Budapest, 04.06.2007

**FINAL REPORT OF THE BIAL GRANT**



*Period:* 2005–2007.

*Grant number:* 168/04

*Title:* Electrocortical studies of the hippocampal-parahippocampal (HP) structures in humans: Foramen ovale (FO) electrodes, as a research tool in human cognition and epilepsy

*Project leader:* Prof. Péter Halász

*Project team:* Zsófia Clemens
Csaba Borbély
Dániel Fabó
Lóránd Erőss
László Entz

## 1. Parahippocampal activity during virtual navigation and REM sleep

Participants: Zsófia Clemens, Csaba Borbély, Dániel Fabó, Péter Halász

Ten patients between the ages of 28 and 51 (mean age: 38±8 years) have been tested within a realistic and large-scale virtual environment designed and constructed by our group using a 3D computer program. Navigation was tested according to three conditions: an acquisition, a recall and a non-learning route-following condition. These recordings were compared with those during resting and REM sleep. Recordings were evaluated both visually and by statistical comparison of spectral power densities (SPD) computed for 1-Hz wide frequency bins up to 10 Hz.

Visual inspection of the traces revealed a shift toward slower frequencies during the three navigation conditions, especially during acquisition when compared with the resting condition. This increase in slow activity could be seen in all foramen ovale (FO) contacts, also at the side of the seizure onset. This increased slow activity was continuously present during the whole task performance periods (Fig. 1).

During REM sleep continuous, highly synchronous and rhythmic delta activity was present, corroborating our earlier data (Bódizs et al., 2001). Visual comparison also revealed that this REM-dependent slow activity had higher amplitude and was also more rhythmic than slow activity during the three navigation conditions (Fig 1).

Statistical evaluation revealed that during acquisition SPD for the 1 Hz ($p=0.0054$), 2 Hz ($p=0.0039$) and 3 Hz ($p=0.0416$) frequency bins were significantly higher compared to resting. All patients showed higher power in the 1 Hz bin and all but one showed higher power in the 2 Hz and in the 3 Hz frequency bins.

Comparison of the recall and the non-learning conditions with resting did not reach significancy although a non-significant tendency toward higher powers in the 1 Hz (recall: $p=0.1351$, non-learning: $p=0.1293$) and the 2 Hz (recall: $p=0.0628$, arrow: $p=0.0526$) frequency bins was present. Comparison between acquisition and recall revealed significant difference only in the 3 Hz frequency range ($p=0.0464$). Comparison between acquisition and the non-learning condition did not reach significancy in either frequency bins.

SPD during REM significantly exceeded those during resting in the 1 Hz ($p=0.0206$), 2 Hz ($p=0.0052$), 3 Hz ($p=0.0013$), 4 Hz ($p=0.0033$) and 5 Hz ($p=0.0238$) frequency bins. Compared to resting, all subjects showed higher power during REM for the 2 and 3 Hz bins and all but one showed higher power for the 1 Hz and the 4 Hz frequency bins. SPD for the 2 Hz ($p=0.0228$), 3 Hz ($p=0.0065$) and 4 Hz ($p=0.0042$) bins during REM also significantly exceeded those during acquisition. SPD means for each frequency bins are presented in Fig 2.

In most patients (eight patients of the 10), slow activity during REM showed high rhythmicity also evidenced by the presence of a definite spectral peak in the 1.25-2.5 Hz range. During acquisition spectral peak was present only in four patients.

Although, these data disagree with those studies reporting on short theta bursts, based on slow activity increases in similar frequency bands during acquisition and REM, its tonic presence in all FO contacts, we consider that delta activity might be a functional analogue of rhythmic slow activity (RSA) in animals.

## 2. Temporal coupling of parahippocampal ripples, sleep spindles and slow oscillations in humans

Participants: Zsófia Clemens, Matthias Mölle, Jan Born, Péter Halász

Ripples are high-frequency oscillation bursts in the mammalian hippocampus mainly present during NonREM sleep. In rodents they occur in association with sharp waves and are grouped by the cortical slow oscillation such that, in parallel with sleep spindles, ripple activity is suppressed during the hyperpolarized down-state and enhanced during the depolarized up-state. The temporal coupling between slow oscillations, spindles and ripples has been suggested to serve a hippocampo-neocortical dialogue underlying memory consolidation during sleep.

Here, we examined whether a similar coupling exists between these oscillatory phenomena in humans. In sleep recordings from seven epileptic patients, scalp-recorded slow oscillations and spindles as well as parahippocampal ripples recorded from FO electrodes were identified by automatic algorithms. Additionally ripple and spindle root mean square activity was determined for relevant frequency bands. Ripple density was distinctly increased during NonREM as compared to REM sleep ($p<0.013$). Ripple activity distinctly decreased time-locked to slow oscillation negative half-waves in the three patients without temporal structural alterations ($p<0.001$), whereas in the four patients with severe mesiotemporal structural alterations this coupling was obscure. In all patients, both ripple measures showed a strong increase time-locked to spindles ($p<0.001$). Ripples were consistently associated with interictal spikes suggesting that spike-ripple complexes represent an epileptic transformation of sharp wave-ripple complexes in the epileptic hippocampus.

Our results provide first evidence for temporal coupling between parahippocampal ripples, sleep spindles and slow oscillations in humans. These findings are consistent with the notion of a hippocampo-to-neocortical information transfer during sleep that is linked to coordinate ripple and spindle activity, and that in the intact temporal lobe is synchronized to cortical slow oscillations.

### 3. Parahippocampal spindles

Participants: Zsófia Clemens, Péter Halász

Sleep spindles normally occur over frontal, central, parietal but not over temporal areas. On this background it is surprising that waveforms resembling sleep spindles were apparent in FO electrodes.

Here our aim was to characterise FO spindles and systematically examine their relation to patient characteristics in order to determine whether these events represent pathologic or physiologic activity.

Full-night recordings from 37 patients were investigated. FO spindles were counted visually and spindle rates were determined for at least 60 min samples of NREM stage 2. Except for a single patient all exhibited FO spindles at least on one side however spindle rates and amplitudes varied considerably between patients. FO spindles mostly occurred independently of scalp spindles and only a smaller proportion occurred together with scalp spindles. There was a moderate negative correlation between spindle rates and epilepsy duration ($r=-0.22$, $p=0.06$). Spindle rates tended to be smaller in bitemporal mezial temoral lobe epilepsy (MTLE) patients compared to unilateral MTLE patients (0.9 vs. 0.43, $p=0.16$). Spindle rates did not clearly lateralize according to seizure onset in unilateral patients and did not show a consistent relationship with other variables such as: age at epilepsy onset, structural alterations evident on MRI (magnetic resonance imaging) scans, the presence of grand mal seizures, the occurrence of febrile seizures during childhood and gender. Nine patients exhibited FO spindles during REM sleep as well. Two of these patients also had FO spindles during waking.

We concluded that spindles in FO electrodes are probably physiologic however the spindle generation might interact with epileptic processes. We suppose this interaction might result in both decreased spindling indicated by decreased spindling with epilepsy duration and in bitemporal cases but also in facilitation of spindles indicated by cases with unusually high spindle amplitudes and the occurrence of spindles in REM sleep or waking. However the reason for this discrepancy remained obscure.

### 4. Temporal and spatial analysis of TLE seizure propagation

Participants: Lóránd Erőss, László Entz, Zsófia Clemens, Péter Halász

TLE patients (even those with exclusively unilateral seizure onset) show several bilateral temporal alterations. Unilateral onset seizures typically spread to the contralateral temporal lobe and develop into a bilateral seizure. However it is not clear how seizures propagate spatially and temporally and why a proportion of patients with unilateral onset do not become seizure free after surgery.

Here we analysed seizure propagation patterns in 58 seizures obtained from 20 patients. The majority of seizures (46 seizures) with unilateral mesiotemporal onset appeared in contralateral FO electrodes earlier than in contralateral scalp electrodes suggesting that contralateral seizure spread relies on an efficient interhippocampal pathway. However in about ¼ of cases (12 seizures) they appeared first in contralateral scalp electrodes and spread to contralateral FO electrodes thereafter suggesting the existence of alternative routes too. Some patients exhibited both patterns. Thirteen patients with exclusively unilateral seizure onset underwent surgery. In the group of patients with typical seizure spread (ipsilateral

FO→contralaterateral FO→contralateral scalp) surgery resulted in total seizure freedom in most patients (in 6 out of 8 patients). By contrast in the group of five patients with predominantly atypical seizure propagation pattern (ipsilateral FO→contralaterateral scalp→contralateral FO) surgery did not result in seizure freedom in either patient. These results suggest that surgical outcome also depend on the pattern of seizure spread and this factor should be taken into account when considering TLE surgery.

**Papers and presentations at scientific meetings**

*Papers*

Clemens Z, Fabó D, Halász P. Twenty-four hours retention of visuospatial memory correlates with the number of parietal sleep spindles. *Neurosci Lett.* 2006;403:52-6.

Clemens Z, Mölle M, Erőss L, Barsi P, Halász P, Born J. Temporal coupling of parahippocampal ripples, sleep spindles and slow oscillations in humans. Accepted in *Brain*.

*Presentations*

Clemens Z, Borbély C, Fabó D, Halász P. Increased parahippocampal delta activity characterises virtual navigation and REM sleep in humans. FENS Forum, Vienna 2006 (poster presentation)

Borbély C, Clemens Z. Increased parahippocampal delta activity characterises virtual navigation and REM sleep in humans. Annual Conference of the Hungarian Cognitive Foundation, Eger, 2007 (oral presentation)

Clemens Z, Mölle M, Erőss L, Barsi P, Halász P, Born J. Temporal coupling of parahippocampal ripples and sleep spindles in humans. 18th Congress of the European Sleep Research Society, Innsbruck, 2006 (poster presentation)

Budapest, June 6th, 2007.

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Prof. Dr. Halász Péter