed LFPg, MUA and CSD analyses of the SPW's spatio-temporal properties. We found that the DG, the CA3 region, and the CA1

region can generate spontaneous SPWs *in vitro*. In the CA3 region, two types of SPWs exhibited differences in recurrence frequency, LFPg pattern and amplitude, MUA increase and CSD pattern. Simultaneous intra- and extracellular recordings of CA3 pyramidal cells and interneurons, as well as pharmacological manipulations indicated that distinct interneuron populations (with the leading role of perisomatic interneurons) are activated during the different SPWs and recruit different ensembles of CA3 pyramidal cells.

1.2 Human neocortical population activity

Human neocortical interictal activity detected on scalp electroencephalographic (EEG) recordings *in vivo* occurs between seizures in epilepsy patients. They are a hallmark in epilepsy diagnosis and are considered to be a pathological synchronization. Interictal discharges in human focal epilepsies are characterised by high amplitude, fast EEG spikes, followed by a slow wave [22]. Slices prepared from the neocortex [23–25] or the hippocampal formation [26–29] of epileptic patients are known to generate spontaneous synchronous discharges in a physiological perfusion solution. When filtered as the EEG (1-100 Hz), these *in vitro* interictal-like events are composed of a high-amplitude fast transient followed by a longer lasting wave [26], while a wide band filtering (1-3000 Hz) shows the increase of cellular activity and fast oscillations [29, 30], similar to *in vivo* interictal discharges [31, 32]. Synchronous population events in neocortical specimens of epileptic patients were detected in all layers, but most frequently emerged in the supragranular layers, associated

with a current sink [33]. Although the population bursts were called sharp wave [24], or were termed interictal-like activity [25, 26, 28, 34], all groups agreed that they might be epilepsy related phenomena.

The question of control tissue is always problematic in case of human studies. Anatomical studies usually include human autopsy tissue [35–37], or healthy monkey tissue [29, 38] as a control, while electrophysiological studies typically operate with rodent tissue [39], sometimes together with one of its corresponding epilepsy models [40]. Furthermore, sclerotic hippocampus is usually compared to non-sclerotic hippocampus derived from epileptic patients [41–44], and human neocortex with focal cortical dysplasia is compared to adjacent non-dysplastic neocortex [45, 46]. The present study uses the best available control for the human epileptic neocortex: neocortical tissue of patients without any clinical signs of epilepsy, which are operated for other reasons, such as brain tumours.

In the present study we could show that spontaneous synchronous population activity (SPA) arises not only in slices from epileptic but also from tumour patients without epilepsy. The data demonstrate that SPAs emerging in slices derived from epileptic and non-epileptic patients are basically similar in their network and cellular characteristics, but they considerably differ from interictal spikes of epileptic patients, and therefore cannot be regarded as their *in vitro* correlate.

2 Methods

All patients gave written consent and the protocol was approved by the Hungarian Ministry of Health. All experiments involving animals were performed according to the EC Council Directive of November the 24th, 1986 and were reviewed and approved by the local ethical committee and the Hungarian Central Agricultural Office.

500 μm thick slices were prepared from the ventral hippocampus of urethane-anesthetised rats or from postoperative human neocortical tissue from 14 patients with pharmacoresistant epilepsy, 5 patients with pharmacologically controlled epilepsy and 7 patients without clinical signs of epilepsy. The brain tissue slices were kept in an interface chamber and perfused with a physiological solution.

The local field potential gradient (LFPg) was obtained by electrophysiological recordings from those slices using a 24 channel laminar microelectrode. Population activity events were detected from the $3-30$ Hz band-passed traces and averaged. Current source density as well as multiunit activity analysis was performed. Single neurons were clustered from a subset of the extracellular recordings using a MatLab routine. Intracellular recordings were performed from the rat hippocampal slices using microelectrode glass pipettes. Cellular firing patterns of intracellularly or extracellularly recorded neurons were analysed using peri-event time histograms (PETHs).

The effects of pharmacological agents on hippocampal SPW activity was investigated by adding the drug to the physiological bath in which the slices were kept. Bicuculline ($GABA_AR$ antag-

onist), CGP52432 ($GABA_BR$ antagonist), NBQX (AMPAR and KA receptor antagonist), AP5 (NMDAR antagonist), DAMGO (μ-opioid receptor agonist), Carbachol (AChR agonist) or DCG-IV (mGluR2 agonist) were applied.

Significance was tested using the non-parametric Mann-Whitney U-test, the Kruskal–Wallis test and/or the Wilcoxon signed rank test. Crosstabs were tested using the Chi-square and/or the Fisher's exact test. In case of the human neocortical data, multiple regression analysis was performed.

3 Results / Thesis Sentences

3.1 Thesis group 1: Rat SPW study findings

Ia *This is the first time a multielectrode has been used to differentiate between different types of rat hippocampal SPWs. Due to the spatial information the multielectrode provides, the different LFPg and current source density patterns of the two SPW types could be discovered.* SPWs with a negative LFPg peak in the str. pyramidale and a positive peak in the str. radiatum (apical dendritic layer) were called type 1. The CSD pattern of T1 SPWs consisted of a sink-source pair in the str. pyramidale. On the other hand, positive LFPg peaks in the str. pyramidale as well as in the str. lacunosum-moleculare (distal apical dendrites) combined with a negative LFPg peak in the str. radiatum (apical dendritic layer) were termed type 2. This type exhibited a sink-source triplet: a source in the str. pyramidale, adjoined by one sink each in the str. oriens and

str. radiatum. They further differed in their amplitude and recurrence frequency. The two types of SPWs could not be distinguished on one-channel referential recordings.

Ib *The two types of SPWs can occur simultaneously in the same recording.* Two overlapping but distinct subpopulations seemed to have created the different synchronous population activities at the same time. Clustered neurons can differentiate between the two types of SPWs, with some of them adjusting their firing pattern accordingly.

Ic *Both types of SPWs depend on both excitatory and inhibitory processes.* This was apparent as both types were blocked during the application of either an AMPAR and KA receptor antagonist (NBQX) or a $GABA_AR$ antagonist (bicuculline).

Id *The two types of SPWs are generated by different mechanisms, involving different subpopulations of interneurons.* This was revealed by the application of DAMGO, a μ-opioid receptor agonist, which reduces the activity of some interneuron subtypes (mostly PV-positive basket and somatostatin-positive O-LM cells), but not others.

3.2 Thesis group 2: Human SPA study findings

IIa *The human epileptic as well as non-epileptic neocortex can generate synchronous population activity (SPA) in vitro.* SPAs from epileptic and non-epileptic tissue appear to be very similar and only differ in their LFPg and CSD amplitudes. SPAs cannot directly be related to epilepsy, as

they occur in tissue from non-epileptic as well as epileptic patients.

IIb *Slices from epileptic human neocortex are able to generate two types of population activity: SPAs and interictal spikes (IIDs)*. They differ in their generation site, LFPg, CSD and MUA amplitudes as well as their recurrence frequency.

IIc *Spatial subtypes of NSAs occurred across different neocortical layers (in the supragranular, granular and/or infragranular layers).* Some NSAs are able to span across more than one cellular layer (sup+gran, gran+inf or entire).

IId *The different spatial types can occur simultaneously.* They can occur independently from each other, but are also able to interact: Some sharing a common refractory period, some triggering each other. Two overlapping but distinct neuronal subpopulations are thought to create the different SPAs at the same time.

IIe *Epilepsy modifies the SPAs as well as the cell behaviour during SPAs.* All discovered differences point to an increased excitability in the epileptic compared to the non-epileptic tissue. This was indicated by a larger LFPg amplitude and a larger proportion of actively participating neurons in epileptic tissue.

IIf *Firing patterns of neurons during SPAs are very heterogeneous.* Together with the fact that PCs and INs do not seem to fire in a clear order, complex interactions between those two neuronal cell types must be assumed.

IIg *SPA is a very local event in regard to neocortical layers.* Neurons mostly respond to the SPA that is located close to their own cell body and often did not respond to SPAs occurring in other neocortical layers.

3.3 Thesis group 3: Data processing and algorithm development

IIIa *I developed a novel algorithm for the purpose of analysing the firing behaviour of neurons during the population activity using a Monte Carlo approach.* Observed spike trains of cells and SPAs are analysed and compared to shuffled versions of themselves. If the observed firing pattern of the neuron was extremely increased or decreased compared to the shuffled versions, it was regarded a significant firing change.

IIIb *I developed a MatLab program with a user interface for the unbiased categorisation of neurons.* Using this program, the user can sort the displayed neurons into categories judging their autocorrelogram and action potential shape, while being blind to factors that should not be taken into account. This ensures an unbiased categorisation in respect to the tissue of origin of the cells.

IIIc *I wrote custom software in C++ for analysing the size and shape of the averaged LFPg and MUA traces of NSAs.*

4 Publications

4.1 Journal publications

- **K. T. Hofer**, Á. Kandrács, I. Ulbert, I. Pál, C. Szabó, L. Héja, L. Wittner. ”The hippocampal CA3 region can generate two distinct types of sharp wave-ripple complexes, in vitro.” Hippocampus 2014. DOI: 10.1002/hipo.22361

- K. Tóth *, **K. T. Hofer** *, Á. Kandrács, L. Entz, A. Bagó, L. Erőss, Z. Jordán, G. Nagy, A. Sólyom, D. Fabó, I. Ulbert and L. Wittner. ”Hyperexcitability of the network contributes to synchronisation processes in the human epileptic neocortex” (* these authors contributed equally) (submitted)

- R. Fiáth, **K. T. Hofer**, V. Csikós, D. Horváth, T. Nánási, K. Tóth, F. Pothof, C. Böhler, M. Asplund, P. Ruther, I. Ulbert. ”Long-term recording performance and biocompatibility of chronically implanted cylindrically-shaped, polymer-based neural interfaces” (submitted)

4.2 Conference posters and presentations

- **K. T. Hofer**, K. Tóth, Á. Kandrács, C. Szabó, A. Bagó, L. Erőss, L. Entz, D. Fabó, I. Ulbert, L. Wittner. ”Heterogeneous neuronal firing patterns during human neocortical population activity in vitro.” FENS regional meeting, Pécs, Hungary, Sep 20th-23rd, 2017 (poster presentation)
- Á. Kandrács, **K. T. Hofer**, K. Tóth, E. Győri, A. Bagó, L. Erőss, L. Entz, D. Fabó, I. Ulbert, L. Wittner. ”Electrophysiological analysis of synchronization applying GABAA receptor antagonist bicuculline in

human neocortex in vitro." FENS regional meeting, Pécs, Hungary, Sep 20th-23rd, 2017 (poster presentation)

- C. Szabó, **K. T. Hofer**, I. Pál, I. Ulbert, L. Wittner. "Investigation of the electrophysiological properties of hippocampal synchronous population activity, in vitro." FENS regional meeting, Pécs, Hungary, Sep 20th-23rd, 2017 (poster)
- B. P. Kerekes, I. Pál, **K. T. Hofer**, K. Tóth, D. Meszéna, V. Matusz, D. Zsíros, D. Dávid, F. Abdul Kader, I. Ulbert. "A microsurgical method to modulate the spontaneous population activity and interictal-like activity in rat brain hippocampus slices" FENS regional meeting, Pécs, Hungary, Sep 20th-23rd, 2017 (poster)
- **K. T. Hofer**, K. Tóth, Á. Kandrács, C. Szabó, A. Bagó, L. Erőss, L. Entz, I. Ulbert, L. Wittner. "Heterogeneous neuronal firing patterns during human neocortical population activity in vitro." From Medicine to Bionics conference, Budapest, Hungary, Nov 17th, 2016 (poster presentation)
- Á. Kandrács, **K. T. Hofer**, K. Tóth, E. Győri, A. Bagó, L. Erőss, L. Entz, I. Ulbert, L. Wittner. "Investigation of the role of GABAergic inhibition in epileptic human neocortex." From Medicine to Bionics conference, Budapest, Hungary, Nov 17th, 2016 (poster)
- **K. T. Hofer**, K. Tóth, Á. Kandrács, C. Szabó, A. Bagó, L. Erőss, L. Entz, I. Ulbert, L. Wittner. "Heterogeneous neuronal firing patterns during human neocortical population activity in vitro." FENS Forum of Neuroscience, Copenhagen, Denmark, Jun 02nd-06th, 2016 (poster)
- Á. Kandrács, **K. T. Hofer**, K. Tóth, E. Győri, A. Bagó, L. Erőss, L. Entz, I. Ulbert, L. Wittner. "Investigation of the role of GABAergic inhibition in epileptic human neocortex." FENS Forum of Neuroscience, Copenhagen, Denmark, Jun 02nd-06th, 2016 (poster)
- C. Szabó, I. Pál, **K. Hofer**, I. Ulbert, L. Wittner. "Synchronous population activity in the hippocampal CA3 region and dentate gyrus, in vitro." FENS Forum of Neuroscience, Copenhagen, Denmark, Jun 02nd-06th, 2016 (poster)
- I. Pál, **K. Hofer**, B. P. Kerekes, K. Tóth, B. Rózsa, D. Meszéna, I. Ulbert. "Modulation of interictal-like and spontaneous population

activity by microsurgical intervention in rat brain slices" FENS Forum of Neuroscience, Copenhagen, Denmark, Jun 02nd-06th, 2016 (poster)

- Á. Kandrács, **K. T. Hofer**, K. Tóth, E. Győri, A. Bagó, L. Erőss, L. Entz, I. Ulbert, L. Wittner. "Investigation of the role of GABAergic inhibition in epileptic human neocortex." IBRO Workshop, Budapest, Hungary, Jan 21st-22nd, 2016 (poster)
- I. Pál, **K. Hofer**, B. Kerekes, K. Tóth, B. Rózsa, I. Ulbert. "Modulation of interictal-like and spontaneous population activity by microsurgical intervention in rat brain slices" IBRO Workshop, Budapest, Hungary, Jan 21st-22nd, 2016 (poster)
- **K. T. Hofer**, K. Tóth, Á. Kandrács, C. Szabó, A. Bagó, L. Erőss, L. Entz, I. Ulbert, L. Wittner. "Heterogeneous neuronal firing patterns during human neocortical population activity in vitro" HuNDoc Hungarian Neuroscience Meeting for Undergraduate Students, Graduate Students and Junior Post-Docs, Budapest, Hungary, Jan 20th, 2016 (selected for oral presentation)
- **K. T. Hofer**, I. Ulbert. "Heterogeneous neuronal behaviour during human neocortical population activity." PhD Proceedings, annual issues of the doctoral school, faculty of information technology & bionics, PPKE, Budapest, Hungary, Jun. 25th-26th, 2015 (oral presentation and report)
- K. Tóth, **K. T. Hofer**, Á. Kandrács, C. Szabó, A. Bagó, L. Erőss, L. Entz, I. Ulbert, L. Wittner. "Patterns of synchronous population activity in the neocortex of patients with epilepsy or tumor, in vitro." Neuronus IBRO & IRUN Neuroscience Forum, Krakow, Poland, Apr. 17th-19th, 2015 (poster presentation)
- Á. Kandrács, K. Tóth, **K. T. Hofer**, C. Szabó, A. Bagó, L. Erőss, L. Entz, I. Ulbert, L. Wittner. "Investigation of the role of GABAerg inhibition in epileptic and non-epileptic human neocortex, in vitro." Neuronus IBRO & IRUN Neuroscience Forum, Krakow, Poland, Apr. 17th-19th, 2015 (poster)
- K. Tóth, **K. Hofer**, Á. Kandrács, C. Szabó, A. Bagó, L. Erőss, L. Entz, I. Ulbert, L. Wittner. "Patterns of synchronous population activity in

the neocortex of patients with epilepsy or tumor, in vitro." 15th Biannual Conference of the Hungarian Neuroscience Society, Budapest, Hungary, Jan. 22nd-23rd, 2015 (poster presentation)

- **K. T. Hofer**, K. Tóth, Á. Kandrács, C. Szabó, A. Bagó, L. Erőss, L. Entz, T. F. Freund, I. Ulbert, L. Wittner, "Patterns of synchronous population activity in the neocortex of patients with epilepsy or tumor, in vitro." MTA TTK Kálmán Erika doktori konferencia, Budapest, Hungary, Dec. 10th-12th, 2014 (oral presentation)
- K. Tóth, **K. Hofer**, Á. Kandrács, C. Szabó, A. Bagó, L. Erőss, L. Entz, I. Ulbert, L. Wittner. "Patterns of synchronous population activity in the neocortex of patients with epilepsy or tumor, in vitro." Hungarian neurological society meeting, Budapest, Hungary, Nov. 20th-22nd, 2014) (poster)
- **K. T. Hofer**, Á. Kandrács, I. Ulbert, I. Pál, C. Szabó, L. Héja, L. Wittner. "The hippocampal CA3 region can generate two types of sharp wave-ripple complexes, in vitro." 9th Forum of European Neuroscience, Milano, Italy, Jul. 5th-9th, 2014. (poster presentation)
- K. Tóth, **K. Hofer**, Á. Kandrács, C. Szabó, A. Bagó, L. Erőss, L. Entz, T. F. Freund, I. Ulbert, L. Wittner. "Patterns of synchronous population activity in the neocortex of patients with epilepsy or tumour, in vitro." 9th Forum of European Neuroscience, Milano, Italy, Jul. 5th-9th, 2014. (poster)
- K. Hofer (supervisor I. Ulbert) "A data analysis program for studying synchronous population activity in the human neocortex in vitro." Pázmány proceedings, Budapest, Hungary, Jun 26th-27th, 2014 (oral presentation and report)
- **K. Hofer**, K. Tóth, Á. Kandrács, C. Szabó, A. Bagó, L. Erőss, L. Entz, I. Ulbert, L. Wittner. "Patterns of synchronous population activity in the neocortex of patients with epilepsy or tumor, in vitro." Neuronus Conference, Krakow, Poland, Apr. 25th-27th, 2014 (poster presentation)
- **K. T. Hofer**, I. Ulbert, I. Pál, C. Szabó, L. Héja, L. Wittner. "The hippocampal network can generate multiple patterns of sharp wave-ripple complexes, in vitro." International Brain Research Organization

(IBRO) Workshop, Debrecen, Hungary, Jan. 15th-17th, 2014 (poster presentation)

- K. Tóth, **K. Hofer**, Á. Kandrács, C. Szabó, A. Bagó, L. Erőss, L. Entz, T. F. Freund, I. Ulbert, L. Wittner. "Patterns of synchronous population activity in the neocortex of patients with epilepsy or tumor, in vitro." International Brain Research Organization (IBRO) Workshop, Debrecen, Hungary, Jan. 15th-17th, 2014 (poster)
- **K. Hofer**, K. Tóth, Á. Kandrács, C. Szabó, A. Bagó, L. Erőss, L. Entz, I. Ulbert, L. Wittner. "Patterns of synchronous population activity in the neocortex of patients with epilepsy or tumor, in vitro." Society for Neuroscience (SfN) annual meeting, San Diego, USA, Nov. 9th-13th, 2013 (poster presentation)
- K. Hofer (supervisor I. Ulbert) "Patterns of neuronal synchronous population activity in the human neocortex in vitro." Pázmány proceedings, Budapest, Hungary, Jul. 1st-2nd, 2013 (oral presentation and report)
- **K. Hofer**, K. Tóth, A. Bagó, L. Erőss, L. Entz, T. Freund, I. Ulbert, L. Wittner. "Patterns of synchronous population activity in the neocortex of patients with epilepsy or tumor, in vitro." YSA PhD symposium, Vienna, Austria, Jun. 19th-20th, 2013 (poster presentation)

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