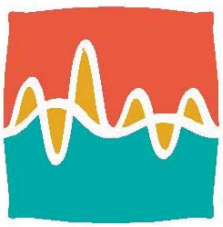

International Conference on Sleep Spindling

Budapest, Hungary / May 12–14, 2016

PROGRAMME

BOOK OF ABSTRACTS

International Conference on Sleep Spindling
12–14 May 2016, Budapest, Hungary

Danubius Hotel Gellért
Szent Gellért tér 1, H-1111 Budapest, Hungary

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WELCOME

"The frequency is on the average an irregular 10 per second,
but frequently very regular bursts lasting 1 to 1 ½ seconds of 14 per second frequency appear.
The amplitude builds regularly to a maximum and then falls regularly
so that we have designated these >>spindles<<, because of their appearance in the record.
Shorter spindles or >>balls<< of 1/4 - 1/3 second duration occasionally appear."
(Loomis, Harvey and Hobart, Science *1935;81:597–8)*

Oscillations are at the heart of living systems. It is our common interest to investigate the origin and functions of neuronal oscillations during sleep. We prepared our international scientific conference on sleep spindling and related phenomena due to recent advances in this specific field of study as well as the key importance of this neural oscillatory pattern in neurobehavioral functioning. Since sleep spindle oscillations are at the crossroad between slow and fast oscillations during sleep, the conference is open to scientific results about a very broad range of neural and behavioural phenomena.

This is the first time the scientific community is able to share ideas about this specific topic, which has tremendous neurobehavioral relevance. The conference aims to be the first of a series of biennial conferences on this subject.

Our host city is Budapest, a lively and beautiful place, which vibrates at a plethora of different frequencies, much like the oscillations we study.

We wish you a pleasant stay in Budapest, and a successful conference.

Yours sincerely,

Róbert Bódizs
Chair of the Organizing Committee

Péter Halász, László Acsády, Péter P. Ujma and Péter Simor
Members of the Organizing Committee

SCIENTIFIC PROGRAM

THURSDAY, MAY 12, 2016

08:00-09:00	*Registration*
09:00-09:10	**Opening Remarks** Róbert BÓDIZS Semmelweis University, Chair of the Scientific Committee
09:10-10:15	**Gatekeepers of Sleep** *Chair: Róbert Bódizs*
09:10-10:00	**KEYNOTE LECTURE** *Spindles and K-complexes, as gatekeepers of our conscious awareness* George KOSTOPOULOS, University of Patras, Greece
10:00-10:15	*Are sleep spindles inhibitory for pain?* Hélène BASTUJI, Lyon Neuroscience Research Center (CRNL), France
10:15-10:35	*Coffee break*
10:35-11:55	**Mesiotemporal Structures and Cross-Frequency Coupling** *Chair: Dániel Fabó*
10:35-11:25	**KEYNOTE LECTURE** *Nature of sleep spindles in mesiotemporal structures* Zsófia CLEMENS, University of Pécs, Hungary
11:25-11:40	*Slow oscillations, spindles and ripples are hierarchically nested in the human hippocampus* Til O. BERGMANN, University Hospital Tübingen, Germany
11:40-11:55	*Phase-amplitude coupling of sleep spindles predicts risk of evolution to dementia in Parkinson disease* André ACHIM, Université du Québec à Montréal, Canada
11:55-14:00	*Lunch break*
14:00-15:45	**Basic Mechanisms and Rhythmogenesis-1** *Chair: Magor Lőrincz*
14:00-14:50	**KEYNOTE LECTURE** *Thalamic cellular interactions and the duration of sleep spindles* László ACSÁDY, Institute of Experimental Medicine of the Hungarian Academy of Sciences, Hungary

14:50-15:15 **INVITED TALK**
Thalamic reticular nucleus, thalamic bursts and cortical spindles
Michael M. HALASSA, New York University, United States

15:15-15:30 *Identification of higly connected brain sites associated with sleep spindles activity*
Mario VALDERRAMA, Universidad de los Andes, Colombia

15:30-15:45 *Spatiotemporal characteristics of the sleep spindle in human electrocorticography*
Giovanni PIANTONI, Massachusetts General Hospital, United States

15:45-16:10 *Coffee break*

16:10-17:15 **Basic Mechanisms and Rhythmogenesis-2**
Chair: László Acsády

16:10-17:00 **KEYNOTE LECTURE**
Sleep spindles in the mouse: so small, yet so powerful
Anita LÜTHI, University of Lausanne, Switzerland

17:00-17:15 *Characterization of topographically specific sleep spindles in mice*
Jee Hyun CHOI, Korea Institute of Science and Technology, South Korea

17:15-18:35 **Sleep Regulation and Sleep Disorders**
Chair: Róbert Bódizs

17:15-18:05 **KEYNOTE LECTURE**
Cortical spindles and sleep homeostasis
Vladyslav V. VYAZOVSKIY, University of Oxford, United Kingdom

18:05-18:20 *Changes of sleep spindle characteristics during split-night studies in patients with obstructive sleep apnea*
Peter ANDERER, Philips Austria GmbH, Austria

18:20-18:35 *Sleep spindle characteristics before and after sleep deprivation in obstructive sleep apnea*
Anna MULLINS, Woolcock Institute of Medical Research, Australia

18:35-20:00 *Welcome Reception*

FRIDAY, MAY 13, 2016

09:00-10:45 **Memory Consolidation**
Chair: Péter Simor

09:00-09:50 **KEYNOTE LECTURE**
The role of sleep spindles for systems consolidation of memory
Jan BORN, University of Tübingen, Germany

09:50-10:15	**INVITED TALK** *Spindles: Coordination with other oscillations and the timing of replay* Lisa GENZEL, The University of Edinburgh, United Kingdom
10:15-10:30	*Sleep-dependent motor memory consolidation from adolescence to adulthood* Kerstin HOEDLMOSER, University of Salzburg, Austria
10:30-10:45	*Local spindle networks in the right hemisphere enhance awareness of regularity after sleep* Juliana YORDANOVA, Bulgarian Academy of Sciences, Bulgaria
10:45-11:10	*Coffee break*
11:10-12:10	**Poster Session** *Behavior, Cognitive Performance and Memory*
12:10-14:00	*Lunch break*
14:00-14:50	**Networks and Functions** *Chair: László Acsády*
14:00-14:50	**KEYNOTE LECTURE** *Sleep spindles: what are they for?* György BUZSÁKI, NYU School of Medicine, United States
14:50-17:00	**Phenotypic Variation and Neurobehavioral Correlates** *Chair: Philippe Peigneux*
14:50-15:40	**KEYNOTE PRESENTATION** *Sleep spindles are sexually dimorphic developmental and trait neurobehavioral markers* Róbert BÓDIZS, Semmelweis University, Hungary
15:40-15:55	*Sleep spindles and intelligence in early childhood – developmental and trait-dependent aspects* Péter P. UJMA, Semmelweis University, Hungary
15:55-16:15	*Coffee break*
16:15-16:30	*Is white matter diffusion implicated in age-related modifications of sleep spindles?* Pierre-Olivier GAUDREAULT, University of Montreal, Canada
16:30-16:45	*Decreased sigma-band EEG connectivity in aging* Maude BOUCHARD, University of Montreal, Canada
16:45-17:00	*Characterizing sleep spindles in 11,630 Individuals* Shaun PURCELL, Icahn School of Medicine at Mount Sinai, United States

17:00-17:30	**Methodological Corner** *Chair: Péter P. Ujma*
17:00-17:15	*A new, minimal assumption, spindle analysis method, applied to PTSD sleep* Lucia M. TALAMINI, University of Amsterdam, The Netherlands
17:15:17:30	*SPISOP – fast replication and sharing of sleep EEG analyis in one toolbox* Frederik D. WEBER, University of Tübingen, Germany
17:30-18:30	**Poster Session** *Basic Mechanisms and Rhythmogenesis*
19:00-22:00	*Gala Dinner (optional)*

SATURDAY MAY 14, 2016

09:00-10:20	**Epilepsy / Biomarkers-1** *Chair: László Acsády*
09:00-09:50	**KEYNOTE PRESENTATION** *Sleep spindles in epilepsy* Daniel FABO, National Institute of Neuroscience, Hungary
09:50-10:05	*Sleep spindles and absence epilepsy in WAG/Rij rats* Evgenia SITNIKOVA, Institute of Higher Nervous Activity, Russian Academy of Sciences, Russia
10:05-10:20	*Genetic absence-related spike-and-wave discharges turn off while spindles turn on during the wake-sleep transition* Didier PINAULT, French National Institute of Health and Medical Research (INSERM), France
10:20-10:40	*Coffee break*
10:40-12:10	**Affective Processes / Consciousness, Memory** *Chair: Philippe Peigneux*
10:40-11:30	**KEYNOTE PRESENTATION** *The effect of sleep and neurofeedback on sleep quality and memory consolidation in insomnia patients* Manuel SCHABUS, University of Salzburg, Austria
11:30-11:55	**INVITED TALK** *Sleep spindle-dependent mechanisms to reorganize the forebrain* Gina R. POE, University of Michigan, United States

11:55-12:10	*Role of sleep spindles and sigma power across multiple sleep bouts on emotional memory in early childhood* Rebecca M. C. SPENCER, University of Massachusetts, Amherst, United States
12:10-14:00	*Lunch break*
14:00-15:00	**Poster Sessions** *Clinical Corner and Biomarkers: Sleep Disorders, Neurology, Psychiatry Methodology*
15:00-15:55	**Epilepsy / Biomarkers-2** *Chair: Róbert Bódizs*
15:00-15:25	**INVITED TALK** *Reduced sleep spindles in schizophrenia: a treatable endophenotype that links risk genes to impaired cognition?* Dara S. MANOACH, Massachusetts General Hospital, United States
15:25-15:40	*Sleep spindle deficit in schizophrenia: a critical overview and novel findings* Armando D'AGOSTINO, The University of Milan, Italy
15:40-15:55	*Microstructue of sleep spindles in a multiple sclerosis animal model* Alejandro OSORIO-FORERO, Universidad de los Andes, Colombia
15:55-16:15	*Coffee break*
16:15-17:10	**Stimulating Sleep Spindles** *Chair: Péter Simor*
16:15-16:40	**INVITED TALK** *Rational design of non-invasive brain stimulation to target oscillations* Flavio FROHLICH, University of North Carolina at Chapel Hill, United States
16:40-16:55	*The impact of transcranial electrical stimulation during sleep on motor sequence learning* Philipp FUCHS, University of Salzburg, Austria
16:55-17:10	*Spatial organization of sleep spindles during acoustic phase-locked stimulation of NREM slow waves* Miguel NAVARRETE, Universidad de los Andes, Colombia
17:10-17:20	**Closing Ceremony** Róbert BÓDIZS *Semmelweis University, Chair of the Scientific Committee*

ORAL PRESENTATIONS

THURSDAY, 12 MAY 2016

Gatekeepers of Sleep

SPINDLES AND K-COMPLEXES, THE GATEKEEPERS OF OUR CONSCIOUS AWARENESS

George K. Kostopoulos

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Keywords: Sleep, spindles, K-complex, arousal, unconscious cognition

For sleep to accomplish its restorative and memory consolidation functions, the brain has to work unbiased by ongoing environmental changes. However, complete disconnection from the environment makes an animal vulnerable to predators and homeostatic emergencies. Possibly in response to this challenge, activity in thalamocortical circuits is occasionally engaged into a phasic rhythmic mode – presented in EEG as 11–15 Hz spindles –, which disrupts all but the early primary sensory cortical responses and thus precludes conscious awareness of changes in the environment, unless these changes are excessive or salient to the sleeper. Taking a decision on the latter without awakening demands unconscious cognitive action with currently unknown neural correlates. To explore them, we have conducted whole night sleep dense EEG recordings in healthy young adults to study the characteristics of spindles and their relationship to K-complexes (KC), a prominent slow wave appearing together with spindles in NREM-2 and hypothesized to play a dual role, as a sentinel for salient stimuli and in their absence as a sleep promoting hypersynchronization (1). Sporadic fast spindles maximizing centro-parietally and fronto-centrally prominent but singular KC were collected from NREM-2 stages throughout the night. Upon coincidence of the two events, spindles invariably stop for the duration of the KC negative wave (2). About 70% of KC were closely followed by spindles starting at the KC positive phase. These spindles were invariably of higher frequency (by about 1 Hz) than the sporadic spindles or even the spindles which the KC interrupted. We found no correlation between the probability that a KC will be closely followed by a spindle and any of all spindles characteristics and the amplitude, duration and wave shape of the preceding KC. Most often, the negative wave of a KC were crowned by a short oscillation in the high theta range (3). This intra-KC-oscillation had two characteristics not shared by KC negative wave: its sequence of 2–4 wavelets had a power maximum relocating antero-posteriorly, while their

intervals became shorter, i.e. the oscillating frequency increased towards lower alpha. This quick spatio-spectral shift may reflect an arousing process during the KC and play a role in the unconscious cognitive function of sentinel (1). We conclude that spindles, KC and intra-KC-theta-oscillations are dynamically linked, but not necessarily causally – more likely they are grouped by a slower brain process.

References
1. Halász P. The K-complex as a special reactive sleep slow wave - A theoretical update. Sleep Med Rev. 2015 Oct 8;29:34-40.
2. Kokkinos V, Kostopoulos GK. Human non-rapid eye movement stage II sleep spindles are blocked upon spontaneous K-complex coincidence and resume as higher frequency spindles afterwards. J Sleep Res. 2011 Mar;20(1 Pt 1):57-72.
3. Kokkinos V, Koupparis AM, Kostopoulos GK. An intra-K-complex oscillation with independent and labile frequency and topography in NREM sleep. Front Hum Neurosci. 2013 Apr 26;7:163. doi: 10.3389/fnhum.2013.00163. eCollection 2013.

ARE SLEEP SPINDLES INHIBITORY FOR PAIN?

Léa Claude [1] *– Florian Chouchou* [1] *– Laury Callegari* [1] *– Germán Prados* [1] *– Maïté Castro* [1] *– Barbara DeBlay* [1] *– Caroline Perchet* [1] *– Luis García-Larrea* [1] *– Stéphanie Mazza* [2] *– Hélène Bastuji* [1,3]

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[2] Université Claude Bernard, Lyon, France
[3] LEMC, Université Lumière, Lyon, France

Keywords: Sleep spindle, pain, intracerebral EEG, surface EEG, laser evoked potentials

Responsiveness to environmental stimuli decreases during sleep, and sleep spindles are often believed to play a major role in inhibiting sensory inputs (1). In the present study, we tested the effect of spindles on behavioural, autonomic and cortical responses to pain, in three experiments assessing surface and intracerebral responses to nociceptive stimuli during the all-night N2 sleep stage.

The percentage of arousals remained unchanged as a result of the presence of spindles. Neither cortical nociceptive responses, nor autonomic cardiovascular reactivity were depressed when elicited within a spindle. These results could be replicated in human intracerebral recordings, where sleep spindle activity in the posterior thalamus failed to depress the thalamocortical nociceptive transmission, as measured by sensory responses within the posterior insula.

The temporal relationship between spindle activity and sensory processing showed that evoked responses were present in any case, but of higher amplitude around the initiation of spindle activity.

Hence, the assumed inhibitory effect of spindles on sensory inputs may not apply to the nociceptive system, possibly as a result of the specificity of spinothalamic pathways and the crucial role of nociceptive information for home-

ostasis (2). Intriguingly, a late scalp response commonly considered to reflect high-order stimulus processing (the 'P3' potential) was significantly enhanced during spindling, suggesting a possible spindle-driven facilitation, rather than attenuation, of cortical nociception.

References
1. Astori et al. Trends in Neurosciences, 2013, 36, 738–748
2. Claude et al. J Physiol. 2015, 15;593:4995-5008

Mesiotemporal Structures and Cross-Frequency Coupling

NATURE OF SLEEP SPINDLES IN MESIOTEMPORAL STRUCTURES

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Keywords: Hippocampus, mesiotemporal spindles, mesiotemporal EEG, foramen ovale, ripples

Recording mesiotemporal activity requires an intracranial monitoring setting which is only used in epilepsy patients undergoing evaluation for surgery. Therefore, the issue as to whether spindles seen in mesiotemporal electrodes represent an epileptic or physiological activity has been debated. In the epilepsy monitoring unit of the National Institute of Clinical Neurosciences, Budapest, we routinely monitor epilepsy patients with semi-invasive foramen ovale (FO) electrodes to assess mesiotemporal activity. Visual and quantitative analysis of the FO recordings reveal important and otherwise inaccessible details of the mesiotemporal electrical activity. Using the FO recordings from 45 epilepsy patients we characterized the nature of mesiotemporal spindles as regards morphology, distribution across sleep stages and relation to pathologic parameters. Spindles were present in the vast majority (91%) of patients and were most frequent during stage NREM2. In 29% of patients spindles also occurred during waking or REM sleep. Spindles were inconsistently related to the laterality of epilepsy. There was a negative relation between left mesiotemporal spindles and age. Given the several parallelisms with regular scalp spindles we assume that FO spindles represent physiological rather than pathological activity. In separate studies we assessed the hierarchical nesting of mesiotemporal spindles on both slow and fine time scales. We showed that there is a temporal relationship between frontal, parietal and mesiotemporal spindles as well as between ripples and spindles in mesiotemporal structures. At a fine time scale of milliseconds, we for the first time showed that mesiotemporal ripple activity is phase-locked to spindle troughs. Coupling of mesiotemporal spindles with other classes of oscillations represents the hierarchical nature of the sleep oscillatory activity.

Specifically, the coupling between spindles and ripples may constitute a mechanism underlying sleep-related memory transfer from hippocampal to neocortical stores.

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SLOW OSCILLATIONS, SPINDLES AND RIPPLES ARE HIERARCHICALLY NESTED IN THE HUMAN HIPPOCAMPUS

Til O. Bergmann [1,2,3,4,*] *– Bernhard P. Staresina* [5,6,*] *– Mathilde Bonnefond* [3] *– Roemer van der Meij* [3] *– Ole Jensen* [3] *– Lorena Deuker* [3] *– Christian E. Elger* [7] *– Nikolai Axmacher* [7,8,9] *– Juergen Fell* [7]

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* These authors contributed equally to this work.

Keywords: Spindle, slow oscillation, ripple, cross-frequency-coupling, hippocampus, human, intracranial EEG

Active system consolidation during sleep is supposed to be mediated by the concerted reactivation of hippocampo-neocortical memory traces, resulting in their redistribution and transformation into neocortico-neocortical representations for long-term storage [1, 2]. The neuronal mechanisms underlying this reactivation process presumably involve cross-frequency coupling of the three cardinal oscillations characterizing human non-rapid-eye-movement (NREM) sleep: Under global control of the neocortical slow oscillation (SO; < 1.25 Hz), thalamo-cortical spindles (12-15 Hz) group hippocampal ripples (~80-100 Hz) for a temporally fine-tuned reactivation of memory traces [1]. Using direct intracranial electroencephalography (iEEG) from human epilepsy patients during natural sleep, we tested the critical assumption that SOs, spindles and ripples are functionally coupled within the hippocampus [3]. Employing cross-frequen-

cy phase-amplitude coupling analyses, we show for the first time that within the hippocampus, spindles are modulated by the up-state of SOs and in turn cluster the occurrence of ripples in their troughs, thereby providing the required temporal resolution for the concerted reactivation of hippocampal memory traces. Results of additional analyses will be presented that characterize the spatial and temporal distribution of sleep spindles across the longitudinal axis of the human hippocampus.

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PHASE-AMPLITUDE COUPLING OF SLEEP SPINDLES PREDICTS RISK OF EVOLUTION TO DEMENTIA IN PARKINSON DISEASE

Fatima Adda [1] – *André Achim* [1] – *Julie Carrier* [2] – *Véronique Latreille* [2] – *Jean-François Gagnon* [1]

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Keywords: Phase-amplitude coupling, sleep spindles, Parkinson disease, dementia

Evolution of Parkinson's disease (PD) to dementia, at re-evaluation 2 to 9 years after initial patient testing, was associated (at $p<.05$) with lower sleep spindle density at central, parietal and occipital sites and lower spindle amplitude at parietal and occipital sites[1]. A large subset of these data, with 13 patients who became dement (PD+d), 45 who remained dementia free (PD-d), and 44 healthy controls, is revisited in terms of phase-amplitude coupling (PAC) of automatically detected sleep spindles for the 64 combinations of 8 channels providing respectively the slow wave (5 frequency bands from 0.6-0.8 Hz to 1.4-1.6 Hz) and the spindle envelopes (filtered 11-13 Hz or 13-15 Hz). For each of these 10 filter combinations, the resulting 64 PAC values were reduced to 3 principal axis factors that were submitted to discriminant analysis to identify which filter combinations discriminate the three groups. The 0.8-1.0/11-13 Hz combination best discriminated these groups ($p=.000052$), followed by 1.2-1.4/13-15 Hz ($p=.00011$), by 1.0-1.2/13-15 Hz ($p=.00036$) and by 0.8-1.0/13-15 Hz ($p=.008$). Step-wise logistic regression to discriminate PD+d from PD-d identified that the latter two filter combinations are redundant with the first two, which provide independent sources of information. Eight of the 13 PD+d were correctly classified with only one false positive among the PD-d. To characterize the two retained ef-

fects, ANOVA's were performed on several meaningful groupings from their original 64 PAC scores. For the 0.8-1.0/11-13 Hz filter combination the PD+d, compared to the controls and the PD-d (who differ only mildly), showed reduced PAC between frontal slow-wave and occipital spindles along with a more pronounced increase of the inverse relationship, namely PAC between occipital slow-wave and frontal spindles. For the 1.2-1.4/13-15 Hz combination, the PD+d differed from the other two groups by higher within region PAC, irrespective of whether the spindles and slow waves are in the same or opposite hemisphere, namely between central slow waves and central spindles, between parietal slow-waves and parietal spindles, and between occipital slow-waves and occipital spindles. Two distinct PAC patterns of early predictors of risk for dementia in PD are thus observed. PD+d show increased PAC of the higher spindle frequencies at central, parietal and occipital, but not frontal areas. They also show increased PAC of the lower frequency content of frontal spindles with occipital slow waves, which is intriguing and might lead to new insights both on spindle dynamics and on brain degradation leading to dementia in PD.

Reference
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Basic Mechanisms and Rhythmogenesis-1

THALAMIC CELLULAR INTERACTIONS AND THE DURATION OF SLEEP SPINDLES

László Acsády

Institute of Experimental Medicine of the Hungarian Academy of Sciences

Sleep spindles govern transient, synchronous activity throughout the thalamocortical network and were proposed to play major role in memory consolidation. For how long these coordinated network events take place will greatly influence their short and long term effects. However, what determines the duration of sleep spindles has been little explored. By simultaneously measuring the activity of interconnected thalamocortical (TC) and thalamic reticular (TRN) cell activity in freely sleeping rats here I demonstrate that spindles with different duration display distinct TRN but not TC activity pattern. In addition, bursting TRN but not TC cells sharply drop their activity before the termination of the spindles indicating a key role of TRN cells in influencing the duration of sleep spindles. Using selective and focal elimination of synaptic GABA-A receptors in TC cells I also demonstrate that during TRN bursts GABA abundantly activate extrasynaptic GABA-A receptors resulting in huge, slow burst IPSCs whereas single action

potential mediated IPSCs activate only synaptic receptors evoking much smaller and shorter IPSCs in TC cells. Since inhibitory activity is crucial for the rebound bursts of TC cells the data together indicate that as TRN cells stop bursting towards the end of the spindles a huge drop in inhibitory drive will result in the inability of TC cells to initiate the next spindle cycle which will result in the termination of spindle.

We conclude that during natural sleep the state of the entire thalamocortical network is read out by TRN activity which determines when and for how long spindling will take place.

Supported by : NKFIH and Hungarian Brain Research Program

THALAMIC RETICULAR NUCLEUS, THALAMIC BURSTS AND CORTICAL SPINDLES

Michael M. Halassa

New York University, United States

The thalamic reticular nucleus (TRN) has been named the guardian of the cortical gateway and has been implicated in spindle generation. However, the underlying functional architecture of these processes has been unknown. In this talk, I will present electrophysiological recordings from the TRN of the freely behaving mouse showing that the TRN is composed of functional subnetworks that map on anatomical territories.

The data also show that the thalamus does not receive uniform inhibition, but that inhibition is spatiotemporally variable. I will discuss the implications related to the generation and function of spindles.

IDENTIFICATION OF HIGLY CONNECTED BRAIN SITES ASSOCIATED WITH SLEEP SPINDLES ACTIVITY

Mario Valderrama [1] *– Catalina Alvarado-Rojas* [2] *– Alonso Botero* [3] *– Miguel Navarrete* [1] *– Liliana Mayor* [1] *– Michel Le Van Quyen* [3]

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Keywords: Brain complex networks, brain hubs, sleep spindles

Complex networks analysis has allowed the study of brain connectivity in anatomical and functional contexts. In sleep particularly, the study of connectivity patterns between different brain regions allows a better understanding of

physiological mechanisms at a network level that can be implicated in numerous functional processes [1]. In this work, we studied connectivity patterns associated with sleep spindles by identifying highly connected sites, or hubs, present in brain networks. In particular, dynamical graphs of brain activity were created from intracranial electrodes (n=768 in total) of epileptic patients (n=12) undergoing an invasive exploration associated with their pathological condition [2]. For most of the recording sites (84%), MNI coordinates were available confirming that 50% and 35% of invasive contacts were located in the left and right hemisphere respectively. From this, 10.5% were located in the frontal lobe, 3.5% in the occipital lobe, 4% in the parietal lobe, 43% in the temporal lobe, 18% in the limbic lobe and % in sub-lobar regions. From each subject, one complete seizure-free night was chosen and only NREM periods were visually selected for the analysis. For each NREM segment, we estimated the slow and fast spindle (8–12 and 12–18 Hz respectively) RMS associated power within consecutive, non-overlapping windows of 3 seconds along the whole period. For each of these bands, we constructed adjacency matrices between all pairs of available electrodes based on the absolute value of the normalized cross-correlation taken from the corresponding pair of frequency activities inside consecutive 1-minute windows. We subsequently defined weighted connected graphs by establishing weighted links between all pair of electrodes (nodes in the network). From this, hubs were defined as such nodes having in median more than 40% of all available possible connections. In total, for the fast spindle networks, we identified 271 hub-nodes present in 9 subjects; most of the hubs were located in the Superior Temporal Gyrus (36), Parahippocampal Gyrus (23), Middle Temporal Gyrus (18), Precentral Gyrus (17), Superior Frontal Gyrus (10), Postcentral Gyrus (9) and Inferior Frontal Gyrus (9); interestingly, though most of the strong (>0.7) and weak (<0.35) connections were not found to be in the immediate vicinity but between 20 and 80 mm linear distance (mid-range connections), most of the intermediate-strength connections (>0.35 and <0.7) were found to be in the range between 0 and 20 mm (short-range connections). Similar connectivity patterns were observed for the slow spindle networks suggesting an involvement of the same brain circuits in the expression of both activities.

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SPATIOTEMPORAL CHARACTERISTICS OF THE SLEEP SPINDLE IN HUMAN ELECTROCORTICOGRAPHY

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Keywords: Human, subdural electrodes, epilepsy

A source of controversy in the literature is whether spindles are local events in terms of their characteristics and spatiotemporal organization. To address this question, we measured brain activity during sleep using intracranial electrodes placed directly on the pial surface in eight patients undergoing evaluation for epilepsy.

We found that spindles arising from different brain regions have significantly different characteristics, particularly in terms of density and peak frequency within the spindle band. Spindles are temporally a local phenomenon restricted to one or very few recording channels at any given time, though there are spindles that occur over widespread areas, often the lateral prefrontal cortex and the superior temporal gyrus.

These findings indicate that spindles are regulated at a local level, but the local characteristics and synchronization profiles are organized across cortical regions.

We propose that the coexistence of local and widespread characteristics might arise from the known anatomical difference between the spatially limited core and the diffuse matrix thalamo-cortical pathways.

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Basic Mechanisms and Rhythmogenesis-2

SLEEP SPINDLES IN THE MOUSE: SO SMALL, YET SO POWERFUL

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Keywords: Infra-slow periodicity, power fluctuation, fast spindles, heart rate, off-line states, sensory protection

Sleep spindles are discrete, spindle-shaped bursts of oscillatory activity that appear in the human EEG during periods of drowsiness and light sleep. Mouse sleep spindles occur throughout NREMS of mice, and many of the corresponding EEG events do not show the well-delineated, discrete character of spindles in higher mammals. Therefore, can we rely on rodents in advancing insight into not only the mechanisms, but also the function of these brief EEG rhythms? Our work started from the hypothesis that if sleep spindles contribute to sensory protection and memory consolidation during sleep, they should emerge in a behaviourally guided sleep analysis that is based on the reactivity of sleeping mice to external stimuli. Through this approach, we have identified fluctuations of spindle power during NREMS in mouse (10-15 Hz frequency band of the NREMS power spectrum) that occur on an infra-slow time scale of ~45 s and that divide sleep into 20-25 s periods of high- and low reactivity to acoustic noise (n = 10). Mice woke up when infra-slow fluctuations declined during noise, whereas they slept through when spindle power rose, which coincided with enhanced hippocampal ripple activity. Infra-slow fluctuations thus correspond to alternating periods of elevated sleep fragility and robust offline states during NREMS. Multi-site simultaneous local field potential recordings revealed that these infra-slow fluctuations occurred prominently in sensory cortical circuits. When the same analysis was carried out for sleep of healthy humans, infra-slow fluctuations in spindle power were prevalent during light sleep (stage 2 sleep), and emerged particularly clearly for the 2 Hz-frequency band corresponding to the fast spindles of each individual (n = 27). In both species, heart rate changes aligned to and preceded the infra-slow power fluctuations, suggesting that hemodynamic processes accompany spindle power variability. Therefore, infra-slow fluctuations in spindle power are coordinated along the brain-body axis and dictate, from mouse to human, an enhanced sleep fragility in exchange with an offline state that is conducive for memory processing.

CHARACTERIZATION OF TOPOGRAPHICALLY SPECIFIC SLEEP SPINDLES IN MICE

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Study Objective: Sleep spindles in human have been classified to slow anterior and fast posterior spindles, and recent findings indicate that their profiles differ according to pharmacology, pathology, and function. However, little is known about the generation mechanisms within the thalamocortical system for different types of spindles. In this study, we aim to investigate the electrophysiological behaviors of the topographically distinctive spindles within the thalamocortical system by applying high-density EEG and simultaneous thalamic LFP recordings in mice.

Design: 32 channel extracranial EEG and 2 channel thalamic LFP were recorded simultaneously in freely behaving mice to acquire spindles during spontaneous sleep.

Animals: Hybrid F1 male mice of C57BL/6J and 129S4/svJae

Measurements and Results: Spindle events in each channel were detected by spindle detection algorithm and then a cluster analysis was applied to classify the topographically distinctive spindles. All sleep spindles were successfully classified into 3 groups: anterior, posterior, and global spindles. Each spindle type showed distinct thalamocortical activity patterns regarding the extent of similarity, phase synchrony, and time lags between cortical and thalamic areas during spindle oscillation. We also found that sleep slow waves were likely to associate with all types of sleep spindles, but also that the ongoing cortical decruitment/recruitment dynamics before the onset of spindles and their relationship with spindle generation were also variable, depending on the spindle types.

Conclusion: Topographically specific sleep spindles have shown distinctive thalamocortical network behaviors.

Sleep Regulation and Sleep Disorders

CORTICAL SPINDLES AND SLEEP HOMEOSTASIS

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Keywords: NREM sleep, REM sleep, sleep homeostasis, local spindles, cortical neuronal activity

Homeostatic regulation of sleep refers to the maintenance of a balance between waking and sleep on a time scale of approximately 24 hours. While sleep timing and duration are influenced by circadian time, preceding sleep-wake history is considered an important determinant of sleep intensity. According to this notion, prolonged wakefulness is followed by a deeper sleep, which is reflected in the expression of EEG slow waves. Traditionally, EEG spectral power between 0.5–4 Hz (SWA) has been considered as a marker of sleep intensity and homeostatic sleep need. Recently, it was established that characteristics of individual EEG or LFP slow waves, such as their amplitude, incidence, duration and slopes, correlate with specific changes at the level of cortical neuronal activity, such as the duration of network UP/ON and DOWN/OFF periods, and neuronal synchronisation. Notably, it has been shown that individual slow waves are often local, and preceding sleep-wake history affects spatio-temporal synchronisation of slow waves. While slow waves are often considered the main hallmark of cortical activity during NREM sleep, and have been linked, mechanistically and functionally, to homeostatic regulation of sleep, the role of another major sleep oscillation, sleep spindles, is unclear in this context. Sleep spindles represent bursts of EEG or LFP occurring at approximately 9–16 Hz, which are typically associated with network UP states. On the time scale of hours, sleep spindles generally show a reciprocal relationship with the time course of SWA. Although sleep spindles are typically enhanced at the beginning and the end of individual sleep episodes, clear cut sleep spindles also occur even during deep phases of NREM sleep. Recently, human studies have shown that sleep spindles are also local events, and in most cases manifest in a subset of cortical areas only, although the functional significance of local spindles is unclear. There are several fundamental questions which remain to be addressed. First, little is known about the local and global occurrence of spindles in rodents, and whether EEG provides an accurate estimate of spindles occurring in localised cortical networks. Second, it is unknown whether isolated spindles and those spindles linked to slow waves, can be distinguished by such parameters as their duration or frequency. Likewise, it remains to be determined whether slow waves linked to spindle events show similar homeostatic dynamics as slow waves occurring in isolation. Third, it is unclear whether individual cortical neurons recruited in sleep spindles are

functionally different from those neurons, which do not fire selectively in association with spindling. Finally, it remains to be investigated whether preceding wake duration or specific waking behaviours affect the local and global dynamics of sleep spindles in a vigilance state- and region-specific manner. Overall, it is concluded that investigating spatio-temporal dynamics of sleep spindles is essential for understanding network mechanisms and the functional significance of sleep homeostasis.

CHANGES OF SLEEP SPINDLE CHARACTERISTICS DURING SPLIT-NIGHT STUDIES IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA

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Keywords: Automated sleep spindle detector, sleep respiratory disturbances, CPAP therapy, OSA

Objective: Sleep architecture in patients with obstructive sleep apnea (OSA) is characterized by a high degree of sleep fragmentation by arousals, resulting in an abnormal distribution of sleep microstructures, such as sleep spindles. The aim of the present study is to examine whether sleep spindle characteristics differ between the diagnostic and the therapeutic part of a split night in OSA patients.

Methods: Split-night studies from 30 patients and diagnostic studies from 31 patients were scored by the sleep classification system Somnolyzer 24x7 as described by Punjabi et al. [1]. Sleep spindle densities per minute N2 sleep (SSD) were determined for all spindles (11–16 Hz), for fast spindles (>=13Hz at the initial part of the spindle event) and for slow spindles (<13Hz before termination) using 3 different sensitivity settings: maximum sensitivity, balanced and maximum precision [2].

Results: In split-night studies all-SSD and slow-SSD remained unchanged while fast-SSD decreased (p=.010), resulting in an increased percentage of slow spindles (p=.033) and a decreased percentage of fast spindles (p=.010) during the CPAP treatment part. Patients without treatment showed opposite changes from the first to the second part of the night: slow-SSD decreased (p=.012) while all-SSD and fast-SSD remained unchanged resulting in a decreased percentage of slow (p=.046) and increased percentage of fast spindles (p=.042) in the second part of the night. Interestingly, these differences were most pronounced with the maximum sensitivity setting.

Discussion: The relative increase of spindles with slow frequencies during the CPAP treatment as compared to the untreated part of the night may represent a first sign of normalization of the reported loss of sleep spindle frequency deceleration in untreated OSA [3] and may suggest an increased contribution of the prefrontal spindle source, which oscillates typically at frequencies below 13 Hz [4].

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SLEEP SPINDLE CHARACTERISTICS BEFORE AND AFTER SLEEP DEPRIVATION IN OBSTRUCTIVE SLEEP APNEA

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Keywords: Quantitative EEG analysis, electroencephalography, sleep-dependent cognition, sleep-disordered breathing, extended wakefulness

Introduction: Obstructive Sleep Apnea (OSA) is associated with sleep disruption and impaired cognition. Sleep spindles play a pivotal role in maintaining sleep-dependent cognitive processes. We sought to investigate the effects of sleep deprivation on sleep spindle density and morphology during NREM sleep in OSA patients and healthy adults (HA). The relationship between sleep spindles and neurobehavioural performance after 24-h awake was also explored.

Methods: Eight males with OSA (AHI 49.8±24.7 per hour; age 45±8.5 yrs) and 9 healthy adults (1 F; AHI 4.5±2.7; age 28±3.6 yrs) underwent baseline overnight polysomnography (PSG), followed by 40 hrs of extended wakefulness with 2-hourly assessments of simulated driving, and followed by a recovery sleep PSG. Frontal (Fz), central (C3, Cz, C4), parietal (Pz) and occipital (Oz) EEG signals were analysed using an automated spindle detection algorithm based on a band-passing finite-impulse-response filter and Hibert transformation. Sleep

spindle density and morphology (duration, frequency, amplitude and symmetry) during NREM sleep were compared between groups, and before and after sleep deprivation. Baseline spindle densities were investigated in relation to neurobehavioural performance after 24-h awake.

Results: OSA patients showed significantly reduced spindle density (per minute) during NREM sleep at C3; OSA vs HA: (1.8 vs 3.3, p=0.018) and Pz (3.6 vs 5.2, p=0.045) and had shorter spindle durations (sec) at all derivations compared to healthy adults (e.g. C3; OSA vs HA: 0.71 vs 0.78, p=0.015). During recovery sleep, spindle densities were significantly reduced at central and parietal derivations in both groups and frontally in OSA patients only. Spindle amplitude and mean frequency were significantly reduced at frontal and central derivations in healthy adults and spindle durations in OSA patients were significantly reduced across the scalp in recovery sleep compared to baseline. Lower spindle densities across the cortex were strongly correlated (rho 0.7-0.97) with worse driving performance (greater steering deviation) in healthy adults but not in OSA patients.

Conclusions: OSA patients have reduced spindle densities compared to healthy adults; however, these differences may be attributed to increasing age. Recovery sleep after extended wakefulness results in reduced spindle density and changes in morphology both in healthy adults and to a greater extent in OSA patients. Vulnerability to performance impairment after sleep deprivation in healthy adults may be predicted by sleep spindle densities.

FRIDAY, 13 MAY 2016

Memory Consolidation

THE ROLE OF SLEEP SPINDLES FOR SYSTEMS CONSOLIDATION OF MEMORY

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I will first introduce into our concept of an active systems consolidation of memory during sleep. The concept is based on findings indicating (i) that sleep preferentially consolidates hippocampus-dependent declarative memories, (ii) that representations in the hippocampus-dependent declarative memory system undergo a qualitative reorganization during sleep, (iii) that consolidation of these memories takes place during slow wave sleep (SWS), and (iv) it originates from the reactivation of representations in hippocampal networks. The concept assumes that such reactivations promote the redistribution of the representation from hippocampal networks that serve as an initial store, to neocortical networks that serve as long-term store. In a second part, I will concentrate on the role of EEG spindles in this concept: Memory reactivations in the hippocampus lead to a transfer of the reactivated memory information from hippocampus towards neocortical networks. This transfer appears to be primed by the occurrence of a hierarchical nesting of SWS-related EEG oscillations, where hippocampal ripples (and enwrapped reactivated memory information) nest into the excitable troughs of a thalamic spindle, and where such spindle-ripple events themselves nest into the excitable up-states of the neocortical (<1Hz) slow oscillation. Thalamic spindles play a central role in this transfer because they do not only phase-lock hippocampal reactivations but also contribute to the generation of neocortical slow oscillations.

SPINDLES: COORDINATION WITH OTHER OSCILLATIONS AND THE TIMING OF REPLAY

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Sleep spindles are hallmark for NREM sleep and have been implicated with multiple functions, but their true meaning remains a mystery. One function that has been associated with sleep spindles is memory consolidation. In this talk I will

focus on discussing the timing of sleep spindles together with other oscillatory phenomena associated to memory consolidation during sleep, such as hippocampal sharp-wave-ripples and cortical slow oscillations, and how this could influence memory consolidation. For example, prefrontal cortex spindles seem to occur after sharp-wave-ripples while parietal spindles occur simultaneously. Further, I will highlight recent evidence regarding the actual processes thought to occur during sleep - memory replay and homeostatic scaling – and how sleep spindles may relate to these.

SLEEP-DEPENDENT MOTOR MEMORY CONSOLIDATION FROM ADOLESCENCE TO ADULTHOOD

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Despite profound experience supporting the hypothesis that sleep plays a functional role in the consolidation of fine-motor sequence learning, the impact of sleep on the consolidation of motor adaptation tasks as well as complex gross-motor learning is still debated. Furthermore, in children (7–11 years) it has been shown that there is a lack of sleep-dependent motor memory consolidation. We here examined effects of sleep and wakefulness on 3-ball-cascade juggling in adolescents (12–15 years) in comparison to adults (19–29 years). Juggling requires accurate bimanual arm movements, grasping and visual tracking in the periphery; thus constituting a complex visuo-motor skill. Similar to earlier results in children we found that sleep in adolescents does not lead to an increase but to a decrease in motor performance, whereas across the wake retention interval performance remained stable. This was exactly contrary to the findings in our adult population: juggling performance after sleep was stabilized but deteriorated after wakefulness. Whereas the sleep-dependent stabilization in the adults was positively associated with fast sleep spindle activity (13–15Hz) but negatively with REM sleep during sleep after training, no such relationships were revealed for the adolescents. This absence of overnight consolidation in adolescents can be interpreted in terms of diminished capabilities to integrate complex sensory and sensorimotor inputs into already existing motor representations especially at an early stage of implicit motor learning (also see Wilhelm et al., 2012). Astonishingly, data contradicting the classical sleep-dependent memory consolidation hypothesis seem to be accumulating, particularly when focusing on motor learning and early development.

Wilhelm I, Prehn-Kristensen A, Born J. Sleep-dependent memory consolidation - What can be learnt from children? Neurosci Biobehav Rev 2012;36:718–28

LOCAL SPINDLE NETWORKS IN THE RIGHT HEMISPHERE ENHANCE AWARENESS OF REGULARITY AFTER SLEEP

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Keywords: Sleep spindles, serial response time task, implicit learning, regularity awareness

This study explored signatures of offline processing during sleep (Diekelmann and Born, 2010) and their effects on awareness of high-order information after sleep (Wagner et al., 2004; Yordanova et al., 2009, 2010, 2012; Verleger et al., 2013). Fifty-three participants performed a serial response time task (SRTT) where, unknown to participants, stimuli were presented in a hidden repeating sequence. Re-processing of task-specific information during sleep was explored by having participants perform the task before sleep either on the right or left side of their body, allowing for task-specific engram encoding either in the left or in the right hemisphere. Moreover, it was tested if explicit sequence knowledge after sleep would be preceded by features of sleep neurophysiology, possibly dependent on implicit sequence knowledge acquired before sleep. Sleep spindles were used as the principal measure during sleep stage 2 (S2) and slow wave sleep (SWS) in two nights, before and after task performance. Major results show that spindle activity (1) was not modulated by the side of task performance, (2) preceded explicit sequence knowledge after sleep in two ways, trait-dependent (i.e., before any task performance) and learning-dependent, and (3) in relation to subsequent awareness specific right-lateralized local sleep networks were engaged, with trait-dependent slow spindles during SWS, and learning-dependent fast spindles during SWS and S2. Thus, formation of the representation of a repeatedly experienced sensorimotor regularity during sleep relies on local spindle networks in the frontal-central regions of the right hemisphere, which are sensitive to pre-sleep implicit learning. Neuroplasticity of these networks reflects individual abilities for explicit rule extraction in a trait-dependent manner.

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Networks and Functions

SLEEP SPINDLES: WHAT ARE THEY FOR?

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Phenotypic Variation and Neurobehavioral Correlates

SLEEP SPINDLES ARE SEXUALLY DIMORPHIC DEVELOPMENTAL AND TRAIT NEUROBEHAVIORAL MARKERS

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Keywords: Intelligence, hemispheric laterality, EEG synchronization, sex differences, ontogeny

Thalamocortical origin, sleep protection and offline neural plasticity are major functional aspects of sleep spindles [1]. Ontogenetic development is paralleled by specific changes in sleep spindle features, including amplitude, duration, density and peak frequency. Overwhelming evidence suggests the high phenotypical variability, individual-specificity and internight reliability of sleep spindle measures. However, a particularly conspicuous drawback of dominant approaches of the issue is the lack of (an intention to create) a deliberate formal definition of sleep spindles (instead of the visual scoring-based, quasi-formalised methods) hindering significant progress and producing high levels of confusion in the field. By defining sleep spindles as those wave segments that contribute to the individual- and derivation-specific 9–16 Hz spectral peaks of average NREM sleep EEG periodograms [2, 3], we unravelled significant sexual dimorphism in the development, phenotypic features and cognitive correlates (general fluid intelligence [fIQ]) of these oscillations. Specifically, spindle peak frequencies were lower in men than is women. Furthermore, lower amplitude, accentuated local (posterior) occurrence, left hemispheric lateralization, and lower synchronization (weighted phase lag index [WPLI]) where distinct features of fast sleep spindles in men, as compared to women. Sex-differences in spindle synchronization were evident for both intra- and interhemispheric derivation pairs. Local-global, hemispheric dominance-related and WPLI-derived sex-differences were unrelated to fIQ and were present in both adolescent and adult, but not child samples of 4–8 years of age. In turn, fast sleep spindle amplitudes in adolescent and

adult females, as well as fast sleep spindle densities in adolescent females were shown to correlate positively with fIQ. Correlations largely survived age-control and peaked in the (fronto-)central regions. None of the above mentioned positive correlations were evidenced in adolescent or adult males [4–6]. Altogether, these findings indicate the utmost relevance of sleep spindle analysis in unravelling individual neurocognitive architecture and functional neural connectivity, as well as the striking sexual dimorphism of sleep spindling. Moreover, findings cohere with former reports indicating the preferential involvement of white matter structures in cognitive performances of women as compared to grey matter-based processing in men.

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SLEEP SPINDLES AND INTELLIGENCE IN EARLY CHILDHOOD – DEVELOPMENTAL AND TRAIT-DEPENDENT ASPECTS

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Keywords: Sleep spindles, Raven Colored Progressive Matrices, maturation, childhood, sex differences, IQ

Sleep, particularly sleep spindling has been demonstrated as a powerful marker of individual differences in cognitive ability, correlating with both age-related changes in cognitive abilities and with the age-independent concept of IQ [1]. Our previous studies, however, found the relationship between intelligence and sleep spindling to be sexually dimorphic and more prominent in females [2, 3]. Based on these findings we investigated the relationship between age, Raven Colored Progressive Matrices and sleep spindle density, duration and amplitude in twenty-nine young children (age 4-8 years). We specifically investigated potential sex differences in the psychometric correlates of sleep spindling. We also aimed to separate the correlates of sleep spindles which are due to age-related maturation from other effects which reflect an age-independent relationship between sleep spindles and general intelligence. Our results revealed a positive correlation between the number of fast spindles per minute and raw Raven score as well as age, but only in male children. In female children, a positive

association between Raven score and slow spindle amplitude was revealed, but only after correcting for the effects of age. Overall, our results show that sleep spindles are rather a maturational marker in male children, but they are a correlate of trait-like intelligence in female children, in line with previous studies in adolescent and adult subjects. More efficient thalamocortical white matter connectivity may be the underlying mechanism behind both higher spindle amplitude and higher intelligence in female, but not male subjects.

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IS WHITE MATTER DIFFUSION IMPLICATED IN AGE-RELATED MODIFICATIONS OF SLEEP SPINDLES?

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Keywords: Aging, diffusion MRI, sleep spindles, tract-based spatial statistics, wholebrain mediation

Introduction: Aging is a natural process that causes important changes both in sleep and brain microarchitecture. The amplitude, density, and duration of sleep spindles (SS) show a decrease in middle-aged and older subjects[1]. White matter diffusion, assessed by magnetic resonance imaging (MRI), also undergoes important changes during aging[2]. The goal of this study was to investigate whether diffusion variables are implicated in age-related decrease of SS characteristics. *Methods:* Thirty young (20-30 yo) and 31 middle-aged subjects (50-70 yo) underwent a night of polysomnographic recording and a 3T MRI acquisition including a diffusion sequence. Fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity

(AD), and radial diffusivity (RD) were computed from a diffusion tensor imaging model. Tract-based spatial statistics were carried out for voxelwise white matter diffusion analyses. SS were automatically detected on artefact-free non-rapid eye movement (NREM) sleep on F3 (linked-ears). Whole brain voxelwise mediation analyses were performed to estimate whether aging shows an indirect effect on SS characteristics through white matter diffusion markers. *Results:* Compared to the young, middle-aged subjects showed lower SS amplitude, density and duration in F3 ($p<0.001$). Aging effects on SS amplitude were found to be mediated by decreased FA and increased MD and RD, predominantly in the frontal region including the anterior thalamic radiation, minor forceps, inferior fronto-occipital fasciculus, superior longitudinal fasciculus and uncinate fasciculus ($p<0.05$), showing indirect effects of age on SS amplitude through white matter diffusion. Diffusion tensor decomposition further suggested that the main white matter effect is driven by higher diffusion throughout the axons membrane. Similar indirect effects of age were found for SS duration through decreased AD in similar regions but also in parts of the corticospinal tract ($p<0.05$). *Conclusion:* Our results indicate that white matter diffusion modifications in frontal areas, suggestive of axonal and myelin degeneration, partially explain age-related changes in specific SS characteristics in the same region. Further analyses will estimate whether these regions where indirect effects were found are specific to frontal SS or implicated in more diffuse brain NREM sleep oscillations.

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DECREASED SIGMA-BAND EEG CONNECTIVITY IN AGING

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Keywords: Electroencephalography, imaginary coherence, aging, NREM sleep, sleep spindle, EEG connectivity

Objectives: Sleep is a largely dynamic process and cerebral functional connectivity (FC) varies across the night. EEG coherence assesses how signals fluctuate together and can be used as a cerebral FC index. Aging is associated with impor-

tant NREM sleep and white matter modifications, but the impact of aging on cerebral FC during sleep is unknown. Here, we aimed to compare NREM sleep EEG coherence in young and older individuals with a specific emphasis on frequencies associated with spindles (sigma).

Methods: One night of polysomnography was recorded in 30 young (20-30yo) and 29 older (50-70yo) healthy participants. Imaginary coherence[1] (for sleep stages N2 and N3 combined) was computed separately for the first three cycles of the night between interhemispheric and intrahemispheric pairs of electrodes. Spectral bands were subdivided in 4Hz intervals for which imaginary coherence values were averaged. Significant differences in connectivity ($p<0.01$) were computed using nonparametric statistics and were corrected for multiple spatial comparisons between the electrode pairs.[2]

Results: Compared to the young subjects, older subjects showed lower intra and interhemispheric imaginary coherence in the 11-15Hz band in prefrontal, frontal and central derivations for cycles 1 and 2 and in prefrontal and frontal derivations for cycle 3.

Conclusions: Corticothalamic connections are crucial for thalamic oscillation coherence[3] and human brain imaging studies suggest that their integrity is compromised in aging, especially in anterior regions.[4] Future studies should evaluate whether age-related decrease in sigma EEG coherence is explained by white matter integrity.

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CHARACTERIZING SLEEP SPINDLES IN 11,630 INDIVIDUALS

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Keywords: Sleep spindles, genetics, aging, wavelet analysis

Sleep spindle activity has been associated with various aspects of learning and memory and is a potential biomarker of neuropsychiatric disease risk [1, 2]. Although twin studies indicate that spindle activity is partially heritable [3], specific genes are yet to be identified. Molecular genetic studies of sleep spindles in humans will likely require large samples, robust automated spindle detection algorithms and careful consideration of possible confounders. Towards these ends, here we detect and characterize spindle phenotypes in 11,630 individuals (aged 5 to 95) as a prelude to future genome-wide molecular studies.

We compiled whole-night polysomnography, demographic and medical data from the US National Sleep Research Resource [4], yielding over 20,000 hours of N2 sleep. After automated artifact rejection, we applied band-pass filtering and wavelet analyses to detect spindles from two central electrodes, centered at both canonical (13.5Hz) and variable (8-18Hz) frequencies. We identified and corrected a potential confound of body mass index on spindle density, mediated by increased ECG contamination of EEG signals. Based on a subset of 2,622 individuals with sleep data at two time-points (approximately 5 years apart), spindle and spectral phenotypes demonstrated high test-retest reliabilities.

Spindle density, frequency, duration and amplitude showed distinct developmental trajectories across the lifecourse. We characterized spindle parameters in relation to general sleep architecture, spectral power and other demographic and clinical measures including educational attainment, disordered sleep and medication use. We additionally considered heterogeneity in spindles across the night and also during N3 sleep. Finally, for 730 individuals, at least one first-degree relative was present in the dataset, enabling the estimation of heritability and genetic correlation across all aforementioned sleep phenotypes. In general, we observed evidence for robust genetic influences on spindle phenotypes, controlling for a range of demographic and clinical covariates. This work can inform future genetic studies – in this and other samples – that aim to understand better the genetic architecture of spindles and their relation to neuropsychiatric disease.

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Methodological Corner

A NEW, MINIMAL ASSUMPTION, SPINDLE ANALYSIS METHOD, APPLIED TO PTSD SLEEP

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Keywords: PTSD, method, spindle analysis

Neurophysiological mechanisms underlying spindling involve interactions between inhibitory cells in the thalamic reticular nucleus (RE) and bursting thalamocortical (TC) relay neurons. Gradual cell recruitment in RE-TC-RE loops is linked to the waxing of spindles. The cause of spindle waning is less clear, but a depolarizing action by the thalamic IH current may be involved. The influence of these neurophysiological mechanisms on spindle morphology in the scalp EEG is still to be clarified.

Given the transient nature of spindling and incomplete knowledge of precise underlying mechanisms the analysis of scalp EEG spindles may best be performed with a minimum of assumptions and high temporal resolution. We have recently implemented these requirements in a statistical approach to determine the dynamics of sigma power in the scalp EEG.[1] Here, we apply this automated procedure to an analysis of spindling in post-traumatic stress disorder (PTSD).

The algorithm entails EEG band-pass filtering (11.0–16.0 Hz) using a FIR-filter. The standard deviation of the signal is computed with a moving window of 0.2 second. The resulting power has a time resolution of the sample rate of the signal. Waxing and waning characteristics of sigma fluctuations are represented by the time-variant characteristics of the power. A pattern recognition algorithm detects all waxing/waning couplets. Various characteristics like peak power, total intensity, duration, symmetry, polarization / depolarization speed, etc., are calculated for each waxing and waning couplet. In addition, power dynamics in different spindle bands are calculated.

Preliminary findings indicate increased spindles in PTSD patients compared to traumatised control subjects without PTSD, possibly reflecting excessive reprocessing and consolidation of trauma-related memories. The statistical analyses without prior assumptions revealed details regarding spindle abnormalities in PTSD that would likely have been missed by analysing only heuristically detected spindles.

In conclusion, analysing waxing/waning patterns in the sigma band, without prior criteria like amplitude, duration etc. appears useful. The spindle abnormalities in PTSD may form part of the mechanism through which the profound sleep disturbance in this disorder contributes to emotional memory problems.

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3. Review PTSD sleep

SPISOP – FAST REPLICATION AND SHARING OF SLEEP EEG ANALYIS IN ONE TOOLBOX

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Keywords: EEG, sleep spindles, slow oscillations, power spectrum, big data, feature extraction, signal detection analyses

Replicating a comprehensive sleep EEG analysis is a challenge, but is it the only means to overcome the prevailing conflicts in reports on the mechanisms and function of hallmark sleep EEG features, including sleep spindles. Even minor methodological changes at the base of sleep EEG analysis can have vast consequences on conclusions drawn from them and complicate their communication to other researchers. To address the abundance of methodological variation and their implementation to extract any sleep EEG feature is an overload to any researcher. Those difficulties do not only hinder a researcher's investigation and focus but also undermines the progression of the field. Furthermore, any sleep feature is hard to understand in isolation and requires parallel assessment of related other features to investigate their putative relationships, i.e. temporal, phasic and topographical occurrence and co-occurrence and their sources. This calls for a free and easy to use tool for the execution and sharing of such sleep EEG analyses approaches to be replicated rapidly by other researchers using the same standards or alterations of them. Here I introduce 'SpiSOP', a parallel computing toolbox for Matlab to be used by non-experts to address the easy and fast processing of large datasets and the quick exchange of used methodology. On basis of sleep scored EEG data it supports automated detection and reporting of (fast and slow) sleep spindles, slow oscillations, their co-occurrence or search for respective sleep stage matching 'non-events' as well as power density of specific spectra or frequency bands. Automatized exclusion of typical confounding sleep EEG artefact epochs is also supported. Analysis is according to wished channels,

their various combinations, specified dynamic sleep stages, various detection thresholds and further parameters. Methods are standardized and support most basic features as they were reported in current sleep and memory research. Replication of results is fast and requires only minimal intervention of the researcher with minor adaptions and to adjust vastly flexible standard parameters. Core functions are based on the Fieldtrip toolbox to cope with almost any available EEG data and recording settings. SpiSOP does not require any Matlab programming skills but only a short introduction in handling. A complete standard EEG analysis can be set up, changed and started within minutes and the setup shared to others to be replicated on other datasets. This represents a first step in analysing large sleep data quanta across researchers, studies, designs, tasks and species, and thus simplifies a precise understanding of the fine-tuned relationships of sleep EEG phenomena.

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Epilepsy / Biomarkers-1

SLEEP SPINDLES IN EPILEPSY

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Sleep spindles are thalamically driven hallmark EEG waves of non-REM sleep involved in specific memory consolidation processes, thus having essential role in synaptic plasticity in learning. Beside the wave type behavior of sleep spindles, they are characteristic for paroxysmal and reactive occurrence, sharing this feature with epileptic paroxysms. Sleep spindles harbor abundant amount of high frequency oscillations another membrane oscillation that has strong relationship with memory consolidation and epileptogenicity.

Sleep spindles had been associated to epileptogenic process long ago in acute dysinhibition type of animal models of epilepsy showing spindles transforming to spike-wave discharges that was questioned by others.

To understand the relationship between epileptic and spindle activities we need data on the cortical generators, and also cortical and thalamic appearance of both. Invasive presurgical evaluation with subdural electrodes gives excellent possibilities to introduce intracortical sensors in human neocortex to analyse layer specific information of spindling. Recent advancement of neuromodulation therapy in epilepsy, the anterior-thalamus DBS intervention, opens a special window to look into the thalamic processes in epilepsy.

We can conclude that if, according to the sentence, epilepsy is the price that we pay for our ability to learn, then sleep spindles are our wallets.

SLEEP SPINDLES AND ABSENCE EPILEPSY IN WAG/RIJ RATS

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Keywords: Absence epilepsy, EEG, rat model, time-frequency analysis, continuous wavelet transform

The WAG/Rij strain of rats is a well-known genetic model of absence epilepsy [1]. Absence seizures in these animals appear spontaneously and they are accompanied by characteristic hypersynchronous spike-wave discharges (SWD) in the

EEG. The number and duration of absence seizures in WAG/Rij rats increase with age. SWD and sleep spindles share the same thalamocortical neuronal circuitry, however, a physiological relationship between them is still a subject of debate [2, 3]. With the aid of continuous wavelet analysis, we examined time-frequency parameters of sleep spindles in WAG/Rij rats and in non-epileptic control Wistar rats. First, we found that the mean frequency of sleep spindles in WAG/Rij was 1.9 Hz lower than in non-epileptic control Wistar rats (11.3 vs 13.2 Hz at the age of 9 months) [4]. The mean frequency in about 40% of sleep spindles in WAG/Rij was below 10 Hz, and in Wistar rats this percentage was significantly lower (11-17%) [4]. Therefore, absence epilepsy in our animals was associated with the occurrence of slow (<10 Hz) sleep spindles. Second, we examined the instantaneous frequency of sleep spindles. In non-epileptic controls as well as in young WAG/Rij rats (in which epileptic activity was not fully developed, preclinical stage), the instantaneous frequency increased from the beginning to the end of sleep spindles [5]. This effect was no longer present in old WAG/Rij rats who expressed full-blown SWD in the EEG and showed no changes in the intrinsic frequency of sleep spindles.

In general, the inner frequency parameters of sleep spindles convey important (prognostic and diagnostic) information about absence epilepsy.

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GENETIC ABSENCE-RELATED SPIKE-AND-WAVE DISCHARGES TURN OFF WHILE SPINDLES TURN ON DURING THE WAKE-SLEEP TRANSITION

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The pathophysiological mechanisms underlying the electrogenesis of absence-related spike-and-wave discharges (SWDs) are still elusive. Since the second half of the 20th century, in vivo and in vitro, neurophysio-pharmacological studies have been supporting the concept that recurrent SWDs originate from thalamically-generated sleep spindles. Recent in vivo electrophysiological findings from Genetic Absence Epilepsy Rats from Strasbourg (GAERS) support the hypothesis that SWDs are generated during quiet immobile wakefulness in the somatosensory thalamocortical system from a physiological cortically-generated theta (5–9 Hz) rhythm, this wake-related cortical activity being more pro-epileptogenic than thalamically-generated sleep spindles. Therefore, in the present study we wanted to establish a link between SWDs and spindles. We performed high-resolution electroencephalographic recordings of the frontoparietal cortex in GAERS during the wake-sleep transition, under the influence of the spindle promoter carbamazepine or barbiturate, the anti-absence ethosuximide or the psychoactive drug ketamine. Recurrent SWDs systematically turned off while sleep spindles turned on during the wake-sleep transition. During the first stages of sleep SWDs systematically became abortive, often extended by spindles. These findings comfort the hypothesis that genetic absence-related SWDs originate from a wake-related corticothalamic theta oscillation, not from sleep-related thalamocortical spindles.

Affective Processes / Consciousness, Memory

THE EFFECT OF SLEEP AND NEUROFEEDBACK ON SLEEP QUALITY AND MEMORY CONSOLIDATION IN INSOMNIA PATIENTS

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The suggested functions of sleep are manifold, involving adaptive strategies, physical recovery and more recently "offline" information reprocessing.

Here we now present a study in which the same type of declarative (word-pair learning) and procedural (finger-tapping) task was conducted four times (weeks apart) in the evening with subsequent interference manipulation the next morning in insomnia patients. In addition 36 healthy controls spend 3 nights in the laboratory to test for sleep-dependent memory consolidation in participants without sleep complaints. In addition, 12-15Hz "sensorimotor rhythm" (SMR) as well as placebo "neurofeedback" was conducted (12 sessions each) in the insomnia group.

With respect to the susceptibility to interference it becomes evident that interfering material after sleep affects the declarative memory domain much more than the procedural one. Forgetting from initial evening learning to a delayed recall after a week (as well as after interference) is also found more pronounced in insomnia patients than healthy controls.

Analyses of the sleep EEG and sleep spindles reveal a trait-like relationship between spindle activity (SpA) and (i) the initial learning levels in the declarative memory as well as (ii) an association with the declarative overnight memory change. Spindles seem to support the "offline consolidation" process.

Last but not least our double-blind neurofeedback protocol indicates that patients suffering from insomnia are able to enhance SMR-power and sleep spindles over the course of 12 SMR training sessions. Yet direct benefits for sleep quality or memory consolidation were not observed, rather the subjective sleep complaint decreased unspecifically across both conditions.

Current results indicate that healthy as well as younger, subclinical insomnia patients do show associations of overnight memory performance and (fast) sleep spindle activity. These participants are also able to increase spindles by means of instrumental 12-15Hz EEG conditioning and benefit in better sleep quality and memory performance. Older and more severe insomnia patients on the other hand seem to be unable to efficiently increase their SMR (and consequently spindle activity) and therefore lack the beneficial outcomes.

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SLEEP SPINDLE-DEPENDENT MECHANISMS TO REORGANIZE THE FOREBRAIN

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Sleep spindles are originated in the thalamic reticular nucleus in the absence of the depolarizing neurotransmitters norepinephrine, serotonin, and acetyl-

choline. All three neurotransmitters are uniquely absent during the transient transition to REM (TR) sleep state, also known as ascending Stage 2 sleep in humans. Spindles and Stage 2 sleep have been associated with both intelligence and memory improvements across sleep in a preponderance of studies. Through a series of experiments we have found that the unique absence of norepinephrine during REM sleep and Non-REM sleep spindles allows an orderly incorporation of new information into established schema. Reversal learning tasks like the extinction of fear, remapping a route, or remembering where your car is parked today as opposed to yesterday, requires depotentiation as well as long term potentiation of synapses. Using a variety of manipulations and techniques, we have tested the role of norepinephrine, REM sleep, and sleep spindles in learning and reversal learning, including multiple single unit recordings in the freely behaving rat hippocampus and locus coeruleus, local micro infusions of norepinephrine, use of selective norepinephrine reuptake inhibitors (e.g. the antidepressant desipramine), REM and TR sleep deprivation, optogenetic stimulation of the locus coeruleus, and appetitively-motivated hippocampus and procedural tasks as well as aversive learning. Experimental results have resulted in a coherent theory of how silences in the locus coeruleus noradrenergic system during TR and REM sleep, and bursts during non-REM sleep, reshape the synaptic networks encoding memory and protect them against spurious modifications. These results also reveal how manipulations or failures of this sleep-dependent system can lead to memory impairments and emotional disorders like memory loss in Alzheimer's disease and post-traumatic stress disorder (PTSD).

ROLE OF SLEEP SPINDLES AND SIGMA POWER ACROSS MULTIPLE SLEEP BOUTS ON EMOTIONAL MEMORY IN EARLY CHILDHOOD

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Keywords: Nap, childhood, emotion

From infancy to early childhood, sleep is distributed across naps and overnight sleep, both of which benefit cognition. We examined the interaction between these sleep bouts on emotional memory in young children. Children (34–64 months) were presented with neutral faces paired with mean or nice descriptions. Recognition of the images was probed immediately following both a nap and an equivalent wake interval (within-subjects design), and again 24-hrs after encoding. Recognition accuracy did not differ immediately following the nap compared to wake. However, following overnight sleep, recognition accuracy

was greater when children napped the previous day. Specifically, sigma power in the nap and in the overnight sleep following a nap resulted in improved recognition memory for positive stimuli. These results suggest that distributed sleep bouts can interact to benefit memory consolidation in early childhood.

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Epilepsy / Biomarkers-2

REDUCED SLEEP SPINDLES IN SCHIZOPHRENIA: A TREATABLE ENDOPHENOTYPE THAT LINKS RISK GENES TO IMPAIRED COGNITION?

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Keywords: Schizophrenia, sleep spindles, memory, cognition, genetics, endophenotype

Although schizophrenia is defined by waking phenomena, abnormal sleep is a common feature. In particular, there is accumulating evidence of a sleep spindle deficit. Sleep spindles correlate with IQ and are thought to promote long-term potentiation and enhance memory consolidation. I will review evidence that reduced spindle activity in schizophrenia is an endophenotype that impairs sleep-dependent memory consolidation, contributes to symptoms and is a novel treatment biomarker. Studies showing that spindles can be pharmacologically enhanced in schizophrenia and that increasing spindles improves memory in healthy individuals suggest that treating spindle deficits in schizophrenia may improve cognition. Spindle activity is highly heritable and recent large-scale genome-wide association studies have identified schizophrenia risk genes that may contribute to spindle deficits and illuminate their mechanisms. My talk will highlight the importance of deficient sleep-dependent memory consolidation among the cognitive deficits of schizophrenia and implicate reduced sleep spindles as a potentially treatable mechanism. The ultimate goal of this research program is to forge empirical links in causal chains from risk genes to proteins and cellular

functions, through to endophenotypes, cognitive impairments, symptoms and diagnosis, with the hope of advancing the mechanistic understanding and treatment of schizophrenia.

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SLEEP SPINDLE DEFICIT IN SCHIZOPHRENIA: A CRITICAL OVERVIEW AND NOVEL FINDINGS

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Keywords: Schizophrenia spectrum, psychosis, dense-array EEG

Schizophrenia (SCZ) is a heterogeneous syndrome with a chronic course that leads to relevant psychosocial impairment. The clinical phenomenology is typically defined by "positive" symptoms such as hallucinations and delusions and "negative" symptoms such as avolition and anhedonia, which are often associated with a progressive cognitive decline. Despite intensive research on the etiopathogenetic mechanisms of this disorder, clearly defined biological markers are still lacking. On the neurophysiological level, a marked reduction of sleep spindle activity has recently been described in patients with both chronic, medicated and drug-naïve, early-course SCZ (1,2) . Whether such deficit can be considered a reliable marker of or an endophenotype of the disorder remains to be cleared.

My presentation will give an overview of available findings in order to define the current state of the art and to identify critical limitations to the current published data. I will also present novel, unpublished data from two ongoing studies of our group. In the first, a high-density electroencephalogram (hd-EEG) with 256 channels was used to study a whole night of sleep in First-Degree Relatives (FDRs) of SCZ patients and in a sample of age-and gender-matched healthy control subjects. None of the recruited subjects had received treatment with psychotropic medication. Among several analysed parameters of sleep macrosructure and microarchitecture, hd-EEG measurements revealed a significant reduction of Integrated Spindle Activity (ISAs) in FDR subjects. No relevant differences were observed in terms of spindle density and duration. Preliminary results from a small subgroup of drug-naïve, First-Episode Psychosis patients will also be reported.

Sleep spindle deficit could be a highly unspecific marker of aberrant thalamocortical oscillatory activity that is shared by severe neurodevelopmental/neurodegenerative disorders. However, spindle activity seems to adequately differentiate patients with SCZ from other patients with typical late-adolescence to young-adulthood onset disorders in psychiatry. Progression of knowledge in this field will lead to a more profound understanding of the relationship between thalamocortical neurophysiology and complex interactions of cognitive, emotional and behavioural function.

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MICROSTRUCTURE OF SLEEP SPINDLES IN A MULTIPLE SCLEROSIS ANIMAL MODEL

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Keywords: Multiple sclerosis, sleep spindles, cuprizone

Cuprizone-induced demyelination is a known animal model for multiple-sclerosis (MS) [1]; here we study the effects of an eight weeks cuprizone intake on the sleep spindles architecture in the rat. For this, seven days after electrode implantation surgery, we performed a 72h EEG (ipsilateral frontal and parietal sites) and neck EMG recording in four free moving Wistar rats; then, a daily cuprizone (2 g/kg/day) food was given for eight weeks and a final 72h recording was made. Manual sleep staging was done for all recordings, and a 24h light cycle (12 h day and 12 h night) before and after cuprizone from each rat were chosen for further analysis. Power in three frequency ranges within the spindle band (10–14, 14–18 and 10–18 Hz) were computed for slow wave sleep (SWS) stages in 10s epochs and an automatic sleep spindle detection was performed. For each detected event, the preferential frequency and duration were obtained for the two EEG electrode sites as well as the correlation and phase synchronization between both cortical locations. Power was significantly reduced (Permutation test (PT): $p < 0.001$) in two rats and increased in the other two (PT: $p < 0.001$) for the three

frequency bands. After cuprizone intake, an increase on the number of spindles (t-test: p <0.01) was found for all rats, especially for the slow spindles events (t-test: p<0.001). Furthermore, the preferential frequency for individual spindles was significantly reduced in all subjects (PT: p <0.001), and the spindle duration was significantly reduced (PT: p <0.001) in two subjects and in the other two only at night time. Finally, phase synchrony and amplitude correlation during spindles between electrodes was increased (PT: p <0.001) across all subjects. Our results provide evidences of sleep disturbances in MS subjects, disturbances that have been proposed as an important target for possible MS treatments [2]. Furthermore, sleep spindles are important hallmarks of neural physiology and their characteristics have been proposed as possible biomarkers for clinically relevant entities such as dementia [3]. To our knowledge, this is the first study on the microstructure sleep patterns in MS animal models.

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Stimulating Sleep Spindles

RATIONAL DESIGN OF NON-INVASIVE BRAIN STIMULATION TO TARGET OSCILLATIONS

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Keywords: Transcranial current stimulation, feedback stimulation, transcranial alternating current stimulation (tACS), sleep spindles, memory consolidation

Cortical oscillations have emerged as a promising target for non-invasive brain stimulation with periodic stimulation waveforms. In particular, transcranial current stimulation with a sine-wave stimulation waveform (transcranial alternating current stimulation, tACS) has been shown to modulate cortical oscillations (reviewed in [1]) and to enhance cognitive function associated with cortical oscillations such as sensory processing, fluid intelligence, and creativity (reviewed in [2]). In this talk, I will provide an overview of how tACS paradigms can be developed using rational design, which combines insights into the behavioural

relevance of specific oscillatory brain activity patterns with a mechanistic understanding of how weak electric fields modulate network dynamics. In particular, I will demonstrate how network oscillations are particularly sensitive to periodic perturbation and review how computer simulations of large networks of spiking neuron models have provided testable hypotheses on the principles of target engagement. I will then discuss the existing experimental evidence for these target engagement rules and attempt to establish practical principles that need to be taken into account when designing non-invasive brain stimulation paradigms for the modulation of brain oscillations. Lastly, I will highlight recent results from a study where we leveraged these design principles to develop real-time closed-loop tACS to target sleep spindles. In this study, we selectively enhanced the oscillation power in the spindle frequency band (thus demonstrating successful target engagement) and found a significant correlation with enhanced motor memory consolidation. This approach not only helped to demonstrate a causal role of sleep spindles in memory consolidation but also may become an effective treatment for neurological and psychiatric disorders associated with impaired sleep spindles.

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THE IMPACT OF TRANSCRANIAL ELECTRICAL STIMULATION DURING SLEEP ON MOTOR SEQUENCE LEARNING

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Keywords: Sleep spindles, nap, motor memory consolidation, tACS, otDCS, TES

Transcranial electrical stimulation (TES) allows us to modulate specific brain oscillations. There are two different types of oscillating TES [1]: (i) alternating at a certain frequency (tACS), and (ii) alternating and direct current combination (otDCS). Previous evidence suggests a strong connection between sleep spindles (11-15Hz) and the memory consolidation of motor tasks [2]. We therefore strive to investigate the influence of sleep spindle TES during a daytime nap on the memory consolidation of a motor sequence learning task. 17 healthy subjects

(7 male, 10 female) aged between 19 and 28 years (*M*=21.5 years, *SD*=2.2 years) were tested on 4 consecutive days after habituating to a controlled sleep rhythm for 5 days (randomized within-subject design). On the first day the EEG and TES setup was applied during nap for adaptation purposes. On the following 3 days, the subjects were randomly assigned to 3 stimulation conditions: (i) sham, (ii) tACS, and (iii) otDCS. Before the nap, they were trained on the finger-tapping task (FTT) [3], during which they had to type a sequence of five numbers (e.g. 1 3 4 2 1) for six minutes. A different sequence was used on each day. TES was applied at Fz and Pz. Stimulation started after the participants went to bed and lasted for 35 minutes, separated in alternating 5 minutes blocks (on/off), summing up to 20 minutes of stimulation, followed by a 50 minutes stimulation free period. The individual sleep spindle frequency was used for each participant. A 2x3 repeated measures ANOVA with the factors TIME (pre nap / post nap) x STIMULATION CONDITION (sham, tACS, otDCS) disclosed a significant main effect for TIME ($F(1,16)=18.7$, $p<.001$) on performance during the FTT. Post-hoc pairwise comparisons revealed a significant increase in performance restricted to the tACS ($t(16)=-2.37$, $p=0.03$) and the otDCS condition ($t(16)=–6.75$, $p<.001$). We further found a significant relationship ($r=0.49$, $p=0.048$) between the number of fast sleep spindles at C3 and over-nap performance improvement only, in the tACS condition. The current results suggest that TES with an individually adjusted sleep spindle frequency during a daytime nap improves memory consolidation for motor sequence learning.

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SPATIAL ORGANIZATION OF SLEEP SPINDLES DURING ACOUSTIC PHASE-LOCKED STIMULATION OF NREM SLOW WAVES

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Keywords: Induced sleep spindles, sleep slow oscillations, phase lock stimulation, acoustic stimulation

Sleep spindles (SS) are driven by cortical slow oscillations (SO) during NREM sleep. In particular, it has been shown that acoustic phase-locked stimulation during the positive cycle of the SO enhances spindle activity, especially in frontocentral regions [1]. Despite this, little is known about the differences in the functional modifications of the underlying brain networks when the on-phase stimulus is performed during K-complexes (KC) or SO-trains (SO-t) and at different sub-phases of the positive cycle. Although it is considered that SO and KC share the same neural mechanisms [2], these oscillations may represent different sensory processing and arousal processes [3]. To get insight on this, six healthy subjects (mean age: 23 ± 1.6 years) were registered with a 10–20 EEG system during a 120-min afternoon nap under stimulus and sham conditions. In stimulus condition, a real-time algorithm for automatic detection and stimulation delivered two consecutive acoustic pulses at targeted phases of the SO. Phases of the positive cycle were categorized in three groups: rising slope (G1), cycle maxima (G2) and falling slope (G3). For each electrode, the induced spindle activity (10-15Hz) for two subsequent SO cycles (~2s) was examined from the inter-trial time-frequency power, aligned to the first stimulus at the respective phase. Spatial organization was studied based on the prevalence of significant increase ($p < 0.05$) in spindle activity, and the spindle synchronization was measured with the phase locking value between all electrode pairs for stimulus and sham conditions. KC and SO-t in N2 and N3 were further identified for offline analysis. We report that for both KC and SO-t, the increasing of spindle activity was prevalent in the frontocentral and frontopolar regions when stimuli were given at G1 and G2 phase groups. The increment of temporal SS activity was significant during SO-t stimulations. Phase synchrony presented a significant variation between stimulus and sham conditions, but the increasing or the decreasing of synchrony was not consistent between subjects and electrode pairs. In particular, frontocentral regions were more prone to differences in synchrony during G1 and G2 phases, and parietotemporal areas to differences in synchrony during G3 phases for SO-t. Furthermore, differences were observed in the level of synchrony variation between KC and SO-t for each subject, but these differences were not significant. Taken together, these results suggest that stimulation during the rising slope and peak of SO is more effective for SS enhancement and that SS synchrony is affected by the phase of the stimulus, but the synchrony variation is not stimulus dependent. In general, no major differences were found between KC and SO-t stimulations, indicating that SS can be induced at early N2 stages using this type of stimulation.

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Behavior, Cognitive Performance and Memory

SLEEP AND DIRECTED FORGETTING: THE ROLE OF NAPPING IN THE CONSOLIDATION OF RELEVANT AND IRRELEVANT MEMORIES

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Keywords: Napping, memory consolidation, EEG, sigma activity

A growing number of studies support the idea of an active and positive effect of sleep on memory consolidation (Diekelmann & Born, 2010). This positive effect is assumed to be the result of a spontaneous memory reactivation during sleep, along which important memories are replayed and reinforced (Oudiette & Paller, 2013). The importance of a memory could be determined by instructions and intentions, giving us the opportunity to compare the consolidation of relevant and irrelevant memories. In the current research we aimed to manipulate the perceived relevance of memory elements and examined the effects of daytime naps on memory performance within the frames of a list-method directed forgetting paradigm. Our participants were university students between the age of 18 and 35. According to the procedure of the list-method directed forgetting task they were randomly divided into napping and awake groups, and remember and forget subgroups. Traditional EEG was used to monitor the naps. The research is currently at the data analytical phase, but our preliminary analysis indicated a significant directed forgetting effect after two-hour delay in both groups (nap, wake). This effect was more prominent in the nap group. The examination of the performance in the napping group and their sleep microstructure shed light on some interesting correlations. Our results indicated a positive association between the spectral power of parietal sigma (13–16 Hz) activity and the recall of the elements of the to-be remembered word list within the forget subgroup. This result could support the assumption (Gais, Mölle, Helms, & Born, 2002) that sigma activity (and related sleep spindles) during an afternoon nap play a prominent role in the enhancement of newly acquired, relevant information. Final results will be presented at the conference.

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SLEEP SPINDLES IN INFANT MEMORY CONSOLIDATION

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Keywords: Infants, learning, memory consolidation, categorization, generalization, word meanings

Numerous studies in adults have evidenced that sleep promotes the consolidation of memories. Recently, first studies have shown that sleep affects memory even in early infancy[1, 2]. In these studies, infants, who had stayed awake after learning, forgot their recent experiences, while during sleep, infants consolidated the newly encoded information. Moreover, in infants aged from 9 to 16 months sleep spindles were found to be involved in the fusion of recently encoded similar object-word pairings into generalized meanings of words[1].

In the present study, infants between 6 and 8 months of age were exposed to a similar, but less complex learning task. Eight novel words were used as labels for eight novel object categories. During the training session, each word was presented once with each of eight similar objects forming a category. In a control condition, eight words were paired once with each of eight distinct objects. In the deferred memory test, four novel objects of each category were presented ones with the trained category name (correct pairings) and ones with the name of another category (incorrect pairings).

As in older infants, the event-related potential (ERP) of the younger infants did not show a generalization effect during learning. Likewise, the brain responses of infants who had stayed awake during the retention period, did not differ between correct and incorrect pairings in the memory test, and therefore did not evidence generalized memory. Infants of the nap group strongly varied in their nap duration (10–74 min). In the whole nap group, the generalization effect was also not found, but the ERP difference in the time range of the expected generalization effect was correlated with total sleep time (TST), and in particular with the time spent in sleep stage 2. When performing a median split according to N2 duration, the group with long N2 periods (mean 18.7 min), but not the

group with short N2 periods (mean 4.7 min), showed the generalization effect observed in older infants. Moreover, in the long-N2 group, spindle activity (EEG power density) was correlated with the generalization effect, while in infants of the short-N2 group, such a correlation was missing, even though power density in the spindle band did not significantly differ between groups. The results suggest that the spindle-driven neural mechanism that supports sleep-dependent generalization is established very early in human life. However, at the age of 6 to 8 months, sufficient N2 time is necessary for sleep spindles to be effective.

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SIGMA FREQUENCY DEPENDENT MOTOR LEARNING IN WILLIAMS SYNDROME

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Keywords: Sigma frequency, sleep spindle, Williams syndrome, motor sequence learning

Williams syndrome (WS) is a neurodevelopmental disorder with a genetic origin that is characterized by atypical sleep architecture, accelerated sigma peak frequencies (Bodizs et al., 2012), and deficits in fine motor function. Learning of fine motor sequences has practice dependent and offline consolidation phases. The latter is featured by sleep-dependent improvement in performance without any subsequent practice. Post-sleep improvement has been shown to correlate with NREM sleep parameters in the sigma frequency band: fast-sigma oscillations and sleep spindles, especially fast sleep spindles, contribute to the activation of the cerebral network involved in consolidation (Barakat et al., 2013; Morin et al., 2008).

The present study investigated the relationship between motor learning characteristics and sleep parameters in WS. Improvement in a four-element finger tapping (FT) sequence was measured during a five-day-practice session in four-

teen individuals with WS and typical development (TD). The same WS individuals participated in whole night ambulatory polysomnographic recordings. Although these were not simultaneous with the learning sessions, we analysed the relationship between FT and sleep measures: correlations of z-transformed EEG spectral values (8–16 Hz) and automatically detected sleep spindle features with learning performance were calculated.

With respect to improvement in FT performance, we found improvement in accuracy both in WS and in TD following the first night, with WS participants showing great individual variability. Earlier reports on WS vs TD differences in sigma band activity and peak frequency were partially replicated in this subgroup. Participants with higher parietal peak frequency had a decreased Day-1 offline learning improvement in terms of FT accuracy ($r = –.60$; $p = .03$). On the other hand, bins of z-transformed 11.5–13.25 Hz EEG power correlated positively with offline improvement in accuracy following the first night in WS ($r_{max} = .70$; $p = .007$). When long term learning capacity (practice-dependent and offline improvement over 5 days) was analysed by aggregating both FT accuracy and speed, WS subjects fell below TD participants. This long term learning capacity was also correlated with higher slow sleep spindle amplitude in WS ($r_{max} = .65$; $p < .02$). We conclude that the substantial motor learning deficiency found in WS might be a result of the altered function of neural networks involved in sigma band activity (sleep spindling).

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DYNAMIC TEMPORAL RELATIONSHIPS BETWEEN SLEEP SPINDLES AND SLOW OSCILLATIONS DURING SLOW WAVE SLEEP AS A MECHANISM FOR OFFLINE INFORMATION PROCESSING

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Keywords: Sleep spindles, slow oscillations, temporal relationship, SRTT, offline processing

Both slow oscillations (SOs) and sleep spindles, the major neuroelectric signatures of slow wave sleep (SWS), may support offline memory consolidation (Huber et al., 2004; Marshall et al., 2006). However, whether they act concurrently is not known (Mölle et al., 2002). Here, we analysed the temporal associations between SOs (0.5–4 Hz) and slow (9–12 Hz) and fast (13–16 Hz) spindle activity

during SWS to explore if co-existent SOs and sleep spindles represent a specific functional mechanism for offline information processing. A visual serial reaction time task (SRTT) containing a hidden rule about stimulus/response sequence, was learned implicitly before sleep either on the left or the right side to activate predominantly the right or the left hemisphere. To characterize the temporal stability of spindle activity accompanying SO generation independently of spindle power, multi-channel sleep EEG triggered by SO during SWS was decomposed and analysed in the time-frequency domain. Effects of pre-sleep side of training, pre-sleep gain of implicit knowledge about the hidden rule, and post-sleep awareness of the hidden rule were examined. Slow spindle activity was temporally linked to the waning down-state of SO, whereas fast spindle activity emerged during the up-state of SO (Mölle et al., 2002). Pre-sleep learning, as compared to a night without learning, modulated the strength of temporal associations between spindle activity and SO in directions of both increase and decrease (decoupling) at specific cortical regions. The coupling of SO-related slow spindle activity increased in relation to enhanced awareness of task regularity after sleep. In contrast, a post-learning temporal decoupling between SO and fast spindle activity corresponded topographically to the inter-hemispheric asymmetries of functional activations during learning in the left or right hemisphere. These results provide original evidence for the functional role of the temporal associations between SO and spindle activity during SWS in offline information processing, different for slow and fast spindle activity. It is demonstrated that temporally-linked SO and sleep spindle activity are involved in local sleep circuits distinct from those engaging spindle power.

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DIFFERENTIAL EFFECTS OF SO-TDCS ON MEMORY

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Keywords: Memory, transcranial weak electric stimulation, slow oscillation, spindle

Transcranial slow oscillatory weak electric stimulation has been applied during NREM sleep to modulate ongoing brain electric activity and improve memory

consolidation in several studies. Beneficial effects on memory retention have been found (e.g. 1–3). Failure to improve memory with slow oscillatory stimulation has however also been reported (e.g. 4, 5). Furthermore, slow oscillation stimulation during NREM sleep has been shown to differentially modulate or not modulate endogenous EEG slow oscillation and spindle activity. Technical as well physiological and psychological differences between studies may underlie these discrepancies (6).

In the present study we investigated a wide range of memory tasks and analyzed modulatory effects of slow oscillatory weak electric stimulation on several cognitive functions.

Young healthy students (n=14, 8 females) participated in three experimental sessions of nocturnal sleep separated by at least 7 days: Two learning sessions (Stimulation, Sham) and one baseline session without learning. In the learning conditions participants learned on five different memory tasks at night before sleep (mirror tracing, finger tapping, spatial memory, verbal and nonverbal paired-associate tasks) and had to recall memory the following morning. Individual slow oscillating transcranial direct current stimulation (SO-tDCS) (mean frequency 0.82Hz) was applied during early nocturnal NREM sleep in blocks of 5 minutes followed 60-sec stimulation free intervals.

Participants improved on the non-verbal paired-associate task significantly during stimulation condition as compared to sham ($p < 0.01$). During NREM sleep subsequent to the termination of the five blocks of stimulation & sham stimulation, fast spindle (11–15 Hz) count and density were significantly higher than sham at centro-parietal regions (e.g. $p < 0.004$ at Pz). Preliminary analyses did not detect, however, strong correlations between the memory task and endogenous EEG activity.

Our study suggests that externally applied electric fields can alter endogenous oscillations during NREM sleep in the hours following stimulation and that this has an impact on memory consolidation. The paucity of correlations suggests a possible indirect mediator.

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IDENTIFICATION OF MEMORY REACTIVATION DURING SLEEP BY EEG CLASSIFICATION

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Keywords: memory reactivation, slow-wave sleep, memory consolidation

The neural reactivation of memories during sleep is an important mechanism for memory consolidation. As this reactivation is spatially distributed across the brain and can occur at any time during sleep, it is difficult to measure in humans. Here, we test whether memory reactivation can be detected noninvasively in using electroencephalography (EEG).

We used targeted memory reactivation (TMR) [2], in which sounds previously associated with a memory are re-played during sleep to elicit reactivation. Participants performed a serial reaction time task (SRTT) [1], in which a fixed sequence of finger presses was cued using audio/visual stimuli. After intensive training, participants were re-exposed to the audio/visual cues, but asked to imagine making the appropriate finger response ('Imagery' condition). The auditory tones were then re-played during subsequent NREM sleep to trigger neural reactivation. EEG from the wakeful Imagery condition was used to train a density based linear discriminant classifier which was then used to determine how successfully each tone elicited neural memory reactivation in sleep. This showed above chance classification in all 12 participants during slow wave sleep (SWS). In stage two (S2) sleep the classification rate was significantly smaller, suggesting that TMR stimulation is more effective in SWS. The SWS classification rate predicted behavioural plasticity across the sleep period, suggesting that our classification method measures behaviourally relevant reactivation. The classification rate in SWS, but not S2 reduced across the night.

Overall, we developed a multivariate classification method that can identify reactivations during sleep. We used this method to show that features of reactivation in SWS are more similar to task imagining during wake and this is more strongly associated with memory consolidation than reactivation in S2. This approach will provide a useful tool for future investigations of offline reactivation and its role in memory consolidation.

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OLDER AGE AS A MEDIATING FACTOR IN THE ROLE THAT SLEEP SPINDLES PLAY IN DECLARATIVE MEMORY CONSOLIDATION

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Keywords: Sleep, sleep spindles, older adults, declarative memory, ageing

Previous research shows that sleep spindles play a crucial role in the consolidation of declarative and non-declarative sleep-dependent memory. Sleep spindles, characteristic of NREM sleep, are purported to drive memory consolidation through a synchronisation of hippocampal ripple activity in the hippocampal-to-neocortical dialogue. However, this process is not well understood in the ageing population as sleep architecture undergoes significant changes (Fogel et al., 2012). Particularly, sleep spindles show a typical reduction in amplitude, duration and density (Martin et al., 2013). Older adults also show a simultaneous decline in declarative memory. Thus the aim of this research is to investigate sleep spindle characteristics and declarative memory performance in older (60–65yrs) and younger (18–30yrs) females. Using a mixed study design, 14 older women and 15 younger women performed a cued-recall of 90 word pairs and data were obtained during a baseline and experimental night of polysomnographic recording. Preliminary data analysis indicates that older females show a marked reduction in spindle density (at baseline $p = .038$) and memory retention (post-sleep: $p = .032$), compared to younger females. This is in line with the current sleep spindle literature. Further analyses with a larger sample will be conducted. It is hypothesized that (a) higher spindle densities will be seen in younger females and will positively correlate with better memory performance, and (b) reduced spindle density seen in older females will predict less overnight improvement. Such findings might suggest that large spindle reductions typically seen in older adults may be a mediating factor in declarative sleep-dependent memory consolidation.

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VISUALLY DETECTED NREM-S2 SLEEP SPINDLES OF FIVE YEAR OLD KINDERGARTEN CHILDREN CORRELATED WITH MORE PROSOCIAL BEHAVIOR AT BASELINE AND ONE AND FOUR YEARS LATER

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Keywords: NREM-S2 sleep spindles, pre-schoolers, emotional/behavioural difficulties, prosocial behaviour, hyperactivity

Objectives: Sleep electroencephalogram (EEG) spindles are associated with efficient cortical–subcortical connectivity, and intellectual and learning abilities. Moreover, in a previous study (1), visually detected NREM-S2-spindles of 5 year old kindergarten children were correlated with emotional/behavioural characteristics cross-sectionally and at follow-up one year later. Now, we present follow-up data of the same cohort at the age of nine years. Our aim was to examine, if NREM-S2-spindles of five year olds would predict even longer trajectories of emotional/behavioural development.

Methods: A total of 19 children at 5 years of age underwent objective sleep-EEG monitoring in their homes. Emotional and behavioural dimensions were assessed by parents and teachers with the Strengths & Difficulties Questionnaire (SDQ) at the age of 5 years (baseline), and at the age of 6 and 9 years. NREM S2 spindles were visually scored and compared with SDQ dimensions.

Results: A higher number of NREM S2 spindles at the age of 5 years was associated with more prosocial behaviour at the age of 5, 6 and 9 years, as rated by the parents, and with more prosocial behavior and less hyperactivity at the age of 9 years, as rated by teachers. Regarding trajectories of emotional/behavioural development from the age of 5 to 9 years, participants with a higher number of NREM S2 spindles (median-split) at 5 years also presented with more prosocial behavior at the age of 5, 6 and 9 years ($F_{1,16} = 5.60$, $p = 0.03$, $\eta^2 = 0.26$).

Conclusion: Objectively assessed NREM S2 spindles at the age of five years seem to predict dimensions of emotional/behavioural characteristics at the age of six and nine years.

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SPINDLE ACTIVITY RELATED TO MOTOR PROCEDURAL LEARNING IN PATIENTS WITH SCHIZOPHRENIA

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Keywords: Sleep spindles, schizophrenia, MEG, EEG

Sleep spindles, an EEG oscillation characteristic of stage 2 non-rapid eye movement sleep (N2), are thought to mediate sleep-dependent memory consolidation. Patients with schizophrenia (SZ) have reduced sleep spindle density (spindles per minute) during N2 and a correlated deficit in sleep-dependent motor procedural learning. In this study we are examining whether learning a motor procedural task increases spindle activity within the motor network in the nap that follows learning, whether these local increases in spindle activity correlate with post-nap performance improvement and whether SZ patients share the same spatially specific changes in spindle activity as healthy controls.

Fourteen patients with SZ and 9 healthy control participants (still recruiting) were trained on the finger tapping motor sequence task (MST) and their performance tested again after a short nap. Continuous electroencephalographic (EEG) and magnetoencephalographic (MEG) data were acquired simultaneously during the training, the nap period and the testing of MST.

Preliminary analyses suggest that patients show reduced overnight performance improvement compared to the healthy subjects. The source localization of the motor networks that were activated during the performance of the MST task, display subtle differences between the two groups.

Our results replicate previous findings of reduced sleep-dependent motor skill improvement in SZ patients. We are presently conducting analyses to reveal the spatial and temporal characteristics of spindle activity in the subsequent nap and comparing these characteristics between SZ patients and controls.

PHASE-LOCKING OF A SPINDLE-LIKE OPTOGENETIC STIMULATION TO SLOW OSCILLATIONS ENHANCES MEMORY

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Keywords: Optogenetics, closed-loop stimulation, contextual fear conditioning, object place recognition

The brain exhibits a repertoire of rhythms that coordinate the communication between brain structures and thereby provide the foundation for cognition. In particular, during slow wave sleep three cardinal rhythms, namely the <1-Hz cortical slow oscillation, the thalamo-cortical spindle (7–15 Hz), and the hippocampal ripple oscillation (100–250 Hz), have been associated with the consolidation of hippocampal-dependent memory during sleep. By integrating a spindle-like optogenetic stimulation targeting the thalamic spindle generating networks in mice into a closed-loop controlled framework, we demonstrate that the functionality of these rhythms critically depends on their temporal alignment: Only induced spindle activity, which was phase-locked to slow oscillation up-states, showed a promoting effect on memory performance in contextual fear conditioning and object place recognition tasks, whereas an out-of-phase stimulation, i.e. in the absence of slow oscillations, and a control condition without stimulation, remained ineffective. Furthermore, a subsequent EEG analysis confirmed a nesting of ripple activity into the spindle troughs, a mechanism thought to underlie the transfer of memory traces from the hippocampus into neocortical long-term memory. Altogether, these results corroborate that memory formation during sleep is based on a complex dialogue mediated by characteristic brain rhythms from each contributing structure.

GROSS MOTOR SEQUENCE LEARNING AND SLEEP SPINDLE DENSITY

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Keywords: Motor learning, sleep, memory consolidation, motor sequence, gross motor skill

Accumulating evidence suggests sleep spindles increase in number and duration in sleep following new learning and are correlated with performance improvements. We tested the notion of sleep spindle density being functionally related to memory consolidation on a complex gross motor task (arm-reaching-movement). Following an adaptation night with polysomnographic recordings, participants spent two additional experimental nights and, before sleep, either learned a ten-element arm movement sequence (10 blocks of 10 trials) or performed an equivalent motor task without any sequence acquisition. The order of task nights was randomized between subjects. Participants used their non-dominant left hand to produce the sequence task as fast and with as few errors as possible. The night after sequence acquisition, participants were retested in the morning (3 blocks of 10 trials). Data were analyzed for 13 participants (25.6 ± 6 years; 5 females). Dependent behavioral variables were number of erroneous sequences and sequence execution time (correct sequences only), averaged per subject and trial block. Error rate dropped during the first 4 practice blocks (p=.002, eta^2=.366) and remained unchanged from thereon. Sequence execution time decreased from start (blocks 1–3) to end of practice (blocks 8–10; p<.001, eta^2=.957), and then again from end of practice to retention the following morning, (p=.039, eta^2=.309). This latter result is indicative of sleep-related offline consolidation, as has been found previously in a similar task (Malangré et al., 2014). Preliminary analyses for EEG data (n=12) showed longer total sleep duration in the night after sequence acquisition (t=–3.06; p=.01; 33 minutes mean difference), but proportion of sleep stages did not differ between experimental nights (all p>.113). In the night following sequence acquisition higher spindle density of the learning hemisphere (electrode site C4) was predictive for stronger offline improvements in sequence execution time (r=.536), but only reaching borderline significance (p=.072). Hemispheric difference in spindle density for the learning versus the the non-learning hemisphere (C4 minus C3; Nishida and Walker, 2007), reduced the predictive power for offline improvements (r=.425; p=.168). More conclusive results will be presented at the conference.

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A ROLE FOR SPINDLE-SLOW WAVE SYNCHRONY IN SLEEP-DEPENDENT DECLARATIVE MEMORY CONSOLIDATION

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Keywords: Spindle, slow wave, delta, phase-amplitude coupling, memory consolidation, sleep

Objectives: Spindles fit within a hierarchy of finely orchestrated sleep oscillations, from cortical slow waves to hippocampal ripples. Together, they are believed to support sleep-dependent memory consolidation through precise temporal synchronization[1]. Much behaviourally-based work has established that consolidation is enhanced with increased spindles[2] and slow waves[3], but the specific contribution of their relative timing to this consolidation remains unknown. This study examined whether precise coupling of spindles and slow waves supports sleep-dependent memory consolidation.

Methods: Ten healthy participants (5F, mean age 23.3 ± 3.2) performed a declarative (word-pair association) task and a non-learning control task, on separate nights. Following each task, full-night sleep was recorded with polysomnography including 18-channel scalp electroencephalography (EEG). In the learning condition, participants performed cued recall before sleep and again in the morning. Non-artefacted epochs of stage N2 and N3 EEG signal at Cz and Fz were filtered for slow wave activity (SWA) (.25-4 Hz) and spindle activity in the sigma frequency range (adapted bands). The phase-amplitude coupling (PAC) of sigma amplitude by SWA phase was assessed per 30-s epoch and averaged for each night. PAC was quantified by the modulation index.

Results: Slow wave-sigma PAC at Cz was significantly increased during post-learning sleep, compared to post-non-learning sleep. This effect was not observed at Fz. Instead, decreased PAC at Fz post-learning was associated with greater overnight stabilization of memory performance.

Conclusion: Our results provide preliminary evidence that sleep-dependent memory consolidation is mediated by spindle-slow wave synchrony. This contribution may be topographically differentiated, with central recruitment balanced by frontal disengagement.

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VERBATIM TARGETED MEMORY REACTIVATION OF WORD PAIRS DURING NREM SLEEP PARADOXICALLY BLOCKS MEMORY CONSOLIDATION BENEFITS

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Keywords: Declarative memory, sigma band, spindles, targeted memory reactivation

Targeted Memory Reactivation (TMR), i.e. the exposure to learning-related cues during subsequent sleep, is known to selectively enhance memory consolidation for declarative memory material. In the present study, we investigated whether verbatim presentation of the learned word pairs (providing a feedback about the correct association between the first and the second word) during non-rapid eye movement (NREM) sleep is equally or more beneficial to consolidation in declarative memory. Twenty-seven healthy participants learned a list of 40 pairs of words followed by a 90-minute retention interval spent either awake of asleep (diurnal nap). During the retention interval, half of the learned word pairs were presented. The first word was aurally presented then followed by its paired associate after 1000 msec. Memory for all learned pairs was then tested. Contrary to expectations, verbatim presentation of the pairs of words during NREM sleep was not beneficial to memory consolidation, but the procedure selectively improved performance when applied in the wake interval. Spectral power analyses revealed increased sigma power following the presentation of the first word during sleep, but not after the presentation of the second word of the pair. These

results are in agreement with another study where we showed that retention of learned word pairs is selectively improved by presentation solely of the first word of the pair (i.e., the cue) during NREM sleep, as compared to non-cued word pairs, an effect associated with spectral power changes in the delta and sigma frequency bands (Gilson et al., submitted), which suggest a role for slow and spindle frequency-related oscillations in the processing of cued memories during NREM sleep. Altogether, our results concur with prior findings (Schreiner and Rasch, 2014; Schreiner et al. 2015) to suggest that the temporal succession of the two associated elements in a pair of words paradoxically impairs the ongoing processes of memory consolidation, by disrupting NREM spindle sigma-related hippocampal activity elicited by the presentation of the first word in the pair.

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COGNITIVE PERFORMANCE AND SLEEP SPINDLES IN ADOLESCENTS: A SUMMARY AND PRELIMINARY DATA FROM A SLEEP RESTRICTION PROTOCOL

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Keywords: Sleep spindles, adolescents, cognition, sleep restriction

Sleep spindles are quickly becoming a large area of interest in sleep research, however the relationship between spindles and cognitive performance in adolescents is under-studied. A systematic review was conducted of 13 studies published between February 2009 and June 2015. The studies, which are mainly correlational, show strong relationships between various sleep spindle characteristics and cognitive areas of fluid intelligence, working memory and overnight learning of skills. There were key differences between the studies in samples used, method of spindle analysis and detection, cognitive area investigated and spindle characteristics of interest (e.g. density, frequency, amplitude, etc.). Prominent similarities were the use of an overnight lab study and the inclusion of sleep spindle density as a characteristic of interest. An analysis of effect sizes showed that spindle frequency holds the strongest relationship with cognitive

function (correlation coefficient *r* ranging from 0.59–0.73 depending on cognitive area investigated) while spindle amplitude showed the weakest relationship to cognition, specifically fluid intelligence (*r* = 0.41). The studies also showed diversity in the proposed mechanism underlying the link between cognition and spindle activity.

In our current experimental study investigating sleep restriction in adolescents aged 15–17 yrs (n = 36), participants attended a sleep laboratory for 10 days and received 3 separate 'doses' of sleep: 5 hrs, 7.5 hrs or 10 hrs. The study involved 2 baseline nights of 10 hrs of sleep, followed by 5 consecutive nights of restricted sleep to mimic an adolescent's potential self-restriction of sleep during the school week. Adolescents then had 2 nights of recovery sleep (10 hrs). Sleep spindle characteristics will be correlated with measures of fluid intelligence (Letter Sets Number Series) and working memory (Operation Span Task) across the 3 separate sleep doses. These results will show the effect of restricted sleep on adolescents' cognitive abilities and the role that sleep spindles play in this relationship.

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IMPAIRED DECLARATIVE MEMORY CONSOLIDATION IN PATIENTS IN AN AT-RISK MENTAL STATE FOR PSYCHOSIS (ARMS): CORRELATION WITH REDUCED SLOW SLEEP SPINDLE ACTIVITY

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Keywords: At risk mental state, schizophrenia, declarative memory consolidation, sleep, slow spindles, fast spindles, polysomnography

Background: Sleep-dependent declarative memory consolidation was shown to be impaired in chronically medicated patients with schizophrenia. Whether this impairment already develops in early disease stages is unknown. Also, little is known about the underlying neurophysiological mechanisms.

Methods: 48 subjects (16 patients in an "at-risk mental state" (ARMS), 12 patients with schizophrenia and 20 healthy controls) were investigated with three consecutive nights of polysomnography and verbal declarative memory testing (word pair task) before and after the third night. Sleep architecture was analyzed including fast and slow sleep spindle activity.

Results: Declarative memory consolidation was reduced in ARMS patients and patients with schizophrenia. Memory function correlated with slow but not fast spindle density in controls and ARMS patients, but not in medicated patients with schizophrenia. Frontal slow spindle density was reduced in ARMS patients and correlated with measures of psychopathology.

Conclusion: Deficient declarative memory consolidation already occurs in a clinical risk constellation for psychosis. It is related to reduced frontal slow spindle density in ARMS patients but not in chronic medicated patients with schizophrenia. To evaluate whether this relation points to the neurobiological underpinnings of early stages of psychosis, longitudinal analyses should account for conversion to psychosis rates.

AUDITORY CLOSED-LOOP STIMULATION IN THE MIDDLE-AGED: EFFECTS ON SPINDLES & DECLARATIVE MEMORY

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Keywords: Auditory closed-loop stimulation, slow oscillations, spindles, declarative memory consolidation, ageing

The ~1 Hz slow oscillation (SO) which hallmarks slow wave sleep (SWS) has been implicated to play a vital role in facilitating overnight memory consolidation. By orchestrating temporally coupled, lower-level elements such as thalamocortical spindles and hippocampal ripples, SOs are thought to drive the transfer process of newly learnt declarative memories from temporary, hippocampal to long-term, cortical storage. Throughout the healthy ageing process, decreases in SO and spindle power have been documented. Concurrently, human cognitive abilities, most notably retention of novel memories, decline in later life. Correspondingly, previous research in the middle-aged and elderly has demonstrated a reduced benefit from the overnight consolidation effects found in younger adults.

In the current study, we examine the effects of using benevolent sleep manipulation to improve SO and spindle activity in a cohort of healthy, middle-aged adults (17 participants, age range 49 to 63) and effects of such on overnight memory consolidation. In a within-subject design, we applied an established closed-loop stimulation method[1] and delivered short auditory stimuli in phase with endogenous slow oscillatory activity during SWS. Participants' were taught novel word-pairs prior to sleep and re-tested the following morning. Effects of the stimulation protocol on spindle and slow oscillatory activity, as well as sleep stages and memory performance are explored.

Our findings suggest that the ageing brain is receptive to auditory closed-loop stimulation; however, the extent to which this approach may be used to enhance overnight consolidation of novel declarative memories in middle-aged participants appears to diverge from findings in younger adults[1]. Future investigation should clarify the nature of age-related changes in the temporal coupling of brain rhythms and expected implications for the functionality of such.

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SPINDLES, SLOW WAVES AND GAMMA IN CHILDHOOD: FREQUENCY-SPECIFIC ASSOCIATION WITH PERFORMANCE ENHANCEMENT OR RATHER BASELINE PERFORMANCE?

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Keywords: childhood, sleep, spindles, gamma, slow waves, oscillations, skill learning, memory enhancement

Background and Aims: It has been suggested that slow versus fast sleep spindles differentially affect the overnight enhancement of skill performance. We aimed to determine whether there is indeed such a differential role in school-aged children, or whether these are confounds secondary to differential associations with baseline performance, thus differentially limiting headroom for improvement. Given the strong amplitude of EEG oscillations at this age, we moreover took the opportunity to evaluate the presence of gamma modulation by slow waves, which is difficult to detect in adult EEG.

Methods: 30 children (19 females, 10.7 +/– 0.8 years of age; mean +/– SD) performed finger sequence tapping tasks in a repeated-measures design spanning 4 days including 1 polysomnography (PSG) night. Initial and delayed performance were assessed over 12 h of wake; 12 h with sleep; and 24 h with wake and sleep.

Analyses: Mixed effect regression models evaluated the association of sleep, its macrostructure and spindles and slow wave parameters with initial and delayed speed and accuracy. EEG time-frequency analysis was applied to evaluate the time course of spectral power along the development of a slow wave.

Results: Children enhance their accuracy only over an interval with sleep. Unlike previously reported in adults, children enhance their speed independent of sleep, a capacity that may to be lost in adulthood. Individual differences in the dominant frequency of spindles and slow waves were predictive for performance: children performed better if they had less slow spindles, more fast spindles and faster slow waves. On the other hand, overnight enhancement of accuracy was most pronounced in children with more slow spindles and slower slow waves, i.e., the ones with an initial lower performance. Time-frequency analysis showed that gamma power increased on the rising slope and positive peak of the slow wave. Gamma and spindle activity is strongly suppressed during the negative peak of the slow oscillation.

Conclusions: Studies in children provide a uniquely feasible opportunity to conduct investigations into the role of gamma during sleep using regular EEG instead of MEG. Gamma activity is associated with the up-going slope and peak of the slow wave. Associations of spindle and slow wave characteristics with initial

performance may confound interpretation of their involvement in overnight enhancement. Slower frequencies of characteristic sleep events may mark slower learning and immaturity of networks involved in motor skills..

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Basic Mechanisms and Rhythmogenesis

CORTICOTHALAMIC EFFECTS ON SPINDLE GENERATION IN THALAMUS

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Sleep spindles are generated by the interplay of excitatory thalamocortical (TC) and inhibitory thalamic reticular (nRT) neurons. Stimulation of nRT cells or axon terminals can elicit spindles in a state dependent fashion. The third component of the network, layer 6. of the cortex (L6) provides excitatory feedback to both cell types, however its role in spindle generation is unclear. We recorded multiple single unit activity in the thalamus of urethane anaesthetized NTSR1-ChR mice, a strain expressing channelrhodospin in L6 corticothalamic cells selectively. Brief, pulse-like L6 stimulation elicited mainly inhibition in TC cells, often preceded by a window of brief excitation. nRT cells, on the other hand, were strongly and reliably excited by L6. On the network level, L6 elicited spindles in a fashion similar to direct nRT activation. Namely, no spindles could be evoked during deeply synchronized and desynchronized network states, only during light synchronization, a state analogous to stage 2 sleep, in which spontaneous spindles also appear. Tonic L6 stimulation inhibited thalamic activity, possibly via nRT, but induced no apparent state change.

SLEEP SPINDLES: A LOCAL PHENOMENON IN THE HUMAN THALAMUS?

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Keywords: Sleep spindle, thalamus, human, local sleep

Sleep spindles of non-rapid eye movement (NREM) sleep are believed to subserve many sleep-related functions, from memory consolidation to cortical development. They differ in location and frequency, being slower in frontal than in parietal cortical areas. Recent data using intra cerebral recordings in human showed that they occur across multiple neocortical regions, and are spatially restricted to specific brain regions (1). The aim of the present study was to characterize the location and frequency of sleep spindles in the human posterior thalamus, with the hypothesis that local spindling activity should also be observed in the thalamus.

Using intracranial recordings for pre-surgical evaluation in 15 epileptic patients, we explored spindle activity during stage N2 in 6 thalamic nuclei, ventro-postero-lateral (VPL), central lateral (CL), ventral lateral (VL), lateral posterior (LP), anterior pulvinar (PuA), and medial pulvinar (PuM). Analyses were performed using time-frequency and spectral power in the frequency range of spindling activity.

The frequency, spectral power and density of spindles were different according to the nucleus considered, higher in PuM than in PuA and CL. They were found to be present in one nucleus and not in the adjacent one in up to 40% of the cases.

These preliminary results strongly suggest the presence of local spindles in the human posterior thalamus. Their mean frequencies differ as a function of the thalamic nucleus generating them and their density was comparable to that observed in the parieto-occipital cortex (2). Assessing spindle activity in the cortical areas connected with these thalamic nuclei will test the hypothesis that local cortical spindling activity should be related to local thalamic activity.

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BRAIN-WIDE NETWORKS OF SLEEP OSCILLATIONS

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Keywords: Sleep spindles, slow oscillations, networks, functional connectivity

A large body of evidence indicates sleep benefits memory performance. Current theories of long-term memory suggest that memory traces are initially encoded into highly plastic short-term memory stores before gradually being recoded to more permanent distributed storage facilities in the neocortex. Such memory

reprocessing is postulated to rely on the precisely coordinated reactivation of brain-wide memory networks. During sleep, tightly coupled oscillatory rhythms of slow oscillations (SOs) and sleep spindles have been hypothesized to fulfil this role. In particular, these brain rhythms demonstrate consistent phase relations between distinct brain areas and may serve to bind distributed neocortical networks together. Yet, in spite of the purported involvement of these rhythms in distributed memory systems, surprisingly little is known about the dynamics of spindle and slow wave connectivity at the network level.

We characterized sleep wave interactions in a sample of 15 healthy volunteers during nights following a motor sequence learning task and a non-learning baseline condition. We used full-night high-density EEG to comprehensively assess power and functional connectivity in the spindle and slow wave ranges between each of >1400 pairs of electrodes. We observed enhanced SO power in N3 compared to N2, but similar overall spindle frequency power during the two stages. In addition, we observed increases in phase synchrony for both SOs and spindles from N2 to N3, as well as increased coordination of spindle amplitude fluctuations across electrodes. These results suggest SO-rich sleep facilitates neural communication in the sleep spindle band.

To better understand the interrelations between oscillatory variables, we investigated the temporal evolution of power and connectivity patterns throughout the night. Measures of power and functional connectivity were generally positively correlated, both within and across frequency bands. However, we observed unexpectedly absent or even negative relations during N3 between SO power and spindle power/connectivity. These findings suggest that as SOs become more prominent during deep sleep, brain-wide global spindle connectivity is reduced and gives way to a more localized regime of neural communication. This work offers a novel perspective on sleep wave dynamics and may inform theories of sleep-related memory processing.

HYPOTHALAMIC FEEDFORWARD INHIBITION OF THALAMOCORTICAL NETWORK CONTROLS AROUSAL AND CONSCIOUSNESS

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Keywords: Sleep, Reticular Thamalic Nucleus (TRN), lateral hypothalamus, anesthesia

In mammals, during non-rapid eye movement (NREM) sleep, the electroencephalogram (EEG) activity shows typical signs of brain activity that include a predominant slow wave (<1 Hz) associated with delta oscillations (1–4 Hz) and spindles (11–15 Hz) [1–3]. Synchronous synaptic activity in the thalamocortical network is believed to generate these low-frequency oscillations and that are modulated by inhibitory inputs from the thalamic reticular nucleus (TRN). Whether TRN cells integrate sleep-wake signals from subcortical circuits remains unclear. We identified a monosynaptic GABAergic connectivity between the lateral hypothalamus and the TRN (LH**GABA**-TRN**GABA**) transmission that exerts a strong inhibitory control over TRN neurons. We found that optogenetic activation of this circuit recapitulated state-dependent changes of TRN neuron activity in behaving mice and induced rapid arousal during NREM, but not REM, sleep. During deep anesthesia, activation of this circuit induced sustained cortical arousal. In contrast, optogenetic silencing of LH**GABA**-TRN**GABA** transmission increased the duration of NREM sleep and amplitude of delta (1–4 Hz) oscillations. Collectively, these results demonstrate that TRN cells integrate subcortical arousal inputs selectively during NREM sleep and may participate in sleep intensity.

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DIFFERENTIAL MODULATION OF LOW AND HIGH FREQUENCY OSCILLATIONS IN REM SLEEP BY HOMEOSTATIC SLEEP REGULATION: IMPLICATIONS FOR SLEEP SPINDLE PHYSIOLOGY

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Keywords: Neuronal oscillations, high density EEG, theta, gamma, chronic sleep deprivation, sleep rebound

REM sleep (REMS), with its remarkable signature of highly active wake-like brain state was historically believed to contribute to memory consolidation. The first theoretical proposal of (homeostatic) depotentiation of certain “parasitic associations” was also first attributed to REMS [1]. Later, with accumulating experimental evidence REMS however lost to NON-REMS on both accounts; homeostatic regulation was associated with NON-REMS delta rhythm and consolidation

with spindles. More recently, REMS appears regaining its lost fame in the widely popular sequential hypotheses, based on two key experimental findings. The first [2] demonstrated a role of REMS in homeostatic regulation by linking REMS to post-REMS delta and spindles, the second [3] demonstrated its role in consolidation by linking it to pre-REMS spindles. Slow and fast oscillations play different roles in these processes and we demonstrate in this study using a chronic sleep restriction (CSR) paradigm, that they undergo entirely different adaptations to homeostatic challenge which may benefit different sleep functions.We studied the spatial-temporal alteration of EEG oscillations in REMS during CSR in mice (18hr daily sleep deprivation for 5 days; baseline, SD1 to SD5, 2 days recovery). In this paradigm, REMS rebound settles on a persistent level on SD1 and show no progressive increase over days as sleep debt keeps accumulating. High density EEG, covering the entire cortex from frontal to occipital, revealed marked topographic differences between dominant slow and fast oscillations and their coupling in prefrontal, motor and somatosensory cortex, and underlying hippocampus. The pattern of changes induced by CSR, however, followed a common rule in all areas. Slow oscillations in REMS (<15Hz) repeated the behavioral pattern of REMS alterations, i.e. a permanent increase throughout SD1-SD5, whereas high frequency oscillations showed progressive increases over the course of CSR. Spindle density was also calculated in NON-REMS and was found significantly increased in SD1-SD5. The findings suggest that in REMS, slow oscillations may serve to translate top-down homeostatic control to a wide range of cortical networks whereas fast oscillations might serve as an instrument granting relative independence for local ensembles to synchronize on shorter spatio-temporal scales.

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SELECTIVE SUPRESSION OF SPINDLE ACTIVITY IN NATURALLY SLEEPING MICE BY OPTOGENETIC STIMULATION OF THE MIDLINE THALAMUS

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Keywords: Midline thalamus, spindle, calretinin, arousal

Sleep spindles are important for memory consolidation, however, selective modulation of spindle activity still poses a great challenge. In this study, we tested whether the power of the spindle frequency band (10-15 Hz) can be selectively diminished in freely sleeping animals by weak, subthreshold activation of the midline thalamic nuclei (MT).

MT is considered to be a key hub in the forebrain arousal system, and can be distinguished from neighboring thalamic nuclei by selective expression of calretinin (CR). Here, we selectively expressed channelrhodopsin in MT of CR-Cre mice and delivered optical stimulation to the MT. Sleep-wake states was monitored by EEG signals recorded from bilaterally placed frontal and parietal screws, EMG recordings and video tracking of the animal's movement.

Intense, (10 sec, 10 Hz) optogenetic stimulation of MT during slow wave sleep induced, immediate and persistent arousal accompanied by locomotion, lasting up to tens of minutes. Brief stimulations (1sec, 10 Hz), however evoked only microarousal, defined as 3–5 seconds long, transient muscle activity without any overt sign of behavioral arousal. Microarousals were consistently accompanied by EEG desynchronization with a characteristic drop in the power of delta (1–3 Hz) and spindle bands. The effect on spindle band was larger and lasted longer. Microarousals could be evoked probabilistically, with a log-linear relationship between the applied laser intensity and the probability of microarousal. In cases when MT stimulation failed to evoke microarousals (sleep-throughs), the spindle but not the delta frequency band of the EEG power was selectively suppressed. The magnitude and duration of this suppression correlated with the applied laser intensity and lasted for 20–40 seconds.

Our results provide direct evidence that selective activation of MT could disrupt ongoing natural sleep activity. Depending on the stimulation intensity the effect ranges from selective suppression of spindle activity for tens of seconds without awakening the animal to persistent arousal lasting for tens of minutes. The present findings demonstrate that spindle frequency band is the most sensitive to selective activation of MT. Furthermore MT activation can be used as a powerful tool to investigate questions which require precise regulation of sleep states and arousal. It may especially suitable for selective 'spindle deprivation' to test the role of spindle activity in memory processes.

DISTRIBUTION OF SLEEP SPINDLES AND K-COMPLEXES IN DESCENDING COMPARED TO ASCENDING SLOPE OF THE NREM/ REM SLEEP CYCLE

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Keywords: Sleep spindles, K-complex, sleep cycles, descending, ascending, NREM

Sleep microstructural elements' distribution and features differ between descending (D) and ascending (A) NREM slopes of each sleep cycle, reflecting the asymmetrical dynamics of sleep- and wake-promoting neuronal systems [1]. Among these elements, sleep spindles and K-complexes play significant roles in sleep regulation and sensory processing during sleep.

This study aims to compare the distribution of sleep spindles and spontaneous K-complexes (KC) in D and A NREM sleep.

All-night polysomnographic recordings of young, healthy sleepers were examined and sleep cycles with a regular, uninterrupted by prolonged wakefulness, succession of sleep stages were selected for quantitative analysis. Calculated parameters for D and A slopes of each sleep cycle include their duration, the rate of appearance of sleep spindles and KC, as well as the mean duration and inter-event interval distribution of sleep spindles.

Our results indicate that D NREM slopes of sleep cycles are of longer duration and lower composition in KC than A slopes, confirming previous reports concerning their respective domination by sleep- and wake-promoting mechanisms [1]. Moreover, we found that sleep spindles in D appear more frequently, although have comparable 0.2–0.3 Hz periodicity and mean duration to those in A NREM sleep.

We view the above results as providing support to the hypothesis of sensory input-driven NREM sleep regulation [1].

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INFRA-SLOW SIGMA POWER FLUCTUATIONS PREDICT BEHAVIORAL AROUSABILITY DURING NREM SLEEP IN MICE

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Keywords: Infra-slow, NREM sleep, noise-induced arousal, heart rate variability, sleep-wake control

Environmental noise at night disrupts sleep and adversely affects general health by causing daytime sleepiness and increasing cardiovascular risk factors. Therefore, a profile of sleep in terms of its fragility to sensory input, taking also into account cardiovascular activity, should be established. Electrophysiological and imaging studies in humans and animals show that thalamocortical sleep rhythms cause substantial sensory response variability. Nevertheless, the telltale signs that determine whether or not noise causes behavioral arousal remain incompletely understood. Here we show that noise-induced arousal is specifically predicted during mouse non-rapid-eye-movement sleep by an infra-slow fluctuation (periodicity ~45 s) in the power of sleep spindles, a 10–15 Hz electroencephalographic rhythm implied in sleep's beneficial actions on memory formation, which is phase-locked to slow components of heart rate variability. By choosing an acoustic stimulus such that mice wake up or sleep through noise at comparable rates, we discovered that, prior to noise onset, sleep spindle power peaked when an arousal followed. Conversely, sleep-through was preceded by a trough in spindle power, concurrent with augmented heart rate fluctuations. Varying arousability hence arises from joint central autonomous and sleep-wake control mechanisms, going beyond traditional views of thalamocortical sensory gating. Infra-slow power fluctuations occurred in sensory and associational cortical areas and were suppressed by zolpidem, a widely used hypnotic drug, substantiating their role as markers for sleep fragility. A first set of analysis in human non-rapid-eye-movement sleep shows the presence of infra-slow fluctuations of sigma power in a comparable frequency range as in mice. The implication of sigma power infra-slow fluctuations in modulating the auditory evoked response in primary sensory areas (Au1 and S1) is currently being investigated using feedback controlled loops and optogenetic approaches. Together, we show for the first time that arousability during mammalian sleep fluctuates constantly due to a specific brain-heart crosstalk. The coordination between a salient sleep rhythm and an index for cardiac health bears the potential for assessing the pathophysiological links between sleep disorders, cognitive deficits, and cardiovascular disturbance.

A BIRD'S BRAIN VIEW ON SPINDLES: INTRACEREBRAL RECORDINGS IN NATURALLY SLEEPING PIGEONS

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Keywords: NREM sleep, bird, spindle, visual hyperpallium

Several studies in mammals suggest that the temporal coupling of cortical slow oscillations (SO), thalamo-cortical spindles, and hippocampal sharp-wave ripples occurring during non-rapid eye movement (NREM) sleep is involved in consolidating episodic memories in mammals. Birds also exhibit episodic-like memory, and NREM and rapid eye-movement (REM) sleep states that are in many, but not all, respects comparable to those in mammals. While SO have been detected during avian NREM sleep, sleep spindles have not been observed in the avian EEG. However, local spindles or spindles occurring in deeper regions of the avian brain might have been missed in EEG recordings.

The aim of the current study was to explore activity in the avian visual hyperpallium, the avian homologue of the mammalian primary visual cortex, during both natural NREM and REM sleep, with a special emphasis on brain rhythms implicated in mammalian memory consolidation (i.e. sleep spindles). We used a 32-channel silicon probe connected to a transmitter to make intracerebral recordings of the hyperpallium in naturally sleeping pigeons (*Columba livia*).

Local field potential (LFP) recordings reveal high amplitude SO (<2 Hz) across most recording sites in the hyperpallium during NREM sleep. However, none of the regions in the hyperpallium, including those that receive thalamic input from the avian lateral geniculate nucleus, showed a peak in power in the spindle range. Visual inspection of the LFP recordings also failed to reveal spindles. Nonetheless, in some birds, bursts of gamma (~80 Hz) activity were observed in thalamo-recipient areas during REM sleep, showing that this brain region is capable of generating high frequency oscillations detectable in LFPs.

The apparent absence of spindles in the hyperpallium suggests that there might be marked differences in how birds and mammals process memories during NREM sleep. However, recordings from other forebrain regions and the thalamus are needed before we can conclude that spindles are completely missing in the avian brain, and the implications that such findings might have for understanding their role in the mammalian brain.

MODULATION OF LOCAL CORTICAL ACTIVITY BY GLOBAL NETWORK OSCILLATIONS

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Keywords: Single unit recording, sigma power, nonrapid eye movement sleep, EEG, mice

Cortical EEG activity during nonrapid eye movement (NREM) sleep is characterised by the occurrence of locally and globally synchronised slow waves (~0.5–4 Hz) and spindles (~9–13Hz). Spiking activity of individual cortical neurons is generally modulated by such global network oscillations, although the functional significance of this relationship remains to be established. We hypothesize that individual neurons may be differentiated based on their preferred spiking in association with specific types of global oscillatory activities. Here we used a 12-hour recording of extracellular neuronal activity from layer 5 of the primary motor cortex and EEG in freely-behaving adult, male C57BL/6 mice (n=10 animals) during spontaneous undisturbed dark period. An average of 42 minutes of artefact-free NREM sleep contributed to this analysis in each animal. Neuronal recordings were subjected to offline spike sorting procedure, which yielded 306 putative single units in total across all animals. Pearson's linear correlations were calculated between EEG spectral power (between 0–20 Hz, 0.25 Hz resolution) and firing rate for each putative neuron. Subsequently, all neurons were grouped utilising an agglomerative hierarchical cluster analysis, which revealed five primary clusters. One cluster of neurons with firing activity unrelated to EEG power across all frequencies (n=103), one with firing rates associated with low EEG power across all frequencies (n=23), one with firing rates associated with high EEG power in slow wave range (0–4Hz, n=18) and two with firing rates associated with high EEG power at higher frequencies (6–20Hz; n=38, n=124). Next, an additional analysis of firing rates of individual neurons was used with respect to their specific co-modulation with EEG power in delta (0–4Hz), theta (4–10Hz), sigma (10–13Hz) and beta/gamma (13–20Hz) frequency bands. We found that 36.3% (n=111) of the 306 putative neurons showed significantly increased firing rate from low to high EEG sigma power (median split t-test, $p<0.05$), with 77% of these neurons belonging to the two high frequency clusters. Notably, firing activity of all 111 putative neurons was unrelated to the variation in EEG power within slow-wave range. However, 92% of these neurons additionally exhibited increased firing behaviour with higher theta and beta/gamma power ($p<0.05$). In summary, our preliminary results indicate that a substantial proportion of cor-

tical neurons are recruited during epochs dominated by EEG power in the spindle-frequency range. However, interestingly, there was also an overlap in activity of these cortical populations during epochs with increased EEG power in a wider high frequency range.

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SYNCHRONIZATION OF CORTICAL DENDRITIC ACTIVITY DURING SLEEP SPINDLES IN RODENTS

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Keywords: Dendrites, spindles, calcium imaging

Sleep has now been linked to brain plasticity at many levels, with converging evidences from the molecular, cellular and behavioural fields. Studies in humans and animals support of specific role for spindles in this process but the underlying physiology remain elusive. It has been suggested that spindle bursts promote Ca^{2+} increase specifically in dendrites, a condition that would favour dendritic plasticity processes[1,2]. Although this hypothesis is supported by computational modeling, to date, evidence that such a relation exist during natural sleep is missing.

To address this issue, we measured Ca^{2+} activity from layer 5 (L5) dendrites in the somato-sensory cortex using 1-photon (fiber-optic) and 2-photon imaging in naturally sleeping rodents. Calcium imaging was combined with EEGs recordings to monitor behavioural states and underlying network oscillations.

Our results show that activity of population of dendrites during slow-wave-sleep was specifically correlated with spindle-beta (9–30 Hz) power changes. Two-photon imaging of single dendrites further suggest that this relationship was largely explained by an increase in synchronization of dendritic activity during spindles. Interestingly, this effect was specific to dendrites as L2/3 and L5 cell bodies did not show such correlation.

Our results support the current hypothesis of a direct link between spindles and dendritic activity regulation and further reveal an important, yet unexplored, functional coupling between spindle (9–16Hz) and beta oscillations (15–30Hz). Further (and ongoing) experiments probing the influences of experience on this

relationship will reveal important information on the physiology of spindles and their role in learning and memory.

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RESPONSES IN RAT CORE AUDITORY CORTEX ARE PRESERVED DURING SLEEP SPINDLE

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Keywords: NREM sleep, auditory cortex, sleep spindles, single-unit, rat

Study Objectives: Sleep is defined as a reversible state of reduction in sensory responsiveness and immobility. A long-standing hypothesis suggests that a high arousal threshold during non-rapid eye movement (NREM) sleep is mediated by sleep spindle oscillations, impairing thalamocortical transmission of incoming sensory stimuli. Here we set out to test this idea directly by examining sensory-evoked neuronal spiking activity during natural sleep.

Methods: We compared neuronal (n = 269) and multiunit activity (MUA), as well as local field potentials (LFP) in rat core auditory cortex (A1) during NREM sleep, comparing responses to sounds depending on the presence or absence of sleep spindles.

Results: We found that sleep spindles robustly modulated the timing of neuronal discharges in A1. However, responses to sounds were nearly identical for all measured signals including isolated neurons, MUA, and LFPs (all differences <10%). Furthermore, in 10% of trials, auditory stimulation led to an early termination of the sleep spindle oscillation around 150–250 msec following stimulus onset. Finally, active ON states and inactive OFF periods during slow waves in NREM sleep affected the auditory response in opposite ways, depending on stimulus intensity.

Conclusions: Responses in core auditory cortex are well preserved regardless of sleep spindles recorded in that area, suggesting that thalamocortical sensory relay remains functional during sleep spindles, and that sensory disconnection in sleep is mediated by other mechanisms.

THE LAMINAR PROFILE OF SLEEP SPINDLES IN EPILEPTIC PATIENTS

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Keywords: Sleep spindles, laminar electrodes, Individual Adjustment Method, epilepsy

Laminar electrodes penetrate the cortex, allowing for the exploration of cortical activity in various cortical layers using electroencephalography with a high temporal resolution. In humans, laminar electrodes are frequently used in the preoperative screening of epileptic patients, but they are also able to provide information about the underlying cortical activity profiles of normal physiological phenomena. Previous publications explored the in-depth cortical activity profile of slow waves [1] and K-complexes [2] in humans, but such data is not yet available for sleep spindles. We used data from two epileptic patients undergoing pre-surgical electrophysiological screening with laminar electrodes and electrocorticography to explore the cortical activity profiles of slow and fast spindles, respectively. Sleep spindles were detected in NREM sleep using the Individual Adjustment Method [3] from corticographic channels without epileptiform activity as well as from laminar channels alone. The analysis of laminar channels reveals the presence of spindle-frequency oscillations during corticographic spindles in both supra- and infragranular layers, but little coupling of multi-unit activity (MUA) indicating the synchronized firing of small neuron populations. Overall, our preliminary results confirm the involvement of various cortical layers in spindle oscillations. Spindle oscillations, unlike slow oscillations, are not only present in superficial layers but also in deeper layers where thalamic inputs terminate.

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EXPLORING THALAMOCORTICAL ACTIVITY DURING NATURAL SLEEP

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In the mammalian brain, the tight interplay between thalamic and cortical activity contributes to slow rhythms and spindle oscillations that form the hallmarks of non rapid-eye-movement sleep (NREMS). However, most of our knowledge about these phenomenae is based on electrophysiological recordings performed either *in vitro* or under anesthesia, and little is known about how the thalamus and the cortex interact during natural sleep. We therefore developed a novel technical approach to perform intra- and extracellular single-unit recordings in the mouse sensory thalamus coupled with local field potentials (LFP) recordings in the somatosensory cortex and polygraphic monitoring of vigilance states (EEG & EMG).

As typically described, NREMS is clearly distinguished from wakefulness by high-voltage delta (0.5–4 Hz) and spindles (10–15 Hz) waves associated with a weak EMG activity. In naturally-sleeping mice, we observed that thalamic cells, while tonically active during wakefulness, exhibited robust bursts of spikes in NREMS, which preceded by 15 ms the peak of cortical field potentials. Intracellular recordings further revealed that thalamic membrane potential was characterized by 1 to 10 mV oscillations correlated with cortical spindle activity. Notably, we found that cortical spindle activity was not homogenously distributed across NREMS episodes, but exhibited a higher density in the second half of the NREMS episodes. Accordingly, thalamic cells exhibited a higher firing rate and more bursts in the later stages of NREMS. In addition, the spindle frequency occurring at the end of the NREMS period dropped compared to the first spindles of the episode.

Thus, our results revealed highly dynamic modulations of the thalamic and cortical activity across the NREMS period which are not apparent under anesthesia, and therefore underline the need for recordings in naturally sleeping animals.

GROUPING OF MEG GAMMA OSCILLATIONS BY FAST AND SLOW SLEEP SPINDLES

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Keywords: Cortical gamma, gamma coherence, magnetoencephalography, electroencephalography, cross-frequency coupling

Sleep spindles are assumed to play an important role in memory consolidation. Cortical gamma (>30 Hz) oscillations are considered to reflect local cortical network processing.

The temporal and regulatory relationships of spindle and gamma activity are therefore of particular importance for sleep related memory processing. We analyzed NonREM rich sleep periods and detected fast (12–15 Hz) and slow (9–12 Hz) spindles in simultaneous MEG and EEG recordings and their local and global co-occurrence and modulation with cortical gamma activity. As expected EEG and MEG spindles co-occurred and were correlated with power increases in the frequency band of the respective first harmonic (20–30 Hz), being most pronounced around their detection site. Cross-frequency coherence analyses indicated a power-to-phase-coupling of the MEG gamma band activity with the spindle rhythm that varied between subjects in cortical areas, as well as gamma and spindle frequencies. Taken together our findings support the idea that spindles provide a fine-tuned temporal frame for integrated cortical memory processing during sleep.

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SATURDAY, 14 MAY 2016

Clinical Corner and Biomarkers: Sleep Disorders, Neurology, Psychiatry

THE ROLE OF THALAMOCORTICAL CONNECTIVITY IN UNDERSTANDING SPINDLE DEFICITS IN SCHIZOPHRENIA

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Keywords: Schizophrenia, thalamus, functional connectivity, MRI

Patients with schizophrenia (SZ) have a specific deficit in sleep spindles that is associated with impaired memory consolidation and symptom severity. Sleep spindles are generated via thalamocortical feedback loops. Here we used resting state functional MRI (fMRI) and diffusion weighted imaging (DWI) to investigate whether spindle deficits in SZ are associated with changes in the connectivity of thalamocortical networks.

Participants were chronic, medicated SZ patients (n = 26) and demographically-matched healthy controls (HC, n = 29). The scanning protocol included resting-state functional MRI (two 6-minute scans) and DWI on a 3T Siemens Trio scanner. For functional scans, we performed a seed based functional connectivity analysis based on the FSL-Oxford thalamic connectivity atlas (7 thalamic segments that are anatomic components of prefrontal, premotor, primary motor, sensory, temporal, posterior parietal, occipital networks). Following standard preprocessing in SPM8, motion artifacts and physiological noise were regressed out and functional connectivity was computed with Conn toolbox. All reported clusters survived a multiple comparison correction of pFDR < .05. In a separate session, nocturnal sleep was monitored with polysomnography (58 EEG channels, EOG and EMG) at the Clinical Research Center. Sleep was scored according to standard criteria and sleep spindles during N2 were identified using an automated wavelet spindle detector.

SZ patients showed marginal but consistent reductions in N2 spindle density that were more prominent in centro-parietal channels (e.g. 5% reduction at Cz, p = .36; 15% reduction at Pz, p = .02). SZ patients also showed increased connectivity in two thalamocortical networks. First, the prefrontal thalamus (consisting

of the mediodorsal, anteromedial and anterodorsal nuclei) was more strongly connected with several cortical regions including the bilateral precentral gyrus, insula, dorsolateral prefrontal, primary motor and sensory cortices. Second, the premotor thalamus (consisting of the ventral lateral and ventral anterior nuclei) is more strongly connected in SZ patients with bilateral premotor and primary motor cortices. Within these thalamocortical networks we investigated which cortical regions correlate with spindle density detected at Cz. We found that connectivity between the prefrontal thalamus and left postcentral gyrus primarily consisting of BA3 (peak: MNI [–32, –34, 52], cluster size: 257 voxels) was negatively correlated with spindle density in both groups (HC: R^2 = .42; SZ: R^2 = .20, difference of slopes n.s.). Similarly, connectivity between the premotor thalamus and left postcentral gyrus primarily consisting of BA7 (peak: MNI [–26, –38, 48], cluster size: 685 voxels) was negatively correlated with spindle density (HC: R^2 = .37; SZ: R^2 = .43, difference of slopes n.s.).

In summary, our preliminary analyses reveal stronger thalamocortical connectivity in SZ patients between prefrontal and premotor thalamic nuclei and premotor and motor cortices; and increased thalamocortical connectivity in both groups correlates with reduced spindle density. Future plans include complementing functional connectivity analysis with measurements of thalamocortical white matter integrity.

SLEEP SPINDLE DENSITY IN NARCOLEPSY

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Keywords: Sleep spindle density, narcolepsy type 1, narcolepsy type 2

Background and aims: Patients with narcolepsy type 1 (NC1) show alterations in sleep state transitions due to the loss of hypocretingic innervation of the reticular activation system (RAS). We aimed to evaluate whether sleep microstructure as determined by sleep spindle (SS) density is altered in patients with NC1 compared to controls and patients with narcolepsy type 2 (NC2).

Methods: All-night recordings from 28 patients with NT1, 19 patients with NT2, 20 control subjects (C) with narcolepsy-like symptoms, but with normal hypocretin levels and multiple sleep latency tests, and 20 healthy controls (HC) were included. SS were automatically detected in rapid-eye-movement (REM) sleep and non-REM sleep N1, N2 and N3 using a central electroencephalographic channel. The detection procedure has been used in several previously published studies[1–3] and involves automatic rejection of electro-myographic artefacts and a threshold on root-mean-square values of 0.25-second windows of a

bandpass-filtered signal. The spindle density was defined as number of SS per minute.

Results: The mean spindle densities in HC were found to be small in REM (0.20±0.19) and N1 (0.71±0.63) sleep and higher in N2 (4.20±0.70) and N3 (2.77±1.36) sleep (figure 1). Between-group comparisons revealed no significant differences between either of the groups, although with a tendency for NT1 patients to show fewer spindles in N2 sleep compared to HC (α=0.053) and NT2 patients (α=0.074).

Conclusion: Our data show that spindle activity is preserved in NC1, suggesting that the ascending neurons from RAS to thalamus and thalamic activation of spindle activity is not significantly affected by the hypocretinergic system.

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SLOW SPINDLES DURING AFTERNOON NAPPING ARE IMPORTANT FOR MEMORY CONSOLIDATION IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT

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Keywords: Quantitative EEG analysis, dementia, sleep-dependent memory, verbal learning

Background: Patients with Mild Cognitive Impairment (MCI) experience memory deficits that place them at heightened risk of dementia. Sleep spindles have been shown to play an important role in memory consolidation and learning. It has been suggested that structured daytime napping consisting of NREM sleep may have positive effects on memory in MCI patients. We aimed to investigate the effect of a daytime nap on memory consolidation in MCI patients, and whether sleep spindles were associated with memory performance following a nap.

Methods: Nine subjects with amnestic MCI (age 73.5 ± 4.3 years) were recruited from the Healthy Brain Ageing Clinic at the Brain and Mind Centre Sydney, Australia. The study was a 2 × 2 single blinded randomised crossover design. On

separate days one week apart, subjects underwent neuropsychological testing which included the Hopkins Verbal Learning Test (HVLT) – a test of verbal learning and memory. This was followed by either a 60-minute nap opportunity or period of passive wakefulness. During both conditions electroencephalography (EEG) was obtained. Subjects were assessed again at 30-minute and 180-minute following the end of either condition. The EEG signals during sleep from frontal (Fz), central (C3) and parietal (Pz) channels were analysed using an automated spindle detection algorithm with a band-passing Finite-Impulse-Response filter (11–16 Hz). A Hilbert transformation was applied to extract envelopes of spindles. Overall sleep spindle (11–16 Hz), fast spindle (13–16 Hz) and slow spindle (11–13Hz) densities (spindles/min) were obtained during NREM sleep across the nap condition in all patients.

Results: All patients napped when presented with the opportunity (mean sleep time 32.4 ± 19.9 min). Memory performance on the HVLT was significantly worse at follow up than during baseline assessment in both the nap ($t = –13.5$, $p < 0.01$) and wake ($t = –11.6$, $p < 0.01$) conditions. The change in memory performance between follow up and baseline assessments did not differ between the two conditions. Sleep quality did not correlate with change in performance from baseline to follow up. An increased slow spindle density (C3 derivation) during the nap condition was significantly correlated with improved memory performance during follow up at both 30min ($r = 0.68$, $p = 0.043$) and 180min ($r = 0.71$, $p = 0.033$).

Conclusions: A greater number of slow sleep spindles during a short NREM sleep in the afternoon is associated with improved retention of memory encoded before the nap. This may have clinical implications in designing interventions aimed at slowing cognitive decline in patients known to be at risk for dementia.

LOCAL AND SELECTIVE DECREASE OF FAST SLEEP SPINDLE DENSITY IN PATIENTS WITH ALZHEIMER'S DISEASE AND MILD COGNITIVE IMPAIRMENT

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Keywords: Fast and slow sleep spindles, Alzheimer's disease, mild cognitive impairment

Patients with Alzheimer's Disease (AD) and Mild Cognitive Impairment (MCI) show alterations of sleep spindle activity. Separating fast (13–15 Hz) and slow (11–13 Hz) sleep spindles, a selective decrease of fast spindles count has been found in AD/MCI, without slow spindles changes. However, evidences about the regional specificity of pathology-related fast spindles alterations, their relation with cognitive deterioration and the comparison between AD and MCI patients are still missing. Moreover, fast and slow spindle density in AD/MCI patients has never been investigated. In the present study, 15 AD patients, 15 amnesic MCI patients and 15 healthy elderly controls (HC) underwent a baseline polysomnographic recording (19 cortical derivations) during a single night of sleep. Spindles detection during non-rapid eye movements (NREM) sleep was performed by means of a customized algorithm. Between-groups differences in spindle density were assessed in the cortical derivations where fast and slow spindles exhibited their density peaks (parietal and frontal, respectively), established by the empirical observation of their topography. A selective parietal fast spindle density decrease in AD and MCI patients compared to HC has been observed, while no significant differences have been found between AD and MCI patients. Fast spindle density and Mini-Mental State Examination scores were positively correlated. These findings suggest the existence of a local (parietal) and frequency-specific (fast) spindle density alteration in AD, that may emerge in an early stage during the pathology development. Moreover, our results are in line with the view of altered spindle activity as a marker of cognitive deterioration.

SIGMA FLUCTUATIONS IN POST-TRAUMATIC STRESS DISORDER

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Keywords: Sigma fluctuations, post-traumatic stress disorder, sleep spindles

PTSD is a significant health problem with an estimated prevalence of 8% in the general population. Key symptoms of the disorder are aversive memory intrusions and overgeneralization of the traumatic event, through flashbacks and nightmares. This may be interpreted as a form of memory disturbance. In fact, the symptoms are reminiscent of runaway consolidation, in which impaired pattern separation leads to the formation of super-strong, overgeneralized memory representations that get reactivated inappropriately. Sleep disturbances are another key symptom of PTSD. Interestingly, sleep has an important role in memory consolidation. In particular, sleep spindles in different cortical areas reflect the reprocessing and consolidation of specific memory traces. Given their strong relationship with memory reprocessing during sleep and the reported memory and sleep alterations in PTSD, sleep spindles may play a role in the aetiology of PTSD. Moreover, thalamic dysfunction has been reported in PTSD patients, which may be linked to abnormalities in spindle generation. In our project, several parameters of sigma fluctuations were analysed and compared between traumatised police officers and military personnel with PTSD (N=13) and without PTSD (N=14). Two approaches were used for this analysis: heuristic spindle detection and a detection method free of a-priori assumptions regarding spindle characteristic, to obtain an unbiased representation of all present sigma fluctuations. In the latter, automatised method, sleep EEG was filtered in the sigma frequency band (11-16 Hz), the standard deviation of the signal was computed (moving window: 0.2s), and all waxing/waning couplets with an amplitude over 5 microvolt were detected. For each detected sigma fluctuation, several variables were computed (e.g. duration, amplitude, etc.). Next, the frequency distribution of each variable, in each non-REM sleep stage, was compared between PTSD patients and trauma controls. Similar analyses were performed for a small subsample of PTSD patients using selective serotonin reuptake inhibitors (SSRIs) to assess possible influences of SSRIs on spindling. Preliminary findings indicate increased spindles in PTSD patients compared to trauma controls, possibly reflecting excessive reprocessing and consolidation of trauma-related memories. SSRIs seem to decrease spindling. The assumption free analyses revealed details regarding spindle abnormalities in PTSD that would have been missed by analysing only heuristically detected spindles. In conclusion, the spindle abnormalities in PTSD may form part of the mechanism through which the profound sleep disturbance in this disorder contributes to emotional memory problems.

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RELATIONSHIPS BETWEEN SLEEP SPINDLES AND CORE SYMPTOMS IN CHILDREN WITH AUTISM SPECTRUM DISORDER

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Keywords: ASD, the Sensory Profile, ADOS-G, spindle index, spindle mean amplitude, duration of sleep spindles

Background: Sleep spindles generated in the thalamus have been reported to play a crucial role in multiple neuronal functions such as learning, cognition and sensory gating. We have found out the frequent sleep spindles with longer duration in children with autism spectrum disorder (ASD), the disorder of the neural connectivity. The aim of this study is to see whether the parameters for sleep spindles correlate with clinical features of ASD such as sensory processing abnormalities.

Methods: Twenty-five children with ASD (mean age 5.8 y; 4 female, 21 male) assessed with the Sensory Profile (SP; The lower SP score indicates the higher sensory processing abnormality [1]) on five sensory area (auditory, visual, vestibular, tactile and oral) and Autism Diagnostic Observation Schedule-Generic (ADOS-G) were subject to the study. The parameters for sleep spindles were evaluated using nap EEG study by ten-twenty electrode montage.Spindle index (number/hour), spindle mean amplitude (μV) and duration (msec/spindles) were calculated by the analysis of spindles in F3, F4, C3 and C4 using EEG component analysis software (Noru Pro Light Systems,Tokyo). Correlations between EEG measures and the scores of SP and ADOS-G were tested using Spearman's rank correlation coefficient (SPSS statistics; IBM Japan).

Result and Conclusion: Scores on oral processing was positively correlated with the spindle index at F3 (r=0.478, p=0.016) and C3 (r=0.429, p=0.032), and auditory processing positively correlated with spindle mean amplitude at F3 (r=0.443, p=0.027), F4 (r=0.396, p=0.050), C3 (r=0.413, p=0.040),and C4 (r=0.434, p=0.030), and vestibular processing negatively correlated with the duration of sleep spindles at C4 (r=-0.418, p=0.037). There was also positive correlations between the duration of sleep spindles at C3 and ADOS-G score per-

taining to reciprocal social interaction (r=0.413, p=0.040), stereotyped behaviors and restricted interests (r=0.417, p=0.043). As sensory processing abnormality in ASD is supposed to be related to impairment of the sensory filter mechanism resulting from abnormality of the thalamic sensory gating system [2], these lines of evidence suggest that the neural circuits responsible for the genesis of sleep spindles may be associated with the neural basis of ASD.

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THE CONNECTION BETWEEN SLEEP SPINDLES AND SEIZURES IN SCHIZENCEPHALY: A CASE REPORT

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Keywords: Sleep spindle, epilepsy, correct diagnosis, electrophsiology

Objective: The aim of this case report is to define the interaction between sleep and epilepsy (and, sleep spindles and seizures), also the importance of electrophysiological follow up in sleep laboratory and correct diagnostic approach.

Background: Sleep spindles are generated from the thalamus. Seizures are results of abnormal, synchronized attacks of electrical activity in a restricted area of connected neurons, called as epileptogenic focus. Several experimental results point to the thalamus having a critical role in the generation of spike and wave discharges. It has been shown that if the thalamus was somehow inactivated, these discharges disappeares. Actually, according to this pattern sleep spindle oscillations can turn into seizures. Sleep spindles and seizures originate from the same type of dynamical system. It has been shown that antagonizing manipulations made on sleep spindles had the same effect on seizures. Schizencephaly is a rare congenital disorder of cell migration with defect in sulcation. It is characterized by gray matter lined clefts. Two types have been described in the literature – Closed Lip (Type I) which consists of fused cleft without hydrocephalous and Open Lip (Type II) consisting of open cleft with hydrocephalous. Diagnosis is made by imaging methods and magnetic resonance imaging is the most sensitive modality in detecting clefts and the associated anomalies

like pachygyria, polymicrogyria, heterotropias, septo-optic dysplasia and absent septum pellucidum.

Results: 23 years old male patient is a student attending university, using left hand dominantly. He had used antidepressants for six months (paroxetine, sertraline) now he is not using the drugs. He has complaints of short-term paresthesia in right arm at daytime and morning. Also there is history of syncope attacks starting with right arm contraction then continuing with loss of consciousness. The patients was diagnosed with Complex Partial Epilepsy (Figure 1). After using of carbamazapin 600 mg 2x1, there were no epileptic seizures for four months. He has complaints of palpitation sweating, fear, left frontal pain continuing for 45–60 minutes, on the bed before sleeping. He has teeth clenching at night. Brain MRI showed us "Cortical Heterotopia" at left temporoparietal area (Figure 2). In polisomnographic (PSG) analysis, there were no sleep spindles, mostly there were delta wave oscillations together with repeated seizures, bruxism, arousals, central and obstructive sleep apnea until morning (AHİ: % 7,6).

Conclusions: The absence of sleep spindles in PSG, presence of epileptic seizures and somatic complaints of the patient together with the appearance of heterotopic area on brain MRI led us to think about the influenced of assosiative thalamocortical tracts. It was attractive that sleep spindles were not produced. The presence of clinical somatic and emotional symptoms, epileptic seizures determined in PSG though absence of seizures at daytime through the drugs, of the totally absence of sleep spindles point to the existence of subcortical ectopic area. Subcortical heterotopic neurons due to schizencephaly may be shown by MR tractography. As a result; this case is so important in regard to understand the physiopathological basis of the relationship between sleep spindle and epilepsy and to lead us to make new clinical studies.

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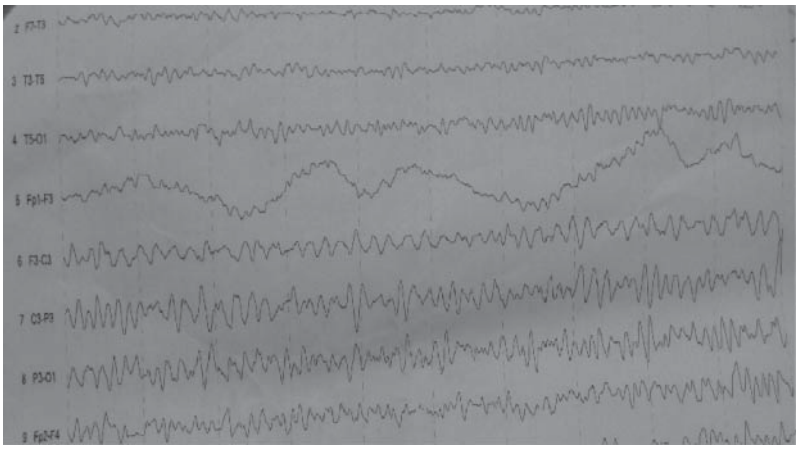

Figure 1: Daytime EEG: Irregular spike, spike wave (or arousal EEG) activities were determined on left frontal, parietal and occipital electrodes. No difference was shown by hypoventilation and fotic stimulation

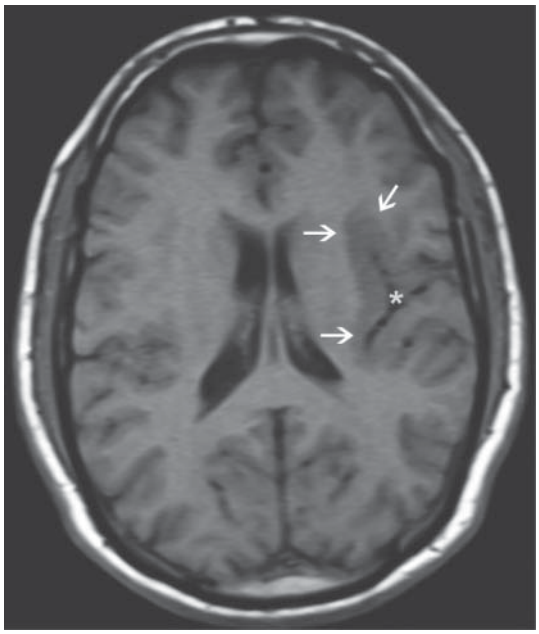

Figure 2: Axial T1 weighted MR image shows left temporo-parietal heterotopic gray matter (arrows) due to a closed-lip schizencephaly (asterisk)

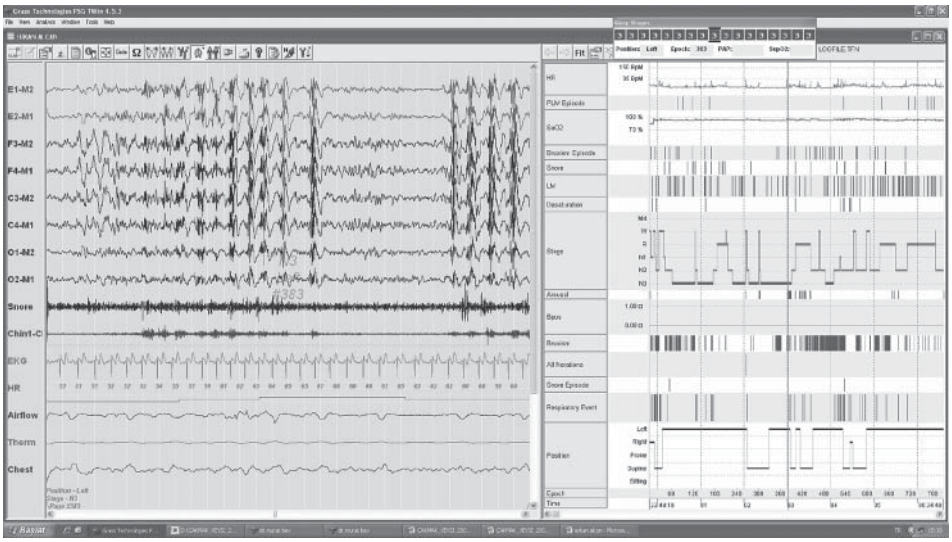

Figure 3: The image of delta wave and epileptic seizure in PSG record continuing an epoch

DONEPEZIL INDUCED SLEEP SPINDLE IN A PATIENT WITH DEMENTIA WITH LEWY BODIES: A CASE REPORT

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Keywords: Acetylcholine, lewy body dementia, donepezil, sleep spindle

Introduction: Dementia with Lewy bodies (DLB) is characterized by movement disorders with rapid eye movement (REM) sleep behavioural disorder (RBD) at the onset of symptoms, accompanied by visual hallucinations and cognitive fluctuations. Donepezil, an acetylcholine (Ach) esterase inhibitor, is gaining acceptance for treatment of cognitive impairment, as well as for behavioural and psychiatric complications. Though its effects on psychotic symptoms are known, there have been no reports on the physiological influence of donepezil on sleep architecture in DLB patients. Here we report a DLB patient in whom donepezil increased spindle activity.

Case Report: A 75-year-old woman presented with a 10-year history of night screaming and a 7-year history of parkinsonism. The patient began to display depressive symptoms 3 years before she presented at out clinic. Her main complaints were anxiety, depressive mood, memory loss and night screaming, which was thought to be a symptom of RBD. Psychiatric treatments were initiated. MMSE revealed the deterioration of visual conceptualization as well as the deterioration of delayed recall. We diagnosed the case as probable DLB. We per-

formed polysomnography (PSG). With respect to spindles, we defined the spindles as rhythmic oscillations ranging between 12 and 16 Hz that last for 0.5–1.5 s. After the first PSG recording, treatment with donepezil was initiated. After taking donepezil, not only did the patient's depressive and psychotic symptoms gradually diminish, but her night screaming also diminished slightly.

Discussion: Cholinergic neurons are critical in the control of REM sleep, so it is reasonable to postulate that donepezil would prolong REM sleep by strengthening levels of extracellular Ach. However, the duration of REM sleep did not increase with donepezil, indicating that the neurochemical mechanism that modulates the Ach system in DLB differs from that in normal subjects. To our knowledge, there have been no reports of PSG recording in DLB cases. When cholinesterase inhibitors are used to stimulate central cholinergic transmission, the natural circadian fluctuations of central cholinergic transmission may have a considerable effect. In addition, interfering with nocturnal cholinergic activity is likely to induce memory problems and sleep disorders. Ach activity during sleep mediates sleep-dependent learning and memory consolidation. We suggest that sleep spindles play a critical role in memory processing involving cholinergic modulation of the thalamocortical neural circuit.

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REDUCED SPINDLE FREQUENCY IS ASSOCIATED WITH INCREASED CEREBROSPINAL P-TAU IN COGNITIVELY NORMAL ELDERLY

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Introduction: Recent evidence suggests that sleep may play a role in AD pathogenesis, but the timing, role, and extent to which sleep disturbances in late life are associated with progression of AD neuropathology and cognitive dysfunction remains unclear. Sleep spindles are one type of several rhythmic brain waves during non-rapid eye movement (NREM) sleep and have been implicated in sleep quality. The thalamus has been implicated in the generation of sleep spindle oscillations and receives inputs from an ascending arousal system beginning largely in the brain stem and hypothalamus. Early in AD pathology, misfolded, hyperphosphorylated tau (P-Tau) protein accumulates in the brainstem, from where it spreads to the entorhinal cortex, hippocampi and other brain regions. Tau in the brainstem could therefore interfere with communication with the thalamus, resulting in down-regulation of sleep spindles and associated sleep disturbances.

Methods: 36 eligible participants were enrolled in the study and completed study procedures, including medical, neurological and laboratory examinations, a structural MRI, a morning lumbar puncture (LP) and a nocturnal polysomnography (NPSG). Five participants were excluded from the present analysis because 3 presented with moderate to severe sleep-disordered breathing (AHI4% ≥15), 1 showed very fragmented sleep with total sleep time (TST) <3 hours, and 1 consumed alcohol prior to the NPSG. In the remaining 36 cognitively normal elderly (Clinical Dementia Rating Score=0) (mean age 66.9 ± 8.3 years), NPSG was performed within 12.9 ±10.1 months of the lumbar puncture and analyzed for spindle frequency and density in stages 1, 2 and 3 and NREM sleep. Sleep spindles were scored using an automated optimization algorithm, which decomposed the input overnight EEG signal into oscillatory and non-oscillatory components. The oscillatory component was used to detect the spindles and a Fourier analysis was performed to evaluate the spindle frequency in 11–16 Hz.

Results: Spindle frequency and density in stage 2 sleep were inversely associated with CSF P-tau ($r=-0.41$, $p<0.05$; $r=-0.35$, $p<0.05$). The relationship between spindle frequency in stage 2 sleep and CSF P-tau remained significant after correcting for age or gender using a partial correlation ($r=-0.36$, $p<0.05$; $r=-0.38$, $p<0.05$ respectively). CSF P-tau showed no associations with spindle frequency or density in stages 1, 3, or total (1–3) NREM sleep, and there were no correlations between spindle density and CSF Aβ42.

Conclusion: In cognitively normal elderly, reduced sleep spindles are associated with increases in CSF P-tau. CSF P-Tau and T-Tau levels in cognitively normal elderly are likely related to the formation of neurofibrillary tangles in the brainstem and limbic system (Braak stages I-IV). While the presence of elevated CSF P-tau does not necessarily imply greater brainstem neurodegeneration, our preliminary data raise the intriguing possibility that downregulation of spindles and sleep fragmentation are an early downstream consequence of tau pathology.

FOCAL INTERICTAL ACTIVITY IN THE MOUSE VISUAL CORTEX INTERFERES WITH SLOW-WAVE OSCILLATIONS AND VISUAL PROCESSING IN THE CONTRALATERAL HEMISPHERE

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Keywords: Interictal spikes, slow wave oscillations, up states, visual cortex

Several studies have addressed the mechanisms and the dynamics of bicuculline-induced interictal spikes (IS), which are a feature often associated with epileptiform activity[1]. However, the physiological impact of an epileptic focus gen-

erated in one cortical region of the brain on the adjacent areas remains poorly understood.

Here, we investigated how the generation of hypersynchronous interictal spikes, focally localized in the visual cortex of one hemisphere, affects the contralateral cortex in the anesthetized mouse. First, we studied the mutual relationship between slow-wave activity and IS. By recording simultaneously the local field potentials in the two hemispheres we observed that in the region interested by IS, slow-wave activity was completely suppressed. Interestingly, the up-states of the ongoing sleep slow oscillation triggered the IS.

In the contralateral hemisphere the slow-wave pattern was subtly disrupted, with a decrease in length and an increase in frequency of up-states. By loose-patch recording and by phase-locked averaging of the local field potential we determined that every IS caused a peculiar change in the firing probability of the contralateral hemisphere: initially, the IS increased lightly the firing probability in this area but, after about 100 ms, the cortex was completely silenced for about 200 ms.

Finally, by testing the visual evoked responses in the opposite hemisphere, we found that they were differentially altered depending on the temporal relationship between IS and stimulus presentation.

Together, our data suggest that IS could interact with other cortical dynamics far from the epileptic focus, disrupting endogenous oscillatory rhythms and affecting brain information processing.

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SIGMA ACTIVTY OF SLEEP EEG INCREASES WITH DEPRESSIVE SYMPTOMS IN KIDNEY TRANSPLANT RECIPIENTS

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Keywords: Depression, insomnia, kidney transplant recipients, sigma power, beta power

Introduction: The prevalence of depression is high among kidney transplant recipients, it is associated with graft rejection and influences negatively quality of life and even mortality. Sleep complaints are also frequent in this patient population, however, the details of the complex relationship between sleep and depression are still unclear. Thus we investigated whether depressive symptoms correlate with sleep macro- and microstructure parameters among kidney transplant recipients.

Methods: Fifty-five kidney transplant recipients participated in the study (34 males, mean age 50±13 years, BMI 26±4 kg/m^2, estimated glomerular filtration rate 52±18 ml/min). Symptoms of depression were assessed by the Center for Epidemiologic Studies – Depression Scale (CES-D). After one-night polysomnography (PSG) each recording was visually scored and sleep macrostructure parameters were defined. EEG absolute spectral power was also computed within the delta (0.75–4 Hz), theta (4.25–8 Hz), alpha (8.25–11 Hz), sigma (11.25–15 Hz) and beta (15.25–25 Hz) frequency bands.

Results: We have found a correlation between CES-D score and NREM sigma and beta (r=0.29; r=0.30), and REM sigma and beta (r=0.27; r=0.28) spectra, respectively ($p<0.05$ for each correlation). In multivariable linear model after controlling for age, sex, kidney function, BMI, sleeping pill use and insomnia symptoms, the CES-D score remained an independent predictor of NREM sigma (β: 0.23; CI: 0.009–0.451). We have not found any significant correlations between CES-D score and the PSG macrostructure variables.

Conclusion: The symptoms of depression correlated with increased beta activity during sleep, which supports the hypothesis that central nervous system

hyperarousal might contribute to the emergence of depression. The positive association of NREM sigma activity and depression symptoms – which was independent of important covariables – suggests an intact sleep protecting mechanism in this population in line with previous suggestions[1]. Further studies are needed to confirm our findings and understand potential clinical implications.

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Methodology

QUANTIFYING PHASE-AMPLITUDE COUPLING OF SLEEP SPINDLES

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Keywords: Phase-amplitude coupling, sleep spindles, Schimmel's ± reference

Phase-amplitude coupling (PAC) of sleep spindles concerns the relationship of spindle envelopes to the phase of a lower frequency signal. The required restriction of the analysis to slow wave cycles that co-occur with spindles causes the averaged envelope amplitude over the slow wave cycles to be bow shaped even in perfect absence of PAC. Schimmel's ± reference[1] may be used to estimate this systematic bias. The procedure requires (1) interpolating each spindle envelope over a constant number of data points irrespective of actual slow wave cycle length, (2) subtracting a local resampling of the spindle envelope randomly centered within its co-occurring slow wave cycle, thus cancelling the bias, and (3) repeatedly calculating the selected PAC quantifier after inverting a random half of the envelope differences, so as to reliably estimate the effect of deviation from perfect flatness in absence of PAC. Seven potential quantifiers are compared, which all perform better when a suitable fractional exponent is applied to make their distribution acceptably symmetrical under a variety of conditions. Applied to a common sample of 45 patients with Parkinson's disease (who did not develope dementia at later assessment, 2–9 years later) and 44 controls, all methods detect PAC in all 64 combinations of 8 channels providing respectively the slow wave signal (0.75–1.25 Hz) and the spindles (11–15 Hz), with an average effect size over the 64 pairs slightly above 1.55. The same quantifiers applied on the same frequency bands but away from spindles detect PAC in only 62 channel pairs (excluding PAC of occipital slow waves with contralateral frontal 11–15 Hz),

with mean effect size around 0.6, where the adapted circular mean method[2] significantly outperformed the remaining quantifiers with a mean effect size of 0.68.

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USING SWITCHING MULTIPLE MODELS FOR THE AUTOMATIC DETECTION OF SPINDLES

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Keywords: Spindles, EEG segmentation, switching multiple models

Sleep EEG data is characterised by various events that allow for the identification of the different sleep stages. Stage 2 in particular is characterised by two morphologically distinct waveforms, specifically spindles and K-complexes. Manual scoring of these events is time consuming and risks being subjectively interpreted; hence there is the need of robust automatic detection techniques. Various approaches have been adopted in the literature, ranging from period-amplitude analysis, to spectral analysis and autoregressive modelling. Most of the adopted techniques follow an episodic approach where the goal is to identify whether an epoch of EEG data contains an event, such as a spindle, or otherwise. The disadvantage of this approach is that it requires the data to be segmented into epochs, risking that an event falls at an epoch boundary, and it has low temporal resolution.

This work proposes the use of an autoregressive switching multiple model for the automatic segmentation and labelling of Stage 2 sleep EEG data characterised by spindles and K-complexes. When this modelling technique was used to identify spindles from background EEG, quantitative results based on a sample by sample basis gave a sensitivity score between 72.39% to 87.51%, depending to which scorer performance was compared. This score corresponds to a specificity that ranges between 78.89% and 90.55% and which increases to a range between 75.52% and 94.64% when performance is measured on an event basis instead [1]. This performance compares well with other spindle detection techniques published in the literature [2, 3].

The advantage of the proposed technique is that it allows for the continuous segmentation of EEG data, it offers a unified framework to detect multiple events with little training data, and it can also be extended to a semi-supervised

approach. The latter, which has also been applied to Stage 2 sleep EEG data, can identify new states in real time, providing a solution that not only replaces the time consuming manual scoring process but it may also provide the clinician with new insights on the data that is being analysed.

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NEW PERSPECTIVES IN THE DETECTION OF SLEEP SPINDLES IN EEG (A COMBINATION OF WAVELETS AND EMPIRICAL MODES)

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Keywords: EEG, express diagnostics, time-frequency analysis, continuous wavelet transform, empirical modes

EEG sleep spindles are sensitive indicators of basic functions of the central nervous systems, and in-depth examination of their time-frequency parameters may contribute to a better understanding of brain functions. There are many reliable systems for the automatic scoring of sleep spindles in the EEG [reviewed in 1]. We suggest a new approach that combines the detection (scoring) of sleep spindles and express diagnostics (based on their time-frequency parameters). The key problem in the automatic detection of sleep spindles is the high variability of their waveforms in the EEG, and it can be dealt with by decomposing EEG signals into a set of simpler components, the empirical mode decomposition (EMD). The EMD is a part of the Hilbert-Huang transform [2], and it extracts independent oscillatory components in the time domain. We examined EEG during sleep in WAG/Rij rats and found that the 1st empirical mode of EEG signal, *c1(t)*, conveyed the most important information about sleep spindle oscillations (10-14 Hz), and the other modes consisted of low frequency components. The continuous wavelet transform (CWT) was used to detect sleep spindles and for

further time-frequency analysis. The native EEG signal contained redundant information about sleep spindles, and the CWT of the non-processed EEG signal was time-consuming. This limited express analysis of sleep spindles in long-term EEG recordings. We used the CWT-based system for the automatic recognition of sleep spindles in 20-24 h EEG recordings in a group of rats and obtained significantly more accurate detections (higher sensitivity and selectivity) with *c1(t)* as input signal than what was found with the native EEG.

Finally, for express diagnostics of sleep spindles in long-term EEG recordings it is beneficial to combine time-domain EEG reprocessing by means of the EMD with time-frequency EEG analysis using the CWT.

This study was financially supported by the Russian Foundation for Basic Research (Grants 15-52-45003 and 16-04-00275).

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AN EEG ANALYSIS METHOD TO ESTIMATE THALAMOCORTICAL CONNECTIVITY

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Keywords: Electroencephalogram, thalamocortical model, parameter estimation, autoregressive model

The thalamus has been recognized to play an important role in sleep onset [1, 2]. Although the direct detection of functional changes of the thalamus is not possible using scalp EEG (electroencephalogram), some inferences may be possible by this method because functional change of the thalamus is thought to affect EEG signals and these effects can be mathematically modelled by the thalamocortical model (TC model) [3]. While some studies have shown the validity and effectiveness of TC models [3, 4], further technical investigation is needed toward practical and clinical applications. One issue, which needs resolution, is time resolution. In most cases, a power spectrum is used for model-fitting [3, 4] but this process deteriorates time resolution because long time data are required to extract reliable power spectrums from noisy (stochastic) EEG data. A second issue is so-called "local minimum" or non-uniqueness in the fitting (optimizing)

procedure, arising from a large number of fitting parameters and nonlinear contributions of parameters to the power spectrum.

In this presentation, we propose a novel method to deal with the abovementioned issues. The basic idea is parallel use of auto-regressive (AR) model with the TC model in data processing. The AR model is a "stochastic" model that shortens the time to extract power spectrums and is also a "linear" model that is free from the local-minimum problem. By identifying the transfer function of the AR model with the transfer function of the TC model, we derived a direct expression of the cortico-thalamo-cortical loop strength using AR coefficients. Sleep-EEG data analysis using this method clearly tracked the wake-sleep transition; the estimated cortico-thalamo-cortical loop connectivity decreases to almost zero during the wake-sleep transition as is consistent with previous studies [1–3].

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