Abstract Book

2nd International Conference on Sleep Spindling and Related Phenomena

May 24–26, 2018 • Budapest, Hungary

Danubius Hotel Gellért

Szent Gellért tér 2, H-1114 Budapest, Hungary

Akadémiai Kiadó / AKCongress
P.O.Box 245, H-1519 Budapest, Hungary

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Sleep spindles and epilepsy

Firing dynamics of cortico-thalamic neuronal assemblies during absence seizures

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Behaviorally and pathologically relevant cortico-thalamo-cortical oscillations are driven by diverse interacting cell-intrinsic and synaptic processes. However, the mechanism that gives rise to the paroxysmal oscillations of absence seizures (ASs) remains unknown. In my talk, I will present novel data showing during ASs in behaving animals, cortico-thalamic excitation drives thalamic firing by preferentially eliciting tonic rather than T-type Ca^{2+} channels (T-channels)-dependent burst firing in thalamocortical (TC), and by temporally framing thalamic output via feed-forward reticular thalamic (NRT)-to-TC neuron inhibition. In TC neurons, overall firing is markedly reduced and bursts rarely occur. Moreover, block of T-channels in cortical and NRT neurons suppresses ASs, but in TC neurons has no effect on seizures or on ictal thalamic output synchrony. These results provide the first mechanistic understanding of cortico-thalamo-cortical network firing dynamics and interactions during ASs in behaving animals.

Low-frequency precursors of sleep spindles in EEG in a rat model of absence epilepsy

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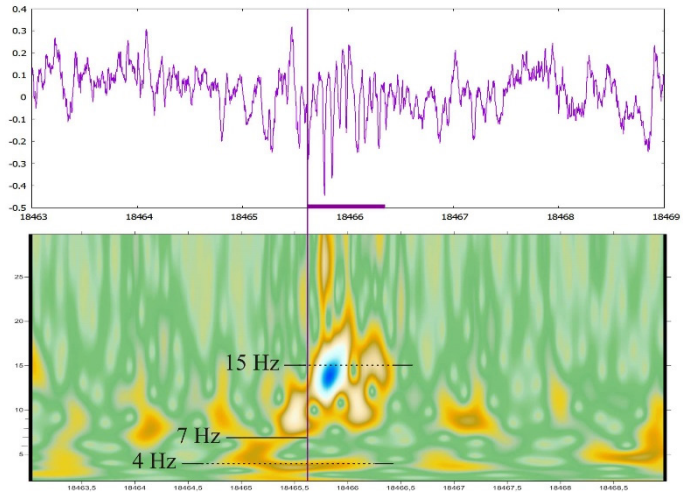
Keywords: absence epilepsy, EEG, time-frequency analysis, continuous wavelet transform

Sleep spindles are generated in the thalamo-cortical neuronal network, as well as epileptic spike-wave discharges (EEG halmarks of absence epilepsy). WAG/Rij rat strain is a well known genetic model of absence epilepsy, but some rats in Moscow's population do not show any seizures (e.g. "non-epileptic" subjects). We described specific associations between time–frequency properties of sleep spindles and intensity absence epilepsy in WAG/Rij rats (reviewed in [1]). Low-frequency components (< 9 Hz) of sleep spindles in the "non-epileptic" subjects were more powerfull than in "epileptic" rats [2]. Continuous wavelet analysis in the frontal EEG indicated that 69% of sleep spindles in the "epileptic" WAG/Rij rats were preceded by 2–7 Hz rhythmic activity, but this percent (43%) in the "non-epileptic" rats was lower.



Continuous wavelet transform of frontal EEG in adult WAG/Rij rat showing that the sleep spindle (~14-15 Hz) is preceeded by low-frequency activity in delta/theta bands (<7 Hz).

As compared to the “non-epileptic”, “epileptic” rats showed fewer sleep spindles with low-frequency rhythmic precursors (<7 Hz), and the amplitude of low-frequency rhythmic precursors of sleep spindles was smaller.

Acknowledgments

This study was financially supported by the Russian Foundation for Basic Research (grant 16-04-00275).

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Sleep slow waves, spindles and thalamic gating I.

Delta waves and UP-DOWN sates – are they separate entities?

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In the last quarter of the 19th century Caton (1875) and Beck (1890) recorded electrical activity from the exposed surface of the brain in rabbits and dogs, and showed that it changed with external stimuli and with the behavior of the animals. About 50 years later Berger (1929) demonstrated that electrical activity of the brain can also be recorded from the scalp of humans. He described α and β patterns in relation to the mental state of the subject, and first used the abbreviation EEG for the electroencephalogram.

Soon it was discovered that EEG has a high diagnostic value in epilepsy, and in detecting the location of cortical tumors, above which large, slow, so called δ waves were described. EEG was also shown to change with sleep and anesthesia. The mass production of ink-writing EEG machines superseding galvanometers and oscillographs helped recording electrical activity of the brain for both scientific and diagnostic purposes resulting in a plethora of scientific papers. EEG societies were formed around the world.

It quickly became clear that cortical and/or cortico-subcortical networks are prone to rhythmic, oscillatory activity at different, mostly slow frequencies. Recording of neuronal activity with extracellular and intracellular microelectrodes around the middle of the 20th century proved that slow (most importantly synaptic) membrane potential changes in cortical neurons are mainly behind the generation of EEG waves.

Electrical activity of the brain can be recorded at several distinct levels: from the scalp (EEG), from the cortical surface (electrocorticogram, ECoG), from the depth of the cortex (LFP), through transcortical electrodes, with electrode arrays, from neurons extracellularly and intracellularly. Recordings can be made in unanesthetized animals and humans, or under the influence of various anesthetics, and in pathological conditions. Even now, it is difficult to find and prove the connection between the different patterns obtained in different subjects, in different conditions, using different recording methods.

In relation to slow waves, Steriade (1993) have shown that during NREM sleep, hyperpolarizing and depolarizing periods alternate in all cortical neurons in cats, similarly to the UP and DOWN states reported earlier by Wilson (1983) in neostriatal neurons.

UP-DOWN transitions in cortical neurons might be behind several types of slow cortical EEG patterns like delta waves recorded during NREM sleep, anesthesia and in pathological conditions. However, it is difficult to obtain direct proof for this claim, because of the different recording methods mentioned above, and because of the different appearance of slow cortical patterns in different conditions.

There is no general agreement about the generator of the slow EEG patterns. Neuronal activity was reported to change in synchrony with cortical UP-DOWN states in several subcortical structures that have interconnections with the cortex: thalamus, BFA, PPT, MFR, etc. These structures probably participate in the generation and shaping of the slow cortical EEG patterns, even if the cortex itself is able to produce slow waves. This suggestion is supported by the fact that spindles can appear during transitions between UP and DOWN states.

It is tempting to suppose that during transitions, the level of ascending subcortical activation, depending on the slope, stays for some time in the range that facilitates spindle generation in the thalamocortical system.

Another interesting point is that we found an increased MUA activity preceding DOWN states in freely moving rats. The intensity of the activation correlated with the depth of the DOWN state. Similar activations can be seen in several publications. Evoked potentials in NREM sleep and in anesthesia are also followed by strong and long inhibitions, i.e. DOWN states, suggesting an increased sensitivity of cortical neurons for activation.

(No) Need to Wake up? Inhibitory Function of Sleep Spindles is Tuned to Stimulus Salience

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Keywords: sleep spindles, high-density electroencephalography, auditory stimulation

While it is nowadays well-established that the brain continues to process external stimuli during sleep despite the organism being in a state of behavioural unresponsiveness (e.g. Blume et al., 2016; Strauss et al., 2015), studies also suggest that sleep-specific oscillatory patterns and in particular sleep spindles can alter processing of environmental stimuli. Schabus et al. (2012) for example report that when they stimulated participants with simple tones during non-REM sleep, responses were comparable to those during wakefulness with the exception of when tones were presented during a spindle, where it was largely absent. However, so far studies have only used stimuli characterised by limited ecological validity such as tones. The aim of the present study therefore was to investigate how sleep spindles relate to processing of more naturalistic stimuli of varying salience.

To this end, we presented participants with linguistic stimuli and varied stimulus salience by manipulating subjective (subject's own name [SON] vs. unfamiliar name [UN]) and paralinguistic emotional relevance (familiar vs. unfamiliar voice, FV/UFV). We studied cognitive processing during sleep by means of event-related oscillatory responses (de-/synchronisation, ERD/ERS) in a 1–15 Hz range using 256-channel electroencephalography (EEG) during a whole night of sleep in n = 17 healthy participants. Specifically, for the spindle analyses we selected trials during N2/N3 sleep where stimulus presentation either overlapped with a sleep spindle (n = 10) or did not. ERD/ERS was calculated between 0 and 1200ms relative to stimulus onset with respect to a 600ms pre-stimulus baseline. For the statistical evaluation of the results we used the cluster-based permutation approach implemented in the Fieldtrip toolbox (Oostenveld et al., 2010) in Matlab (Mathworks, Natick, USA).

We find that even if a sleep spindle overlapped with stimulus presentation the responses elicited by UFV stimuli in the delta through lower alpha range (i.e. up to about 9Hz, Fig. 1A,

C) were similar to the pattern when there were no spindles (Fig. 1B, D). Intriguingly and in contrast to what has been proposed earlier, this implies that the presence of a sleep spindle does not or at least not uniformly inhibit processing of environmental stimuli. Beyond this, the response pattern above ≈9Hz when a spindle overlapped with stimulus presentation was strikingly different from the "no spindle" condition (see Fig. 1E and F) with FV stimuli eliciting stronger ERD than UFV stimuli in the spindle (≈11–15Hz) range. We speculate that this may reflect a relatively stronger release of inhibition by sleep spindles.

Acknowledgments

CB is supported by the Konrad-Adenauer-Stiftung e.V. and CB, MW and DPJH are supported by a grant from the Austrian Science Fund FWF (Y-777). CB, RdG, MW and DPJH are also supported by the Doctoral College ‘‘Imaging the Mind’’ (FWF; W1233-G17).

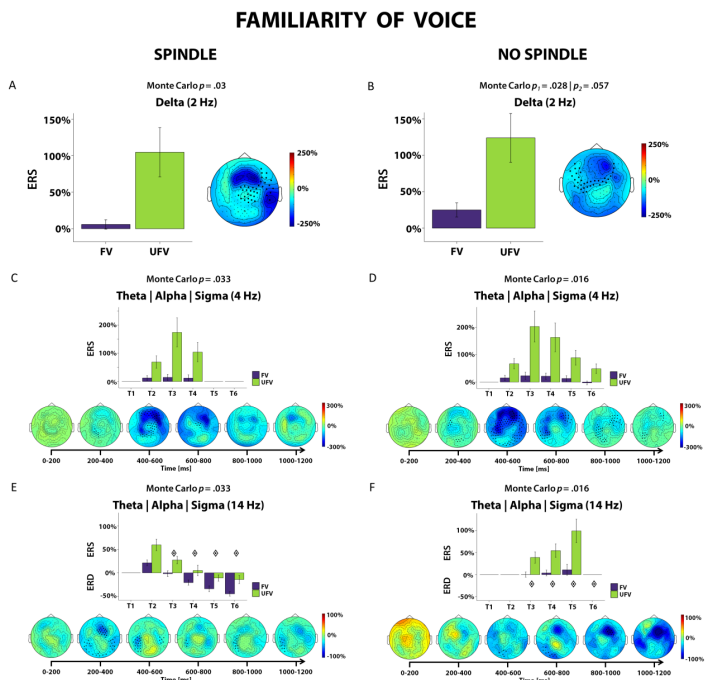

Fig. 1: Event-related responses during N2/N3 sleep depending on the presence/absence of sleep spindles. (A, B) Event-related responses in the delta range at 2 Hz. Bar plots for the averaged effect of voice between 0 and 1200ms (left) and corresponding scalp plot of differences in ERS/ERD between FV and UFV stimuli (right). **(C, D)** Event-related responses in the theta/alpha/sigma (4-15Hz) range at 4Hz and **(E, F)** responses at 14Hz. Bar plots for the effect of voice during the six 200ms time windows (top) and corresponding scalp plots of differences in ERS/ERD between FV and UFV stimuli (bottom). Diamonds in figures E and F indicate the time windows with significant differences between "spindle" and "no spindle" conditions at 14 Hz. Large black dots indicate the electrodes that are part of the significant clusters at 2Hz, 4Hz or 14Hz. Error bars indicate ±1 standard error of the mean. Please note that for illustration purposes we show the effects at representative frequencies (i.e. 2, 4 and 14 Hz) although significant clusters may have comprised a larger frequency range. FV = familiar voice, UFV = unfamiliar voice. Analyses and figures are based on data from n = 10 participants.

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Continued Evaluation of Own Name Stimuli in deep NREM sleep – A hd-EEG study

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Keywords: slow oscillation, delta, high-density electroencephalography, auditory stimulation

While it is a well-established finding that subject's own names (SON) or familiar voices are salient during wakefulness, we here investigated processing of environmental stimuli during sleep including deep N3 and REM sleep. Besides the effects of sleep depth we investigated how sleep-specific EEG patterns (i.e. sleep spindles and slow oscillations [SOs]) relate to stimulus processing. Using 256-channel EEG we studied processing of auditory stimuli by means of event-related oscillatory responses (de-/synchronisation, ERD/ERS) and potentials (ERPs). We varied stimulus salience by manipulating subjective relevance (own name vs. unfamiliar name) and familiarity (familiar vs. unfamiliar voice, FV/UFV). We recruited 20 healthy individuals for the study of which 16 participants (three males) could be included in the final (deep) NREM sleep analysis (median age, 22.6 years, SD = 2.3 years). Mean sleeping time (total sleep time = 430.5) in NREM was 31min in N1, 159.29min in N2 and 147.23min in N3 sleep.

Results reveal that evaluation of voice familiarity continues during all NREM sleep stages and even REM sleep suggesting a 'sentinel processing mode' of the human brain in the absence of consciousness. Especially UFV stimuli elicit larger delta (1–3Hz) synchronization across all sleep stages including NREM stage 1–3 (see Figure 1 A–C) suggesting that these stimuli continue being salient in deep sleep. Beyond this, we show that even irrespective of the slope of a SO (up vs. down-state) UFV stimuli continue to elicit a stronger delta synchronization. Evaluatling event-related potentials likewise confirm these results and show

potential differences with the UFV eliciting larger and more complex waveforms (see Figure 1 D–E).

Altogether the data suggests that in deep NREM sleep as well as different phases of the slow oscillation stimulus processing and inhibition continues to be tuned to stimulus salience. It is open to discussion if these results contradict earlier findings (e.g., Schabus et al. (2012)) because the used stimuli are of higher complexity and ecological relevance than earlier used pure tones.

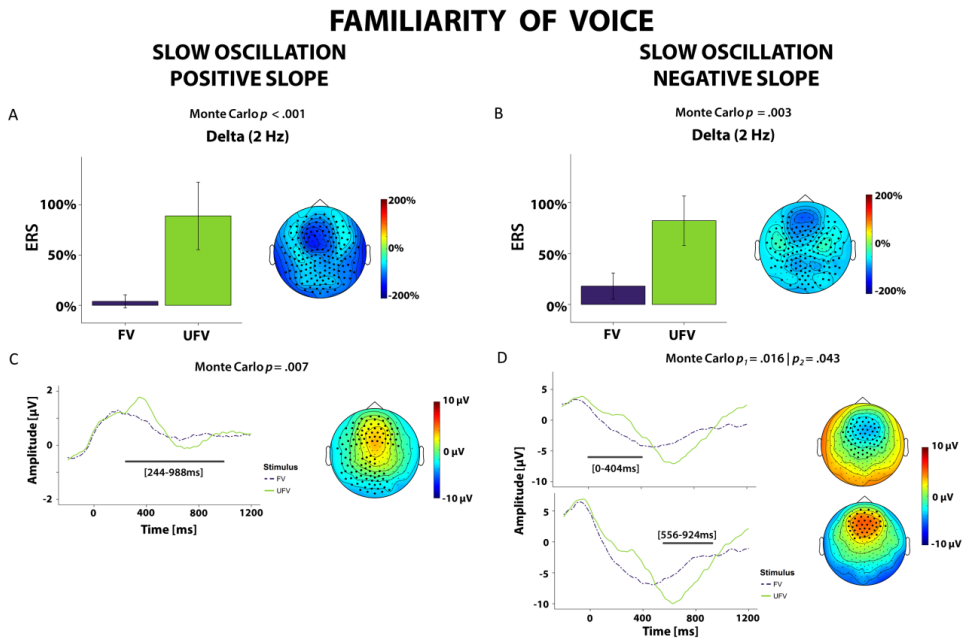

Fig. 1: Event-related responses during N2/N3 sleep when a stimulus was presented along the positive vs. negative slope of the SO. (A, B) Event-related responses in the delta (1-3Hz) range. Bar plots for the effect of familiarity of voice (left) and corresponding scalp plots of differences in ERS between FV and UFV (right). **(C, D)** Grand average of the ERP elicited by FV and UFV stimuli at all electrodes that were part of the cluster (left). Positive values are plotted up-, negative values downwards. The horizontal grey line represents the time window during which the effects were significant. Topoplots (right) show of the difference in the ERP evoked by FV and UFV stimuli in the significant time window(s). Large black dots indicate electrodes that were part of the significant clusters. FV = familiar voice, UFV = unfamiliar voice.

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Thalamic dual-control of sleep and wakefulness

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Keywords: slow-wave, thalamus, sleep, optogenetics

During mammalian non-rapid eye movement sleep (NREMS), cortical activity is characterised by slow wave oscillations (1–4 Hz) resulting from large neuronal ensembles alternating between active (UP) and quiescent (DOWN) states. However, the circuit mechanism underlying the onset, synchrony and travelling of cortical UP-states remains unclear. Here we show that spontaneous centromedial thalamus (CMT) neuronal firing is phase advanced to global cortical UP-state as well as NREMS-to-Wake transitions, distinct from primary sensory thalamic neurons using multisite electrode recordings in freely behaving mice. Optogenetic silencing of CMT neurones inhibits this synchrony, whereas their activation mimics cortical UP-state during sleep and induces NREMS-to-Wake transitions. Importantly, we found that both spontaneous and optogenetically-induced slow waves originating in a CMT-cingulate network travel across the fronto-occipital axis and requires functional antero-dorsal thalamus (AD) relay cell activity. Finally, we demonstrate that this circuit is necessary for sleep recovery. Our results suggest that tuning of CMT neurone firing supports a dual control of sleep slow waves and wakefulness through wide-scale cortical propagation, and provides a circuit mechanism for thalamocortical synchrony during sleep and sleep recovery.

Thalamocortical mechanisms of sleep spindle generation I.

State dependent activity of wake and sleep

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Keywords: slow oscillation, spindles, slow rhythms, performance, optimal state, modulation

Activity in the forebrain is state dependent. During periods of sleep, two prominent rhythms are generated: slow waves and spindle waves. We now know the cellular and network origins of these rhythms. Slow waves are generated as Up and Down states with the Up states resulting from the recurrent excitation roughly balanced by local inhibition within the cortex. The failure of the Up state results in a Down state. Spindle waves, in contrast, are generated as a circuitous interaction of the GABAergic neurons of the thalamic reticular nucleus and thalamocortical relay cells and depends upon the excitation of nRt neurons by relay neurons, the generation of low threshold Ca2+ spikes, and the initiation of synchronized inhibition of thalamocortical cells by this nRt activity. Some of these inhibited relay neurons rebound burst, thus exciting the nRt yet again, starting the next cycle of the spindle wave. The time it takes for this cycle to complete (relay-nRt-relay) sets the frequency of spindle waves (6–15 Hz). Spindle waves recur owing in part to Ca2+ dependent modulation of the h-current. Slow waves and spindle waves interact to generate more complicated rhythms during sleep. On a larger spatial scale, these rhythms appear as travelling waves across the thalamocortical circuitry.

Recent studies in awake behaving mice have revealed that the waking state also contains slow rhythms and the presence of these rhythms strongly influences sensory processing, decision, and action. During quiet waking, cortical networks often exhibit a prominence of activity in the low (< 10 Hz) frequency range, particularly in mice that are sitting still, with a small pupil diameter, indicating drowsiness or inattentiveness. These slow rhythms have many of the same features of the slow oscillation of sleep, yet occur in waking animals. Testing the responsiveness of animals in this state reveals that although they can performed trained tasks, their rate of success is significantly lower and their latencies are more variable and longer (than when the animals in are more attentive and engaged state). Likewise, sensory evoked responses are compromised. Increases in arousal suppresses these slow oscillations. If the cortex enters into a quiet state, the performance of the animal on the trained task may enhance considerably. Further increases in arousal or locomotion results in strong depolarization of cortical neurons and a large increase in spontaneous activity. This state is associated with a strong reduction in the ability of animals to perform auditory or visual detection tasks. These results indicate that the activities of the thalamocortical system previously associated with slow wave sleep also make an appearance in quiet waking and are associated with decreases in processing and performance. The neuromodulatory mechanisms of these rapid variations in waking state are under investivgation.

Acknowledgments
Supported by NIH and DARPA.

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Local, spindle-enriched non-REM sleep in mouse somatosensory cortex enabled through heterogeneous thalamic burst propensity

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Objectives. Sleep is a global vigilance state, yet its cerebral correlates are locally heterogeneous. We explore the expression of locally different sleep features and investigate their underlying cellular and circuit mechanisms, as well as their relevance for local circuit function. Methods. We record in mice the palette of regional activities in-vitro within the major thalamic rhythm pacemaker (the thalamic reticular nucleus TRN), and the local variations of sleep oscillations in multiple cortical areas in-vivo. Results. We identify TRN CaV3.3 calcium channels as a molecular source for cortical heterogeneity in mouse non-REM sleep. CaV3.3-channels enabled a graded form of repetitive burst discharge: strongest in somatosensory, intermediate in auditory, and weak in non-sensory sectors of the TRN. In undisturbed sleep, the corresponding somatosensory (but not auditory and prefrontal) cortices, showed fast, strong and locally synchronous sleep spindles. Without CaV3.3 channels, somatosensory areas expression in delta waves was enriched, and spindles became homogenous across sensory and non-sensory cortices. Furthermore, the tight locking of fast spindles to the upstate of cortical slow-oscillation was disrupted. Conclusions. Here, we unravel the critical role of the thalamus in shaping local heterogeneities of non-REM sleep and in imposing forms of spindle-enriched sleep in the major sensory modality of mouse.

Dissecting local sleep spindles in the thalamocortical system

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Keywords: wavelet function, spike-field coupling, slow wave, optogenetics, thalamic reticular nucleus

Spindles are transient oscillatory events (9–16 Hz) occurring in the thalamocortical network during non-rapid eye movement (NREM) sleep. Spindles can be recorded locally or globally and are hypothesized to stabilize sleep and consolidate memory. Here we report a novel automated spindle detection algorithm by direct comparison of 15 different wavelet families and optimization using sleep recording from human scalp EEG. Next, we used this optimized algorithm to detect spindles in mice from simultaneous EEG, EMG, LFPs and neuronal unit activity recorded from the thalamic and cortical sites. We found that single unit activity was strongly phase-locked to the LFP spindle cycles within the thalamic reticular nucleus (TRN), anterodorsal thalamus (AD), and centromedian thalamus (CMT), and to a lesser extent within the ventrobasal complex (VB), the cingulate cortex (CING), and the somatosensory barrel cortex (BARR). No spike-field coupling was observed for the secondary visual cortex (V2). We further found a strong coupling between slow waves and spindles within the CMT, AD, CING, and V2, but this coupling was weak for the TRN, VB, and BARR. Network analyses showed a high concurrence ratio of sleep-spindles within the thalamus (~82%), but that fewer of these spindles are propagated to the neocortex (~57%). Furthermore, co-occurrence at the cortical level was low (~50%), indicating a localized control of sleep-spindles in the neocortex. The average spindle rate of NREM episodes prior REM sleep was significantly higher than of NREM episodes with a transition to wake. Within a window of 25 s prior REM sleep onset, the spindle rate was ~3 times higher as compared to baseline, and then slightly decreased while approaching the REM sleep onset. This increase before vigilance state transition was specific to REM sleep, since NREM sleep-to-wake transition showed no increase in spindle activity. Finally, optogenetically driving the TRN GABAergic cells using the stabilized step-function opsin (SSFO) significantly increased both the single unit and bursting activity and resulted in significant increase in spindle rate. Together, these results provide a toolbox for detecting local and global sleep spindles, and provide new insights into generation of spindles in the thalamocortical system and their role in the sleep-wake cycles.

The frequency of sleep spindle oscillations

In a search of fast and slow spindles

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Literature points to the presence of two distinct types of sleep spindles: fast (12–15 Hz) and slow (9–12 Hz). In human, the two types of spindles have different properties, including their distinct distribution over the cortical surface, different responses to sodium channel and calcium channel antagonists, different relation to sleep slow wave activity etc. This suggests different cellular mechanisms mediating the generation of the two types of spindles. According to the currently available data obtained mainly in vitro or on anesthetized animals, the spindles are generated in the thalamus as an interaction between reticular thalamic and thalamocortical neurons. In anesthetized animals and in vitro, the frequency of spindles is lower than during natural sleep. Known and accepted mechanisms of thalamic spindle generation do not explain differences in the properties of fast and slow spindles. Our current study demonstrates that in cats, in each recording site the frequency of spindles is not stable and spans from slow to fast, but slower spindles tend to be generated in marginal and posterior suprasylvian gyri. We could not identify clearly fast and slow spindles that co-occurred within a 10 sec timeframe. Cortical slow waves trigger some spindles with higher probability in suprasylvian gyrus and medial prefrontal cortex. Cortical slow waves terminate ongoing spindles. Most of detected spindles were local, but when global they tended to propagate, in particular, within the same gyrus. Our results suggest that, at least in cats, fast and slow spindles generation shares similar mechanisms, which are differently expresses in different unidentified sleep microstates likely mediated by a difference in neuromodulatory tone.

Supported by CIHR and NSERC.

Reflections on sleep spindle frequencies

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Oscillatory frequency is one of the main defining features of sleep spindles. In spite of the crucial importance of this phenomenologically salient aspect of sleep spindles, systematic investigations aiming to determine the factors, mechanisms and conditions defining and/or modulating sleep spindle frequency (SSF) are virtually absent in the literature. In order to fill this gap we aim to review the multiplicity of factors and conditions correlating with SSF. The working definition of SSF is based on the individualized spectral peak frequency in the 9-16 Hz range with 1/16 Hz resolution. SSF is dichotomous: the anterior and posterior regions of the cortex are characterized by slow-anterior and fast-posterior SSFs (mean ± SD fast-slow difference: 2.14 ± 0.74 Hz), respectively, with some thalamic nuclei, or limbic regions

exhibiting a prevailing predominance of one or another type of SSF (slow or fast). Age and sex predicts 8 and 48 % of slow and fast SSFs, respectively. The age-dependent change in SSF between 4 and 69 years is best characterized by a 2nd order polynomial (increase followed by stagnation then decrease). In addition, women have higher SSF than men (slow: 11.65 vs 11.32 Hz; fast: 13.84 vs 13.46 Hz), but there are no sex differences in children and older subjects. Individual SSFs are further modulated by circadian phase (melatonin decelerates SSFs), menstrual cycle phase (progesterone accelerates SSFs), various pharmacological agents (eg. antiepileptic drugs, oral contraceptives, etc), core body temperature (CBT) and developmental disorders (SSF is accelerated in Williams syndrome indicating fine motor learning difficulties). A closer look at the data and possible mechanisms suggests that CBT correlates positively with SSF in humans and other animals, including poikilotherms. CBT vs SSF correlation could contribute to the majority of the sex- and age-, as well as hormone-dependent SSF alterations. Intra-spindle changes in frequency are characterized by deceleration (down-chirp). Theoretically, SSF depends on the length of the synchronized hyperpolarization-rebound sequences of thalamocortical cells, the inhibition of which is caused by the NREM-dependent activation of GABAergic neurons in the reticular thalamic nucleus. However, cortical factors like the duration of the cortical feedback, as well as the time required to the building up of the thalamocortical recruiting response could also affect emerging SSF. Thus, the understanding of the factors affecting SSF is not only of practical importance (proper definition of sleep spindles), but has direct theoretical relevance in understanding the generation and functional importance of sleep spindle oscillations.

Sleep slow waves, spindles and thalamic gating II.

State-dependent activity in the visual thalamus

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In the absence of sensory input, the mammalian brain exhibits a wide array of structured, state dependent spontaneous activities. Periods of active wakefulness are associated with dilated pupils, depolarized cortical membrane potential, asynchronous firing and fast oscillations, whereas periods of quiet wakefulness are asociated with constricted pupils, hyperpolarized cortical membrane potential, synchronous firing and large amplitude low-frequency oscillations. In order to characterize the activity of thalamocortical neurons during these rapid brain state transitions, we performed juxtaacellular or intracellular recordings of identified dorsal lateral geniculate nucleus (dLGN) neurons of awake, head restrained mice while monitoring their pupil size. The firing rate of some dLGN neurons showed clear correlations with the pupil size on a rapid time scale indicating that LGN neurons exhibit brain state dependent activity changes. To reveal the effect of rapid state changes on sensory coding the response to visual stimuli (moving gratings of different orientations) was compared between periods of different pupil diameters. We found that the orientation tuning of some TC neurons is brain state dependent. These results indicate that the activity of TC neurons can change during brain state transitions on a rapid timescale resulting in altered sensory responses.

Coupling gamma and sleep spindles activities through acoustic stimulation during NREM sleep: evidences from direct intracranial EEG recordings

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Keywords: sleep spindles, gamma activities, acoustic stimulation, NREM sleep, slow oscillations, intracranial electrodes

Several studies have suggested that non-rapid eye movement (NREM) sleep plays a fundamental role in the long-term consolidation of recent memories. Specifically, it has been proposed that memory consolidation during sleep is facilitated by a direct dialog between the hippocampus and the neocortex through a precise coordination of activities at different

frequencies among these regions. According to this, a nesting of thalamocortical spindles, neocortical gamma activities and hippocampal ripples within the up-states of sleep slow oscillations (SOs) would be a plausible mechanism for a direct memory consolidation during NREM sleep, as proposed by different human studies [1,2]. Very recently, it has been shown that an enhancement of these processes is possible through the delivery of acoustic stimuli, in-phase with the up-states of SOs. Particularly, acoustic stimulation during sleep not only enhances the amplitude of SOs and the expression of sleep spindles but also improves the consolidation of declarative memories [3]. Nevertheless, there are not currently direct evidences, at the intracranial level, of an improvement on the precise nesting of SOs, sleep spindles and neocortical gamma activities resulting from this type of stimulation. Here, we performed real-time auditory stimulation during sleep in two epileptic patients who were implanted with intracranial electrodes for the treatment of their epilepsy. In particular, we investigated a precise amplitude modulation of gamma activities (Low Gamma, LG: 30–60 Hz and High Gamma, HG: 60–120 Hz) by the phases of sleep spindles (Slow Spindles, SS: 8-12 Hz and Fast Spindles, FS: 12–16 Hz) through the estimation of the phase-amplitude coupling (PAC) between them. In total, 10 intracranial electrodes were analyzed. The electrodes were located in the Superior Temporal Gyrus (STP, n = 4), Middle Temporal Gyrus (MTG, n = 2), Inferior Temporal Gyrus (ITG, n = 2) and Parahippocampal Gyrus (PG, n = 2). For each patient, two nights (sham and stimulation) were included in the study. For the off-line analyses, we first selected individual SOs with sound stimulations during the up-states and that fulfill defined time and amplitude criteria. All selected SOs were visually validated and those presenting inter-ictal activity (i.e. epileptic spikes) were excluded from the analysis. For the PAC estimation we filtered within the above mentioned frequency bands and the phases and magnitudes were computed using a Hilbert transform for spindles and gamma ranges respectively. PAC values were determined from the magnitude of the mean complex vector from all fast-amplitude/slow-phase pairs obtained for windows of 1 second around the next negative SO peak following the stimulation event [4]. We report a statistical significant ($p < 0.05$) enhancement of spindle-gamma PAC for SS-LG in the PG, STG and ITG (n = 3 electrodes); for SS-HG in the STG, MTG, and ITG (n = 3 electrodes); for FS-HG in the STG, MTG, and ITG (3 electrodes); no significant PAC was found for FS-LG. Further experiments are now being carried out in a more representative number of patients and electrodes. Taking together, our results provide new evidences at the intracranial level of possible physiological mechanisms supporting an enhancement of sleep oscillations by external acoustic stimulation.

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From sleep spindles to infraslow oscillation, circadian rhythms, and REM sleep

The circadian and sleep dependent regulation of sleep spindles and associated brain oscillatory activity in health and neurological disease

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Keywords: forced desynchrony, sleep-wake homeostasis, slow waves, Huntington's disease

Sleep spindles are a hallmark of NREM sleep and a characteristic phasic EEG event closely associated with both physiological and cognitive aspects of sleep. Sleep spindle activity is generated in the thalamus and synchronized by the cortical slow oscillation and an infra-slow oscillation at around 0.02 Hz. Age, sex, mental health and neurodegeneration as well as aspects of cognitive performance have been associated with changes in sleep spindle activity. Sleep spindles are modulated by homeostatic (sleep-wake dependent) and circadian processes. Individual differences in spindle activity are pronounced.

It is currently not known to what extent sex modulates the circadian and sleep- dependent regulation of sleep spindles. Furthermore, the contribution of the sleep-wake regulatory system in the interaction of sleep spindles with other spindle related oscillations and its association with waking cognition has not been documented. In this presentation I will present a systematic analysis of sleep spindle activity across the circadian cycle and various sleep pressure conditions based on 231 sleep episodes. The extent to which sleep spindles and their modulation by slow waves and infra-slow oscillations are affected by sleep-wake regulatory mechanism and how the association between sleep spindles and general cognitive faculties is dependent on circadian phase and sleep history beyond brain topography and sex will also be explored. In the last part of my presentation I will investigate the extent to which sleep spindles can be considered a biomarker of neurodegeneration. These progressive conditions are usually accompanied by severe sleep deficits and alterations of the circadian system. I will use Huntington's disease, an autosomal dominant neurodegenerative disorder that has been uniquely associated with an increase of sleep spindle activity, as a case study to illustrate the association between sleep spindles and brain function.

Acknowledgments
This research was supported by a Biotechnology and Biological Sciences Research Council grant (BB/F022883 to DJ.D. and others) and by the CHDI Foundation (CHDI-RG50786), the National Institute for Health Research (BRC-RG64473, R.A.B.). Dr A Lazar is supported by funding from the Wellcome trust (207799/Z/17/Z).

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The 0.02 Hz-oscillation in sigma power times spontaneous transitions out of undisturbed non-REM sleep in mouse

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Mechanisms that regulate the microarchitecture of non-REM sleep (NREMS), in particular fluctuations in arousability, are critical for sleep stability. Arousability varies with respect to changes in the instantaneous spectral composition of NREMS, but there is currently no comprehensive description of how arousal-prone episodes evolve during NREMS. Sleep spindles are discrete (0.5–3 s) oscillatory events in the sigma frequency (~10–15 Hz) band arising from the thalamocortical network, they populate NREMS and are considered as NREMS-protective. We recently found that a 0.02 Hz-oscillation of sigma power divides NREMS into successive 25-s windows of high and low fragility towards external noise (Lecci et al., Science Adv. 2017). Here, we hypothesized that the 0.02 Hz-oscillation is a hallmark for the periodic recurrence of arousal-prone episodes in undisturbed NREMS. Using polysomnographic recordings (EEG/EMG), we investigated spontaneous exits from NREMS with respect to the 0.02 Hz-oscillation in sigma power in a cohort of adult male C57Bl/6J mice sleeping undisturbedly.

Spontaneous transitions from NREMS to wakefulness or REMS occurred during the fragility period, as defined by the descending phase of the 0.02 Hz-oscillation in sigma power and by an accelerated heart rate. Peripheral parasympathetic, but not sympathetic antagonists blocked changes in heart rate but not in cortical sigma power. Every transition was preceded by a surge in sigma power, the amplitude of which was larger for NREM - REMS than for NREMS – wake transitions. Microarousals, defined as waking bouts lasting ≤12 s during NREMS, occurred in ~25% of fragility periods, after which the 0.02 Hz-oscillation continued undisturbed. After prolonged wakefulness or REMS, the 0.02 Hz-oscillation was attenuated yet rebuilt gradually. Together, the 0.02 Hz-oscillation organizes NREMS micro- and macroarchitecture through timing the preferential occurrence of spontaneous transitions. Moreover, the 0.02 Hz-oscillation is found throughout NREMS of mouse, is regulated by the recent sleep-wake behavior, and directs parasympathetic regulation of the periphery.

We propose a cortical correlate for the microarchitecture of NREMS, the 0.02 Hz-oscillation in sigma power. Spontaneous transitions from NREMS occur preferentially during permissive windows defined by the descending phase of the 0.02 Hz-oscillation. We provide a novel parameter to non-invasively characterize moments of fragile NREMS, which could be relevant to detect unwanted intrusions of wakefulness in perturbed sleep.

The heterogeneity of REM sleep: Oscillatory activity during phasic and tonic microstates

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Keywords: REM sleep, alpha power, beta power, synchronization

Rapid Eye Movement (REM) sleep is traditionally viewed as a homogeneous state, characterized by the combination of high cortical activity indexed by low voltage, mixed frequency electroencephalographic (EEG) oscillations and low muscle tone, as well as by the occurrence of relatively fast eye movements. The function of REM sleep was linked to a wide range of neural and cognitive phenomena; however, more than 60 years after its scientific discovery, our knowledge regarding the functions and precise mechanisms of this intriguing neural state is still far from being clear and conclusive. In our view, exploring the structure of REM sleep would shed new light on the nature and function of this sleep state. Although the heterogeneity of NREM sleep regarding sleep stability and arousability are well established, very few studies examined REM sleep in this regard. This is surprising as REM sleep is composed of two markedly different microstates: phasic and tonic periods. These microstates differ in awakening and arousal thresholds, sensory processing, cortical oscillatory activity and functional connectivity. In this study we present our recent findings examining the differences between phasic and tonic states in terms of cortical oscillations, synchronization, and scalp topography. We conclude, that similarly to NREM sleep, REM sleep is also characterized by the alternation of two opposing, but complementary states. We speculate that during phasic REM the brain transitionally decouples from the external environment and submerges in inwardly generated sensory and motor activity, whereas during tonic states vigilance, environmental awareness, and attentional processes reflecting a more wake-like state are partially reinstated.

Acknowledgments
The Project was Supported BY the ÚNKP-17-4 New National Excellence Program of the Ministry of Human Capacities.

Sleep spindle oscillations, REM sleep behavior disorder, and alpha-synucleinopathies

REM Sleep Behavior Disorder (RBD) and α-Synuclein Neurodegenerative Disorders

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Human RBD, formally identified in 1986, is a parasomnia that consists of abnormal behaviors during REM sleep with loss of the physiological skeletal muscle paralysis of REM sleep, "REM-atonia," as recorded by the electromyogram during polysomnography. The predominant RBD clinical profile involves middle aged and older men with violent, injurious dream-enacting behaviors, and >80% will eventually develop an α-synucleinopathy neurodegenerative disorder, usually Parkinson's disease (PD) or Dementia with Lewy Bodies (DLB), with a mean interval from onset of "idiopathic" RBD (iRBD) to overt neurodegeneration in the 12–14 year range. The emergence of REM-sleep-without-atonia in iRBD reflects the damage that the α-synuclein pathology of evolving PD/DLB is doing to the pontine and medullary centers and pathways subserving REM-atonia. iRBD is now considered to be prodromal parkinsonism, and research efforts have identified the iRBD patients most likely to phenoconvert to neurodegenerative disease within 5 years, who can then be enrolled in clinical trials to test promising neuroprotective/disease-modifying agents that are currently being developed. The very strong predictive aspect of iRBD is unique in the field of neurodegenerative α-synucleinopathies; in the Movement Disorder Society prodromal criteria, PSG-proven iRBD carries a likelihood ratio of 130, and has a predictive value >10x higher than any other clinical biomarker, e.g. abnormal striatal presynaptic dopamine uptake by PET/SPECT imaging; abnormal motor exam; olfactory loss; color vision discrimination abnormality; cerebral perfusion abnormality; waking EEG slowing; multi-modal autonomic dysfunction. Sleep spindle abnormalities appear to be another biomarker of neurodegeneration in iRBD, with one study finding significantly lower sleep spindle density in iRBD patients compared to normal controls, and further analysis of the iRBD patients found that sleep spindle densities were lower for fast frequencies, but higher for slow frequencies; the commonly used frequency threshold for separating fast from slow sleep spindle frequency was 13 Hz. Another controlled study found decreased sleep spindle density in patients with iRBD, and in patients with RBD-PD, compared to controls and to PD patients without RBD. Therefore, altered sleep spindle density in iRBD could be an early biomarker of PD. Further research on sleep spindle abnormalities in iRBD is strongly encouraged, which could contribute important new insights into evolving α-synucleinopathy neurodegeneration.

Sleep spindle alterations in REM sleep Behavior Disorder and Parkinson's disease

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Sleep spindles (SS) have been studied in normal and pathological sleep. In this study, we aimed to evaluate SS in patients with comorbid REM sleep behavior disorder (RBD) and Parkinson's disease. (Studies have shown that up to 50% of PD patients have comorbid RBD). We found that SS were reduced or absent in patients with RBD-PD as compared to controls. Furthermore SS showed abnormalities in term of duration, oscillation frequency, maximum peak-to-peak amplitude and density. Specifically, SS density was lower, duration was longer, oscillation frequency was slower, and maximum peak-to-peak amplitude was higher in RBD-PD patients vs. controls. We also found significant changes in inter-expert reliability in SS scoring, and found a significantly lower reliability in scoring definite SS in patients when compared to controls. We found that PD alpha-synucleinopathy neurodegeneration (with comorbid RBD) exerts a strong influence on SS characteristics, most likely due to neurodegenerative involvement of structures generating or controlling SS. The SS morphological changes observed in our study may affect automatic detection of SS in patients with PD or other neurodegenerative disorders. Abnormalities in SS generation likely predict neurodegeneration severity, and future research should address the important factors of disease severity, status of cognitive function, and any comorbidities.

The group effect in phase-amplitude coupling of sleep spindles in Parkinson's disease collapses when filter frequencies are adapted to each sleeper. What does it say about the brain changes?

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Keywords: phase-amplitude coupling, Parkinson's disease, Spindle envelope frequencies

Context. Systematic relationships between the envelope of individual sleep spindles and concurrent low frequency brain activity (CLFA) have been reported at the 2016 meeting. Two independent relationships distinguished patients with Parkinson's disease (PD) who developed dementia at follow-up (PD+d) from PD patients who remained dementia-free (PD-d) and controls (Ctrl). PD+d patients demonstrated increased coupling between 0.8–1.0 Hz filtered occipital CLFA and 11–13 Hz filtered frontal sleep spindles, between 13–15 Hz filtered parietal or central sleep spindles and 1.2–.4 Hz CLFA from the same subset of regions, or both.

The quantification of these phase-amplitude relationships implied several choices, including EEG band parameters, CLFA cycle limits used to identify the cycle concurrent with each sleep spindle, and many other quantifier details. An investigation of alternate possibilities included individual tailoring of the filters for the higher and lower frequency signals (from the average power spectrum of the sleep spindles and of their envelopes respectively, at F3, F4, C3, C4, P3, P4, O1 and O2).

Objectives. Since the strong group effects obtained with the fixed filters previously identified essentially vanished when using custom filters, even though the effects of CLFA cycle limits and of electrode pairs remain comparably strong, it became important to test the suggestion that the original group differences in phase-amplitude coupling might be secondary to some frequency specific characteristic of sleep spindle generation.

Method. The 16 peak spectral frequencies of the sleep spindles and of their envelopes at the 8 recording channels were entered as dependent variables in a 3-group MANOVA (44 Ctrl, 45 PD – d and 14 PD + d). Descriptive sub-tests followed to better characterize the effect.

Results. The main MANOVA revealed a strong group effect ($p = .000027$), with the intermediate PD-d group differing from both Ctrl ($p = .0096$) and PD + d ($p = .0258$). The spectral peaks of the envelopes better differentiated the groups ($p = .000003$, means for Ctrl, PD – d, PD + d: 0.93, 0.98, 1.09 Hz) than those of the spindles ($p = .0051$, respective means: 12.4, 11.9, 11.6 Hz). The effect for envelope peak frequency was particularly marked at C3, C4, P3, P4, O1 and O2, each differentiating the 3 groups at $p < .000003$, the two PD groups at $p < .0004$, and PD-d from Ctrl with p between .0037 and .0407 (respectively at P3 and P4).

Conclusion. Brain changes associated both with PD per se and, within PD, with risk of evolution into dementia strongly affect the dominant frequency at which the sleep spindles envelopes are modulated. Spectral characteristics of sleep spindle envelopes might be worth investigating in other pathology contexts or even in normal aging.

Sleep spindles, memory and neural plasticity I.

Tracking the role of sleep spindles in human memory consolidation

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New memories need to be transformed into more stable representations or they will be forgotten. Just as there are many forms of memory, there are likely many routes whereby these recent memories can be consolidated. It is well established that sleep is one period optimized for consolidation. In my talk, I will address the question, what is the nature of sleep-dependent consolidation in terms of critical electrophysiological events that determine successful memory retrieval? I will review our recent work using pharmacological interventions to explore the critical function for consolidation of individual sleep events in non-rapid eye movement N2 and N3 sleep, including sleep spindles (slow: 9–12Hz; fast 12–15Hz) and slow oscillations (0–1Hz). Recent models of sleep-dependent learning propose a synergistic relation between thalamic spindles and cortical SOs in that memory consolidation is facilitated when spindles coincide with the down-to-up phase of SOs. This temporal coupling may be a key mechanism underlying the communication between memory-related brain areas (e.g., hippocampus, thalamus, and cortex), whereby SOs provide a top-down temporal frame for these oscillatory events. I will provide evidence of the importance of thalamocortical coupling of spindles and SOs for memory improvement in both young and older adults. In summary, I hope to illustrate a dynamic relationship between memory brain areas across wake and sleep that facilitates the consolidation of recent experiences into long-term memories.

Sleep spindle refractoriness segregates periods of memory reactivation

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Keywords: sleep spindles, memory, refractory periods, brain oscillations

Newly formed hippocampal memory traces become reactivated during sleep, suggesting sleep plays an active role in long-term memory stability. Memory reactivation can be induced during post-learning sleep by presenting stimuli that had previously been associated with learning. This method, termed targeted memory reactivation (TMR), offers a unique opportunity to study the physiological conditions underlying memory reactivation with high temporal precision. In our first two experiments1, participants learned unique sound-picture pairs followed by unique locations for those pictures against a background grid. Next, they took a pre-nap location test and napped in the lab. During online indications of slow-wave

sleep, half of the sounds were softly and repeatedly presented. At a post-nap test, cueing benefited memory. Moreover, sigma (spindle band) power increased shortly after TMR cues and predicted later memory retention (Fig 1a). However, we also found spindles exhibit a novel rhythmicity, such that they are more likely to occur approximately 3-6 seconds following prior spindles, suggesting cues may not always be able to induce spindles. Indeed, spindle power shortly before TMR cues prevented the TMR-related spindle increase and negatively predicted later memory retention (Fig 1a). In experiment 3, we leveraged this rhythmicity to further test the role of spindles in memory by using real-time spindle tracking to present cues within versus just after the presumptive refractory period (Fig 1b); as predicted, cues presented just after the refractory period led to better memory (Fig 1c). Our findings reveal a previously undescribed neural mechanism whereby spindles segment sleep into two distinct substates: prime opportunities for reactivation and gaps that segregate reactivation events.

Figure

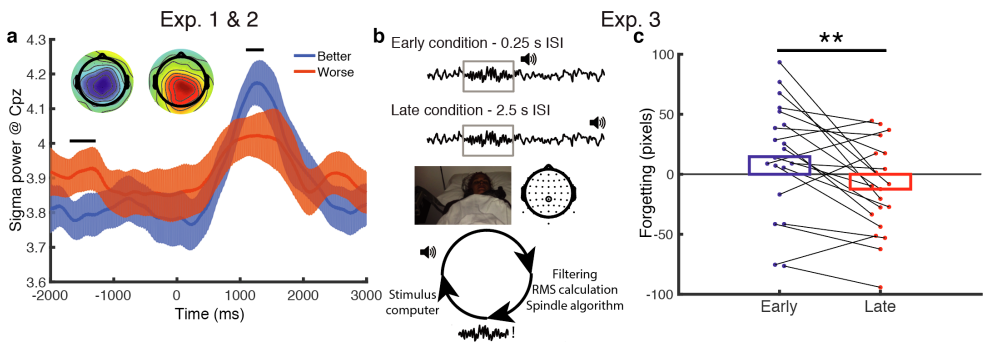

Fig. 1. **(a)** In experiments 1 and 2, sigma (spindle band) power for better-remembered associations over electrode CPz was higher after the cues and lower before the cues. (Inset) Topographical maps of sigma power values for better – worse memory centered at -1550 ms and 1300 ms, respectively. **(b)** In experiment 3, we tracked spindles over CPz in real time to present TMR cues early (0.25 s) or late (2.5 s) after preceding spindles. **(c)** We found better retention (less forgetting) for memories linked with late cues, which were presented outside of the spindle refractory period.

Acknowledgments

This work was supported by NIH F31-MH100958 and a CV Starr fellowship to JWA, and NSF grant BCS-1461088 to KAP and KAN. We thank Neggin Keshavarzian for additional help collecting data, and Nick Depinto with help with the real-time EEG setup.

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Recasting reality: how memory replay in sleep boosts creative problem solving

Penelope A. Lewis, Guenther Knoblich, and Gina Poe

Creative thought relies on the reorganisation of existing knowledge. Sleep is known to be important for creative thinking, but there is a debate about which sleep stage is most relevant, and why. We address this issue by proposing that Rapid Eye Movement sleep or 'REM' and Non-REM facilitate creativity in different ways. Memory replay mechanisms in Non-REM can abstract rules from corpuses of learned information, while equivalent replay in REM may promote novel associations. We propose that the iterative interleaving of REM and Non-REM across a night boosts the formation of complex knowledge frameworks, and allows these frameworks to be restructured – thus facilitating creative thought. We outline a hypothetical computational model which will allow explicit testing of these hypotheses.

A case for strong analogy – The features of human sleep spindles and analogue bursts in the dog change similarly in response to age, sex and learning demand

Ivaylo Iotchev, Anna Kis, Daniel Tejeda, Enikő Kubinyi

Our knowledge about the comparability of sleep spindles across species is restricted to their morphology and characteristics for most species, whereas a connection to learning is restricted to human-rodent comparisons. Sleep spindles were described early in the dog, but with little agreement between authors on internal frequency and no attempts to date to investigate their relationship to function. A general finding is that spindle measures (amplitude, density) descrease with age, increase with tasks demanding learning new information and differ between the sexes. Internal frequency in particular increases with both age and learning demands. Using EEG data from a learning experiment and automatic detection criteria we evaluated transients derived from different hypotheses about dogs' internal spindle freuqency for their ability to predict learning, aging and sexual differences. Our results confirm that transients predicting learning, cycle in a frequency range close to that found in human spindles and their density is similarly different between the sexes. We also share preliminary results comparing spindle characteristics across age, from a large sample of dogs (N = 154) undergoing a 3 hour long polysomnographic recording. As expected from the human literature, we find an age-related decline in amplitude and a surprising rise of density with age in both data sets. We argue that sleep spindles may present promising bio-markers in studying the dog as a natural model of aging, as it shares a similar environment with humans.

Sleep spindles, memory and neural plasticity II.

Spindling in aging: a window on cerebral and cognitive integrity

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Many sleep characteristics change acutely as early as during one's thirties, while others change gradually throughout a person's life span. We will discuss the cerebral mechanisms underlying age-related in NREM sleep oscillations, including sleep spindles and their functional consequences.

Identification of key mechanisms underlying age-related changes in Non-Rapid-Eye-Movement sleep (NREMS) oscillations: Our group put in evidence important changes in non-rapid-eye-movement (NREM) sleep oscillations during aging. We established that with increasing age, decreases in density (number of events per min of NREMS) and amplitude of slow waves (SW: >75uV and <4 Hz) and spindles (waxing and waning waves between 11 and 15Hz) occur predominantly in frontal regions, suggesting impairment in cortical circuits underlying NREMS oscillations. Indeed, our work suggested that these cortical neurons take longer to enter the SW hyperpolarization and depolarization phases in older than in younger individuals. In addition, using Magnetic Resonance Imaging (MRI), we showed that cortical thinning in cerebral regions involved in SW generation explained age-related decreases in SW density and amplitude. On the other hand, white matter (WM) integrity, as assessed through diffusion characteristics in the frontal area, including tracts underlying the thalamocortical loop, explains a significant proportion of the variability in spindles amplitude and sigma power in young subjects. However, age-related changes in WM diffusion metrics do not explain spindles characteristics in the older brain. Key factors explaining age-related changes in human sleep spindles characteristics still need to be uncovered.

NREM sleep oscillations and REM sleep are linked to cerebral and cognitive integrity in older subjects: Our work indicates that higher spindle predict better performance on verbal learning, visual attention and verbal fluency in healthy other individuals. Moreover, in collaborative work, we used fMRI to determine the role of NREMS oscillations in motor learning in young and older participants. Our results suggest that the deficit in sleep-dependent motor memory consolidation in elderly individuals is related to a reduction in sleep spindle oscillations and to an associated decrease of activity in the cortico-striatal network. We also examined whether alterations in NREM sleep oscillations at a baseline visit were associated with increased likelihood of developing dementia at follow-up (4.5 years later) in patients with Parkinson disease (PD). Our results demonstrated that spindle alterations are associated with later development of dementia in PD and thus may serve as an additional predictor of cognitive decline in these patients.

Sleep spindles in depression

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Keywords: major depressive disorder, cognitive performance, memory consolidation, spindle density

Major depression, one of the most prevalent psychiatric disorders, has among others been characterized by changes in sleep architecture. However, the exact role of sleep in major depression pathogenesis and symptomatology is still largely unknown. Given the critical role of sleep spindles in several cognitive functions, such as procedural and declarative memory, which are disrupted in depressed patients, it seems surprising that the role of sleep spindles in depression has only been scarcely investigated. Here, we will provide an overview of sleep spindle alterations depression. We suggest a new model that explains the impairments in sleep spindle related activity in depressed patients and links them to memory consolidation deficits. Conceivably, cognitive impairments might also be explained by subtler sleep spindle characteristics, for example sleep spindle sources, trajectories, interactions with other sleep phenomena. Lastly, we highlight the need for more intricate and reliable methods in analyzing more dynamic aspects of sleep.

Decoding the 'DNA' of sleep: Dynamics, Networks and Associations in sleep EEG

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Keywords: sleep spindles, slow waves, rapid eye movements, heart rate, humans, EEG, polysomnography, power spectrum, correlational analysis, sleep dynamics, sleep cylce

Finding the functions of sleep depends on an understanding of sleep EEG. Valuable insights have been gained from sleep EEG and have mostly relied on sleep scoring, spectral decomposition of sleep stages, and detection of sleep events like sleep spindles, slow waves, rapid eye movements (REMs), arousals and other peripheral activities. How these sleep EEG features are intertwined is often ignored and there is therefore a lack of detail in describing the relations among them, especially alterations over the course of the night or within sleep cycles. Here we explored a detailed description of the temporal and cross-feature sleep-cycle

dynamics related to sleep spindles, slow waves, REMs and sleep-typical EEG frequency band activities as well as heart rate. In particular, we focused on the relevancy among those features and on changes in properties during sleep-stage transitions. We used data of an ethnic diverse and general population including >500 young human individuals (16–19 yrs., National Sleep Research Resource, Cleveland Children's Sleep and Health Study) and generated comprehensive representations of sleep EEG that newly illustrate the fine-grained changes of sleep events and frequency-band characteristics over the course of a typical night. We further explored each prominent separate sleep-feature dynamic for consistent patterns in how they temporally relate or predict each other. This gave rise to relational networks of sleep EEG dynamics that we tested for persistence on individual subsets of data. To further explore if changes in these associations in the network of dynamics bare any significance on sleep's function, we correlated these patterns with available annotation data. Furthermore, we tested the relevancy of such relational network of dynamics on another group of patients with major depressive disorder and healthy controls. In the talk we will discuss how such analyses in general might help to gain insights into the relevance of each separate feature and the relations among them in a human-comprehensible way, as well as how this might be used in getting detailed profiles sleep alterations in clinical populations. The talk will highlight the new attempt to analyze sleep EEG in a complex manner to utilize more information from sleep phenomena in a human-graspable way. By using such complex but comprehensible description of sleep we hope to facilitate targeted sleep research that may utilize these Dynamics, Networks and Associations within sleep EEG to the fullest, that is to use the 'DNA' of sleep.

Increase of sleep spindle density induced by rTMS for major depression

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Introduction: Cortical pyramidal cell is reciprocally connected to both thalamocortical neuron (Th-Cx) and reticular nucleus of the thalamus (RE). It is thought that Th-Cx is delta oscillator and RE is spindle oscillator. We have previously reported that high frequency rTMS to the left DLPFC induced localized power enhancement of the slow wave activity at around the stimulation site. In this study, we investigated whether a series of high frequency rTMS could enhance spindle oscillation.

Methods: Twelve patients with major depression underwent 10 daily rTMS sessions over two weeks. The stimulation frequency was 20 Hz (2s on, 28s off) and stimulation site was left dorsolateral prefrontal cortex (DLPFC), which was determined by ultrasound-based navigation system. Polysomnographic data were recorded 4 times (adaptation, baseline, post 5 sessions and post 10 sessions). Sleep spindles were visually identified by a single rater who was completely blind to sleep EEG data profile.

Results: Sleep spindle density at F3 electrode increased significantly at post 5 rTMS sessions (4.80 /min) as compared to the baseline level (3.37 /min) ($t = 3.70$, $df = 11$, $p = 0.003$).

Also, total amount of sleep spindle was significantly increased (t = 3.33, df = 11, p = 0.007) from the baseline (828.4 /night) to post 5 rTMS sessions (1284.3 /night).

Discussion: A series of high frequency rTMS sessions to the left DLPFC increased the spindle density at the stimulation site. The present result suggests that high frequency rTMS may induce facilitative effect on RE through cortical pyramidal cell, resulting in enhancement of sleep spindle activity.

Enhancement of sleep spindles through closed-loop Transcranial Electrical Stimulation of NREM slow oscillations

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Keywords: sleep spindles, transcranial electric stimulation, NREM sleep, slow oscillations

Sleep oscillations are the manifestation of different physiological and cognitive processes taking place during sleep. In particular, sleep slow oscillations (SOs), the hallmark activity of NREM sleep, represent massive alternations between synchronized firing and silent periods of cortical neurons known respectively as up-and-down states. The up states give rise to faster oscillations and specially to sleep spindles (slow and fast, 8–12 and 12–16 Hz respectively) which coordinated activity seems to be of primary importance for functions such as memory formation and consolidation during sleep (Rasch and Born, 2013). In order to improve the expression of sleep oscillations some previous studies have delivered repetitive transcranial electrical stimulation (TES) during sleep (Marshall et al., 2006; Ladenbauer et al., 2016), some of which have reported an improvement in memory capabilities. Nevertheless, open-loop stimulations do not take into consideration the appropriate timing for the delivery of stimuli and therefore it has been proposed that the stimulation should arrive to the cortex during the up-state phase of the SO for its maximal enhancement (Bellesi et al., 2014). According to this, we have designed and validated a closed-loop system consisting on a stimulation device and a real-time algorithm for automatic detection and TES at positive phases (up-states) of SOs. For the offline analyses, stimulation intervals were extracted from the recorded signals and the power within slow and fast spindles were compared between sham and stimulation conditions. In order to capture the spindling dynamics at a fine scale, a wavelet transform was used for filtering and power estimations. Up to now, two healthy subjects (mean age 26.5 years old) have been recorded during two nights (sham and stimulation conditions) with 8 scalp EEG electrodes and corresponding EOG and EMG polysomnographic signals. For the stimulation condition, electrical stimuli were delivered through 8 mm electrodes located bilaterally at F3-M1 and F4-M2 with anodal outputs connected to

frontal locations. Stimuli consisted on pulses of 100 ms with a maximal current intensity of 200 uA through each stimulation channel. Two consecutive stimuli were delivered for each positive phase detection with a variable delay between them depending on the frequency of the detected wave. Preliminary results suggest an enhancement of fast spindles specially for the second stimulation and for posterior brain regions ($p < 0.05$). For one of the subjects, an additional enhancement of fast spindles was observed in all recorded areas lateral to the electrode side from which the detection was based on (C3). Further experiments will be carried out in a more representative number of subjects. In conjunction, these results point out to an increase of sleep oscillations driven by in-phase TES similar to that induced by external acoustic stimulations (Ngo et al., 2013).

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Sleep spindles in different cortical layers

Heterogeneous origins of human sleep spindles in different cortical layers

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Sleep spindles are a cardinal feature in human NREM sleep and may be important for memory consolidation. We studied the intracortical organization of spindles in men and women by recording spontaneous sleep spindles from different cortical layers using linear microelectrode arrays. Two patterns of spindle generation were identified using visual inspection, and confirmed with factor analysis. Spindles (10–6Hz) were largest and most common in upper and middle channels, with limited involvement of deep channels. Many spindles were observed in only upper or only middle channels, but about half occurred in both. In spindles involving both middle and upper channels, the spindle envelope onset in middle channels led upper by ~25–50ms on average. The phase relationship between spindle waves in upper and middle channels varied dynamically within spindle epochs, and across individuals. Current source density analysis demonstrated that upper and middle channel spindles were both generated by an excitatory supragranular current sink while an additional deep source was present for middle channel spindles only. Only middle channel spindles were accompanied by deep low (25–50Hz) and high (70–170Hz) gamma activity. These results suggest that upper channel spindles are generated by supragranular pyramids, and middle channel by infragranular. Possibly, middle channel spindles are generated by core thalamocortical afferents, and upper channel by matrix. The concurrence of these patterns could reflect engagement of cortical circuits in the integration of more focal and distributed aspects of memory. These results demonstrate that at least two distinct intracortical systems generate human sleep spindles

The intracortical profile of sleep spindles in humans does not differ by spindle frequency and globality

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Keywords: sleep spindle, electrocorticography, laminar recordings, epilepsy

It has been hypothesized that different thalamocortical networks with different cortical innervation patterns contribute to sleep spindles of different frequencies and topographical distributions [1].

In order to evaluate this hypothesis, we assessed the laminar profile of sleep spindles in humans using implanted laminar microelectrode (IME) data from epileptic patients undergoing presurgical electrophysiological monitoring, with an available postoperative histological reconstruction of the electrode track. Sleep spindles were detected from subdurally implanted corticographic grids (ECoG) and also directly from IME.

Spindles occurred ubiquitously, both locally (confined to a single cortical layer or ECoG channel) and co-occurring between multiple sources. IME spindles were detected in all layers with a predominance of superficial layers measured by both local field potential gradients (LFPg) and current source densities (CSD). Most ECoG spindles were concomitant to an IME spindle in at least one cortical layer, but many IME spindles were without a concomitant ECoG spindle. The cortical laminar profile did not differ between local/global, and slow/fast spindles. Single- and multi-unit activity was significantly associated with sleep spindle phases.

Our results indicate that all spindles large enough to be detected by ECoG arise from generating networks with similar cortical innervation patterns, regardless of slow/fast subtype or globality. However, the existence of IME spindles confined to any single cortical layer indicates that extremely local, 'microscopic' spindles can arise from various generating networks and, akin to the also extremely local spindles detected by MEG gradiometers, these are often not registered by electrophysiological recordings with a larger receptive field like ECoG.

Acknowledgments

Supported by 2017-1.2.1-NKP-2017-00002. Péter P. Ujma was supported by the ÚNKP 17-4 New National Excellence Programme of the Ministry of Human Capacities.

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Replication crisis and methodological aspects

Replication in sleep research

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A potential replication crisis has been widely discussed in biomedical and psychological research in recent years: an increasing number of positive results have failed independent replication (Ioannidis, 2005; Collaboration, 2015). However, researchers, journal editor and funding agencies are highly averse to both replications and negative findings, resulting in the proliferation of positive findings in publication (Giner-Sorolla, 2012). In contrast to small studies with negative findings that might remain in the file drawer forever, small studies reporting positive and often large effects have a tendency to get cited even after publication of failed replications by considerably larger studies (Ferguson & Heene, 2012).

Sleep research is effortful and expensive: to acquire a single sleep recording, laboratory-based studies typically require two nights (adaptation + actual recording) of 10+ hours each, beyond the research participant often demanding two researchers being present in an otherwise deserted research facility. Accordingly, most sleep studies work with very small sample sizes compared to other fields of biomedical and psychological research. In contrast, polysomnography as the gold standard in sleep research provides unusually rich datasets: recordings of several hours of multiple modalities, sampled at hundreds of Hertz, harbor a multitude of possible variables to choose from. This combination – weak statistical power, multiple researcher degrees of freedom (Wicherts et al., 2016), and the temptation to exploit expensively collected datasets as much as possible – might leave sleep research particularly prone to chance findings and spurious results. Moreover, this situation might make it particularly difficult to establish a convincing failure of a replication: replication failures may just be the result of low statistical power (Maxwell et al., 2016), yet with multiple researcher degrees of freedom, chances increase to find a positive result in a different but still intuitively related variable. In this talk, I will highlight issues of replicability in sleep research, will give some illustrative examples of such issues, and will discuss potential solutions.

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How slow waves modulate the timing of sleep spindles

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Keywords: sleep spindle, mechanism, generation, model, slow wave, phase-amplitude coupling

Building on previous research 1) suggesting that the likelihood of reticular (RE) cells to participate in sleep spindle activity may be modulated by the underlying state of the network (Bartho et al., 2014), 2) showing phase-amplitude coupling (PAC) between slow waves and spindles (Steriade, 2006), and 3) establishing the role of PAC in various cognitive processes such as learning (Canolty & Knight, 2010), we developed a conceptual model of how network activity modulates sleep spindles. We propose that the probability of RE cells to participate in sleep spindles is modulated by slow waves (0.5–1 Hz), such that the initiation and termination of sleep spindles are phased locked with this wave. As background network activity oscillates as slow waves, the dynamics of the spindling process evolves until it reaches a bifurcation point and start oscillating (similarly for termination). Given the complexity of network interactions and the intrinsically noisy nature of neuronal activity, spindle initiation and termination are only loosely coupled to the phase of the slow waves. Thus, these effects can only be captured statistically by averaging large number of spindles. Based on this model, we proposed a set of a priori hypotheses:

1. As the frequency of the slow wave diminishes, the generated spindles will last longer (on average).
2. Spindles that are initiated in advance of the preferred initiation phase will last longer (on average).
3. Spindles that terminated later than the preferred termination phase will last longer (on average).
4. Higher amplitude slow waves will impose more strongly the starting and ending phase of spindles.

All these hypotheses have been validated experimentally. This model of how background network activity modulates the generation of spindles provides a principled explanation for why, in many conditions (e.g., learning, aging, mental retardation, schizophrenia), the duration of sleep spindles can be shortened or prolonged.

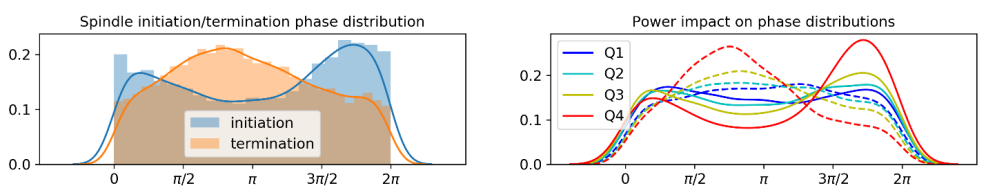

Figure 1. Left panel: Distribution of the phase of the slow wave at which spindles are initiated and terminated. Right panel: Distributions computed by splitting the data in four quartiles with respect to the power of the slow wave (Q1:low power, Q4:high power; solid:initiation, dashed:termination).

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The MODA sleep spindle dataset: A large, open, high quality dataset of annotated spindles.

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Keywords: sleep spindles, crowdsourcing, open data, machine learning, event detection

The sleep spindle, a feature of Stage 2 and Slow Wave Sleep, plays a role in offline memory processing (1,2) and a host of other cognitive benefits (3–5). Understanding and detecting this feature is of upmost importance in understanding sleep, however detection of these events from the polysomnography (PSG) signal by trained human experts is a time consuming and subjective process. Automatic detectors have been developed (e.g. 6,7), and while they report high accuracy, they perform worse than humans in validation studies (8). In other fields, staggering progress has been made in health related classification techniques in recent years (9,10), helped by powerful new signal processing and machine learning algorithms. The efficacy of these techniques is, in part, due to availability of large high quality datasets in their respective fields. To facilitate spindle algorithm development and to provide a benchmark for algorithm comparison, we present a large, high quality database of PSG with over 3541 annotated spindles: The Massive Online Data Annotation (MODA) sleep spindle database.

The PSG data used consisted of 2025 epochs of Stage 2, C3 channel data taken from 100 young adults in the Montreal Achieve of Sleep Studies (11). To annotate epochs, we developed a custom web interface which allowed experts from around the world to draw boxes around each spindle, and rate their confidence in this selection. Each epoch was viewed by at least 5 PSG technicians and half also received 5 or more views from expert sleep researchers. To collate expert opinions and form a gold standard set of spindles we followed a consensus rule which takes spindle-scoring confidence into account.

Compared to the gold standard, average expert recall and precision were 78% and 84% (F1score = 80.9) with experts outperforming researchers (recall 63%, precision 80%; F1score = 70.5). Figure 1 shows distributions of spindle duration (mean=0.81s), amplitude (mean = 39.7uV) and the power spectral density (mode in sigma band = 13.28 Hz). We did not no-

tice a clear distinction between fast and slow spindles, as evidenced by the unimodal peak frequency in the power spectral density. However, fast and slow spindles show topological preferences and individual differences (12) and given the single channel used and averaging employed, this result is unsurprising. s

This gold standard dataset will be made open-source for engineers and signal processing experts to develop state of the art spindle detection algorithms. Phase 2 of data collection is now underway and includes PSG data from older adults, which will aid investigations of spindles characteristics across the lifespan. Future work includes leveraging the custom web interface to crowdsource the collection of K-complexes, slow waves, and other important sleep features.

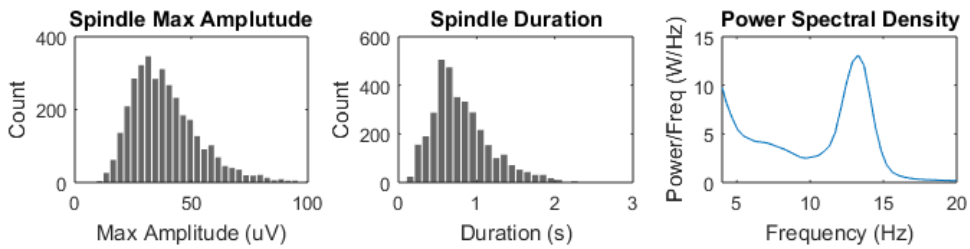

Figure 1: Spindle duration, spindle amplitude, and spindle power across frequency (mean across all spindles)

Acknowledgments

We would like to acknowledge all expert scorers who donated their valuable time to scoring the MODA project.

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Heritability of spindles and spindle characteristics is influenced by spindle detection method used

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Keywords: spindle, heritability, spindle detection, genetics

Sleep spindles are an EEG feature that defines stage 2 sleep, are associated with the consolidation of learning & memory, and are altered in numerous neurological disorders. Sleep spindles are maximal at central electrodes and are found in the frequency range of the EEG (sigma 11-16Hz) that is known to be heritable. Little is known about the heritability of spindles and spindle characteristics. Two prior studies 1, 2 found moderate heritability of spindles, but with conflicting results depending on scalp location and spindle types.

In this study we used 200 individuals (118 monozygotic and 82 dizygotic twins) in the PENN twin cohort with polysomnography data to identify heritable characteristics of spindles at C3 in stage N2 sleep. These characteristics included density, duration, p-p amplitude, and oscillation frequency. We implemented and tested a variety of spindle detection algorithms (each with different strengths and weaknesses 3), as well as a new spindle detection algorithm that emulates human spindle scoring. We used multiple, complementary methods of estimating trait heritability, and in contrast to previous findings, we find robust evidence to support strong (rather than moderate) heritability of spindle density ($H2>0.8$). Importantly we find that the magnitude of heritability of spindle density is dependent on the spindle detection method used. Methodological issues of spindle detection on heritability will be discussed. This study will identify the specific characteristics of spindles that are stable and heritable, and help direct future studies aiming to identify the specific genetic loci involved in modifying the spindle phenotype.

Acknowledgments

Funding for this work was provided by the Chaire Pfizer, Bristol-Myers Squibb, SmithKline Beecham, Eli Lilly en psychopharmacologie de l' Université de Montréal, the Centre de Recherche Hôpital du Sacré-Coeur de Montréal, the Canadian Institutes of Health Research (CIHR), NIH P50 HL060287 and NIH P01 HL094307.

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Thalamocortical mechanisms of sleep spindle generation II.

Cortical feedback and thalamocortical oscillations

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Though the thalamus is generally regarded as the gateway to the neocortex, information flow is not unidirectional, as layer 6. of the cortex provides massive glutamatergic feedback to the thalamus. It has a possible role in selective attention, sleep oscillations, and may even act as a classical modulatory pathway, nevertheless the overall picture is still murky. We investigated this system, using NTSR1-ChR mice, a strain expressing channelrhodospin in L6 cortico-thalamic cells selectively, paired with multichannel silicon probe recordings. At the single cell level we found a combination of excitation and inhibition on thalamocortical, while only excitation on thalamic reticular neurons. The excitation-inhibition profile was dependent on stimulation intensity, as well as the network state. At the network level, brief activation of L6 elicited spindles in a state-dependent fashion. On the other hand, prolonged activation of the corticothalamic feedback could elicit a network change. Low intensity stimulation reduced the occurrence of sleep spindles, while higher intensities desynchronized the thalamocortical network.

Developmental atypicalities and individual differences

Fast sleep spindle density is associated with rs4680 (Val108/158Met) genotype of Catechol-O-Methyltransferase *(COMT)*

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Keywords: sleep spindles, gene polymorphisms, genetics, catechol-O-methyltransferase, dopamine, schizophrenia

Sleep spindles are a hallmark of NREM stage 2 sleep. Fast sleep spindles correlate with cognitive functioning, and have been shown to be reduced in schizophrenia. Although spindle activity is highly genetically determined, distinct genetic mechanisms influencing sleep spindling have not been identified so far. Spindles are generated within a network of reciprocal thalamo-cortical connections. Dopaminergic neurotransmission modulates activity within this network and importantly depends on activity of catechol-O-methyltransferase (COMT). We aimed at investigating whether the common functional rs4680 (Val108/158Met) polymorphism of COMT modulates fast spindle activity in healthy subjects.

In a sample of 150 healthy subjects (93 women, 57 men; mean age 30.9 ± 11.6 years) sleep spindle density was analyzed during the second of two nights of polysomnography. We investigated the effect of the COMT Val108/158Met genotype on fast spindle density in whole night NREM sleep stages N2 and N3.

As predicted, higher Met allele dose correlates with higher fast spindle density. Additional exploratory analysis of the effect of COMT genotype revealed that slow spindle density in heterozygote subjects was lower than that of both homozygote groups. Morphological characteristics of fast and slow spindles did not show significant differences between the three genotypes. COMT genotype had also no significant effect on parameters of general sleep quality.

This is the first report of a distinct gene effect on sleep spindle activity in humans. As variation in the COMT Val108/158Met genotype is associated with differential expression of fast spindles in healthy subjects, genetically determined dopaminergic neurotransmission may modulate spindle oscillations during NREM sleep.

Acknowledgments
The study was supported by the German Federal Ministry of Education and Research (BMBF) through the Integrated Network IntegraMent (Integrated Understanding of Causes and Mechanisms in Mental Disorders), under the auspices of the e:Med Programme (grant 01ZX1314G) and by the German Research Foundation (DFG; grant FOR2107; RI908/11-1 and WI3429/3-1).

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Attention deficit/hyperactivity disorder (ADHD) symptoms are associated with decreased activity of fast sleep spindles and poorer procedural overnight learning during adolescence

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Keywords: ADHD, Adolescence, EEG, Polysomnography, Procedural memory, Memory consolidation, Sleep, Spindle

ADHD and its subclinical symptoms have been associated with both disturbed sleep and weakened memory consolidation. As sleep spindle activity during NREM sleep plays a key role in both sleep maintenance and memory consolidation, we examined the association between ADHD characteristics and sleep spindle activity. Furthermore, we hypothesized that sleep spindle activity would mediate the effect of ADHD characteristics on overnight learning in a procedural memory task. We studied these questions in a community-based cohort of 170 adolescents (58% girls, mean age = 16.9, SD = 0.1 years), who filled in the Adult ADHD Self-Report Scale (ASRS-v1.1), and underwent an overnight sleep EEG coupled with a mirror tracing task before and after sleep. Elevated ADHD symptoms were associated with weaker fast sleep spindle activity both at central and frontal derivations, and poorer overnight learning in the procedural memory test. However, sleep spindles did not mediate the association between ADHD symptoms and overnight learning. Our results support altered brain activity in ADHD during adolescence regarding sleep microstructure patterns, especially as lower sleep spindle activity at frontal areas.

Large-scale structure and individual fingerprints of locally coupled sleep oscillations

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The temporal coordination of slow oscillations and sleep spindles is believed to underlie processes of sleep-dependent memory consolidation and reorganization. Accumulating evidence of the predominantly local expression of these individual oscillatory rhythms suggests that their interaction may have a similar local component. However, it is presently unclear whether local coupling holds uniformly across the scalp, and whether and how these dynamics differ between fast and slow spindles, and sleep stages. Moreover, substantial individual variability in the expression of both spindles and slow oscillations raise the possibility that their cross-frequency interactions show similar individual differences. Using two nights of multi-channel electroencephalography recordings from 24 healthy individuals, we performed a systematic characterization of the topographical characteristics of slow oscillation-spindle coupling. We found that locally coupled oscillations occur over widespread cortical areas, but that their dynamics vary importantly with spindle class, sleep stage, and topographical area. Moreover, different individuals express spindles in markedly different phases of the slow oscillation cycle, with these differences exhibiting pronounced stability across nights. However, individual fingerprints of coupling phase were not associated with overnight memory change. These novel sources of variability expand our understanding of oscillatory dynamics during sleep and inform mechanistic accounts of sleep-related memory reprocessing.

Disorders of consciousness, disorders of sleep

Sleep spindles indicate recovery from severe brain injury

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Keywords: disorders of consciousness, circadian rhythm, sleep spindles

A healthy sleep-wake cycle is characterised by fluctuating levels of consciousness on one hand, and by alterating sequences of sleep stages on the other hand. Further analyses of electrical brain activity reveal a panolpy of underlying PSG graphoelements, which systematically vary across the circadian cycle.

Damage to brain tissue can completely disrupt sleep-wake rhythm and alter the entire EEG apperance. Moreover, people who survive such injury, lack capacity to communicate and sometimes even fail to reveal signs of cognition or consciousness. Mere behavioural observation provides only limited information about cognitive or clinical state of those patients. Instead, complementary PSG analysis can yield valuable insight into preserved brain functions.

Current scientific research provides a large body of information about mechanisms and functions of sleep-specific EEG patterns. This inspired us to evaluate sleep in subjects who suffered severe brain injury. We acquired ~24h bedsite PSG recordings from 35 patients. Based on behavioral evaluation, we assigned each patient into a group of those who revealed fluctuating signs of consciousness (Minimally Consciouss State, n = 17) and those who most evidently remained unaware (Unresponsive Wakefulness Syndrome, n = 18).

Vast EEG spectrum changes rendered it impossible to sleep stage recordings according to standard criteria. Instead, we focused on oscillatory patterns characteristic for non-REM sleep. To that end, we estimated the amount of sleep spindles and slow waves during the circadian day and night-time, and investigated their relation to diagnosis and prognosis. As a reference point we took 8h nocturnal sleep recorded from a sample 26 healthy controls.

Sleep spindles turned out to be related to diagnosis and prognosis of patients. Higher amount of sleep spindles detected during the circadian night was associated with better clinical diagnosis. Furthermore, increased density of sleep spindles indicated a lower risk of passing away in the course of next months or years. Surprisingly, detected slow waves turned out to neither relate to the diagnosis, nor to prognosis.

Emergence of sleep spindles on the scalp manifests preservation of the entire neural machinery supporting their generation, especially proficiency of thalamo-cortical loops, and thereby might be of clinical relevance and deserves more attention.

Acknowledgments
The authors thank all the patients' families for their trust and their kind cooperation in this study. We also thank Daniel Koerner and the Coma Science Group (Liège). This study was financially supported by the FWF project Y777 and by the Doctoral College "Imaging the Mind" at the University of Salzburg (FWF, W1233-G17).

Sleep onset misperception is associated with sleep instability

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Keywords: Sleep state misperception, SOL, EEG, sleep spindles, sleep fragmentation

Chronic insomnia is a widespread problem, affecting about ten percent of the adult population. Insomniacs often overestimate their sleep onset latency (SOL). This misperception might be explained by abnormalities in the sleep EEG, for instance increased hyperarousal, reflected by a lower delta/beta spectral power ratio. Other EEG abnormalities playing a role in sleep onset misperception might be impaired sleep protection mechanisms, reflected by an altered sleep spindle index, or sleep fragmentation, such as more wake after sleep onset (WASO) and increased presence of light sleep stages. In this study, we aim to identify which of these mechanisms are involved in misperception of the SOL.

Standard in-lab polysomnographic (PSG) recordings were performed in 20 insomniacs and 21 self-defined good sleepers. The EEG microstructure was analyzed using Philips Somnolyzer software. Sleep stages were scored visually. We assessed differences between the two groups with respect to objective SOL, delta/beta spectral power ratio, microarousals, sleep spindle index, number of awakenings, WASO and number of sleep stage transitions. Additionally, we assessed the correlation between these variables and misperceived sleep onset. Misperceived sleep onset was expressed as the amount of objectively measured Sleep During Subjective Latency (SDSL), according to Saline et al.(2016)1.

The insomniacs and healthy subjects had comparable objective SOL. Both groups showed sleep onset misperception (SDSL 40 ± 54 vs. 15 ± 29 minutes). Insomniacs had a significantly lower delta/beta spectral power ratio in N2 (45.3 ± 19.0 vs. 65.8 ± 29.6) and more arousals/hour during the combined NREM stages (13.6 ± 5.8 vs. 9.9 ± 5.3). Additionally, insomnia patients had a higher sleep spindle index for both low and high frequency spindles (low: 0.73 ± 0.84 vs. 0.36 ± 0.47 and high: 1.24 ± 1.20 vs. 0.71 ± 0.93). No differences in any other variables were found. The amount of SDSL was positively associated with the percentage of N1 ($r = 0.40$, $p = 0.0095$) and WASO during the first sleep cycle ($r = 0.32$, $p = 0.04$). Delta/beta spectral power ratio, arousals and sleep spindle index were not associated with SDSL.

In this study, insomnia patients showed high frequency EEG activity and an increased number of arousals, which are signs of hyperarousal, as well as an increased sleep spindle index. Interestingly, these characteristics were not associated with sleep onset misperception. Instead, sleep onset misperception was associated with variables indicating lighter and more fragmented sleep. Based on this results and Bonnet's sleep continuity theory2, stating that

an uninterrupted sleep fragment of at least ten minutes is required for restorative sleep, one could hypothesize that too short sleep fragments are not perceived as sleep. Alternatively, based on the association of SDSL with WASO, it is possible that long fragments of WASO alter the perception of the sleep onset and therefore preceding fragments of sleep could be missed.

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Withdrawal from benzodiazepines in older adults with chronic insomnia is associated with a reduction in sleep spindles

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Keywords: benzodiazepines, aging, memory, insomnia

A greater density of sleep spindles is associated with general cognitive abilities, including declarative memory1. In older adults, benzodiazepines (BZDs) are commonly used to treat disturbed sleep and insomnia. BZDs have been shown to increase the density of sleep spindle occurrence2, however their use has also been linked with impaired cognitive performance and cognitive decline in the elderly3. The aim of this study was to investigate the impact of withdrawal from chronic BZD use on metrics of sleep quality including spindles, and the relationship with delayed verbal recall memory. 31 older adults (69.4 ± 3.5 years, 22 female) with chronic insomnia who had been using BZDs or BZD-related hypnotics for ≥3months were recruited from the community. Subjects underwent a baseline PSG and neuropsychological testing which included a 16-item verbal recall task. Subjects were then randomised

to receive either 8 sessions of cognitive behavioural therapy for insomnia (CBT–i; n = 16) or a waitlist condition (n = 15). During both conditions, all patients were instructed to follow a structured and progressive withdrawal plan (over 16 weeks) from their medication and were retested after 4 months. Sleep spindles (C4–O2) were analysed at baseline and post-treatment using an automated detection method (Aseega software, Physip, Paris, France). This method utilised data driven criteria from multiple iterations to determine recording-specific EEG power thresholds, precise temporal localization of spindle events and the validation of detected events based on frequency and duration criteria. At baseline, neither the dose or duration of BZD use were related to spindle density or delayed memory recall. A longer duration of BZD use was associated with a slower spindle mean frequency (rho = 0.41, p = 0.02). Withdrawal success (the percentage reduction in BZD dose) at follow up was not significantly different between the CBT–i and waitlist conditions (77 vs 71%, p = 0.66). There was no effect of CBT-i on any changes in delayed recall performance or spindle activity. Withdrawal success across the whole sample was associated with a reduction in sleep spindle density (rho = –0.38, p = 0.04), but not in spindle amplitude, duration or mean frequency. There was no association between withdrawal success and change in delayed recall performance, however the change in spindle density and change in recall performance were positively correlated (rho = 0.41, p = 0.03). These findings are consistent with previous evidence of paradoxical relationships between BZDs, sleep spindles, and memory. In particular, these findings demonstrate that withdrawal from chronic BZD use leads to a reduction in sleep spindle density but not with a change in verbal memory performance, despite the relationship between spindle density and verbal memory changes. Further work investigating how and why BZDs increase sleep spindles may help elucidate the relationship spindles share with learning and memory.

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Poster Presentations:
The several aspects of sleep spindles

The effect of auditory stimulation on the density, duration and frequency of sleep spindles

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Keywords: sleep, spindles, Auditory stimulation, EEG, N2, Slow-wave sleep

Sleep spindles are phasic events specific for NREM sleep and are considered the hallmark for N2 sleep stage. Previous studies suggest that there are two distinct types of sleep spindles; slow (11–13 Hz) and fast (13–15 Hz) spindles. Slow spindles predominate over frontal areas, while fast spindles prevail over centro-parietal areas and it was shown they recruit distinct cortical networks. However, there is still an ongoing debate on the role of sleep spindles as some studies suggest that they promote sleep protection by blocking brain responses to external stimuli, while other work suggests that there is no effect of sleep spindles on the processing of external stimuli. In an attempt to contribute to resolving this debate, we aim at investigating the effects of auditory stimulation on the characteristics of sleep spindles. We hypothesize that sleep spindles' characteristics will differ based on the presence or absence of auditory stimulation. During a full night sleep, Subject's Own name (SON) was uttered by a familiar voice and an unfamiliar voice throughout the night except for four periods of no stimulation distributed across sleep. In a first step, we compared sleep spindle density in the absence of auditory stimulation versus during auditory stimulation. No significant difference in the total number or the density of sleep spindles was found in relation to the presence or absence of auditory stimulation. In a following step, however, we intend to investigate other characteristics of sleep spindles such as duration and frequency which are less often examined. It has been recently shown that spindle duration is controlled by the activity of dynamically fluctuating thalomocortical network which might indicate an decrease in the duration of spindles by auditory stimulation due to the disruption of the activity of this network. Moreover, sleep spindles exhibit higher frequencies in insomnia patients, which might indicate hyperarousal which is previously described in insomnia patients, therefore, we hypothesize that auditory stimulation will increase the frequency of sleep spindles due to increased arousal. In a final step, we intend to characterize the effect of arousal on sleep spindle characteristics during different stages of sleep. The investigation of the effect of auditory stimulation on sleep spindles will provide further information on the relation between sleep spindles and sensory processing during sleep.

GluA1 knockout mice show reduced EEG sleep spindle activity without presenting long-term memory deficits

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Keywords: spindles, glutamate, memory, schizophrenia

Sleep spindles have been implicated in cognitive functions and memory consolidation1,2, and deficits in spindles have been reported in brain disorders including schizophrenia. GWAS have implicated the GRIA1 gene, which codes for the GluA1 AMPA receptor subunit, in schizophrenia3, while Gria1-/- mice exhibit a phenotype relevant for neuropsychiatric disorders, such as attentional deficits leading to aberrant salience4. Therefore, here we investigated the dynamics of sleep spindles and their relationship with memory performance in Gria1-/-and wild type (WT) mice.

Chronic electroencephalogram (EEG), from the frontal and occipital cortex, and the electromyogram (EMG) were recorded during spontaneous sleep in n = 14 mice. Multichannel recordings of local field potentials (LFP) were also collected in a subset of mice from layer-V somatosensory cortex (SCx), where previous studies in WT mice have identified clear-cut local LFP spindles. Spatial reference memory was assessed in an additional group of mice using a plus maze task, where mice had to learn the location of a fixed-position reward regardless of their start-arm location.

Frontal EEG spectral power during NREM sleep was significantly reduced in the spindle-frequency range (10-15 Hz) in Gria1-/- relative to WT mice. This decrease in EEG spindle frequency power in Gria1-/- mice was especially evident prior to transitions from NREM to REM, when spindle activity is prominent in rodents. EEG spindles were not detected in the occipital derivation in either genotype. Furthermore, individual EEG spindle events were readily detected in WT mice with the automated algorithm, while they were absent in Gria1-/- mice. Interestingly, despite the absence of EEG spindles in Gria1-/- mice, preliminary analyses of LFP signals revealed an occurrence of local spindle events in the SCx in both genotypes. A repeated measures analysis revealed significant spatial-reference learning across training (main effect of day; $F(6,36) = 17.01, p < 0.001$). However, there was no significant differences between Gria1-/- and WT in memory performance (main effect of genotype and interaction by day; $F < 1; p > 0.20$). This is consistent with previous evidence indicating that long-term memory formation is preserved in Gria1-/- mice.

The deletion of the GluA1 AMPA subunit receptor in mice is associated with a profound reduction of EEG sleep spindling activity; yet local cortical sleep spindles may be preserved. Global EEG spindles do not seem necessary for memory consolidation, although a role for local LFP spindles cannot be excluded. These results have important implications for under-

standing the biological role of reduced EEG spindles in patients with schizophrenia, and suggest an important role of the GRIA1 gene in mediating the link between sleep and cognitive function.

Acknowledgments
This work is supported by the Wellcome Trust, MRC NIRG, and the Clarendon Fund.

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Cognitive training increases the frequency of occurrence of fast spindles and sleep stability in subsequent night sleep

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Keywords: sleep spindles, memory, sleep stability

A recent study from our group showed that a complex learning task (requiring the simultaneous activation of several cognitive functions, both simple and executive), intensively administered at bedtime, improves daytime sleep continuity and stability, possibly as a result of ongoing memory consolidation processes (Arzilli et al., 2018).

Here, our aim is to extend these results to night time sleep, also investigating the effect of pre-sleep learning on sleep spindles activity, since it has been suggested that sleep spindles contribute to memory consolidation (Fogel and Smith, 2011).

To this aim, ten young subjects (F = 8; mean age: 28.4 ± 7.6 years) with subjective sleep complaints (PSQI score ≥ 5) were recruited. Each subject underwent, after an adaptation night, three conditions: 1) baseline undisturbed 8-h sleep (BL); 2) post active-control sleep (AC), i.e. a sleep episode preceded by a non-learning control task; 3) post training sleep (TR), with the same time in bed as in BL and AC, but preceded by the learning task described in Arzilli e al. (2018).

Concerning sleep measures, we have considered: classical quantitative sleep measures, sleep stability, sleep continuity and sleep organization, as described in Conte et al. (2012).

Sleep spindles were automatically detected and subdivided in: slow spindles (12-13 Hz) and fast spindles (13–16.7 Hz).

No significant differences between conditions were found for classical quantitative sleep measures and for sleep continuity and organization variables. As for sleep stability, a significant main effect of condition was found for: a) frequency of arousal ($F = 5.07$ $p = .028$, TR < BL), b) frequency of state transitions ($F = 4.54$, $p = .025$, TR < BL, AC < BL), c) total time spent in functional uncertainty (FU) periods ($F = 7.05$, $p = .005$, TR < BL, AC < BL).

Also, an increase in spindles frequency of occurrence was found in TR (1.47 + 1.05) compared to BL (1.18+.97) ($F = 3.51$, $p = .05$), accounted for by a significantly higher frequency of occurrence of fast spindles (TR: 1.33 + .98 vs. BL: 1.09 + .93, $F = 3.33$, $p = .05$).

Finally, no significant correlations were found between sleep spindles variables and sleep stability and continuity measures.

Sleep stability changes observed between conditions are in line with recent results obtained on a daytime nap using the same learning task (Arzilli et al., 2018). Also, as expected, there was an increase in spindle frequency, and specifically in fast spindles occurrence, only when sleep was preceded by the complex learning task, suggesting a role for faster frequencies in sleep-dependent consolidation processes (Tamaki et al., 2008).

The lack of post-training sleep changes in the frequency of occurrence of slow spindles, which seems to have a role in sleep continuity (Normand et al., 2016), suggests that the observed sleep stability improvements do not primarily depend on a protective role of spindles on sleep.

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Wonambi: an open source toolbox for the analysis of sleep spindles and related EEG oscillations

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Keywords: analysis, automatic detection, polysomnography, electroencephalography, scoring, graphoelements, graphical user interface, Python

Visual identification by experts is often regarded as the gold standard for spindle detection, however this is a slow and subjective process. Due to the rapidly growing biological and clinical interest in sleep spindles, several automated methods of spindle detection have been developed to facilitate the speed and standardization of spindle detection 1,2,3,4. These detection algorithms are based on distinct methodological strategies, which may perform differently, and might be affected by the type of population under investigation (e.g., different age groups or clinical conditions, medications). Furthermore, these detection approaches generally require experience and skills in programming language, which can hinder analysis for some researchers. We present Wonambi, an open source spindle computing toolbox for Python available to non-experts in programming, to address the easy detection and analysis of sleep spindles from EEG data. The toolbox allows for the implementation of multiple different spindle detection algorithms previously used in the sleep spindle literature 1,2,3,4. Analysis can be quantified per specific channel or any combination of channels, dynamic sleep stages, sleep cycles, various detection thresholds as well as further additional parameters. It allows for visualization of the results via a GUI that can be used to manually score sleep stages, spindle events, or other graphoelements. Dynamic analysis is also available for power spectral density and phase-amplitude coupling. Uniquely, Wonambi maintains a separation between its core functions and the GUI, so that its tools are also available to experienced programmers for scripting and batching. This multi-functional and flexible toolbox will aid the detection and analysis of spindle events in sleep EEG data.

Further documentation and information surrouding the download and installation of Wonambi can be found at: https://github.com/wonambi-python/wonambi

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Figures

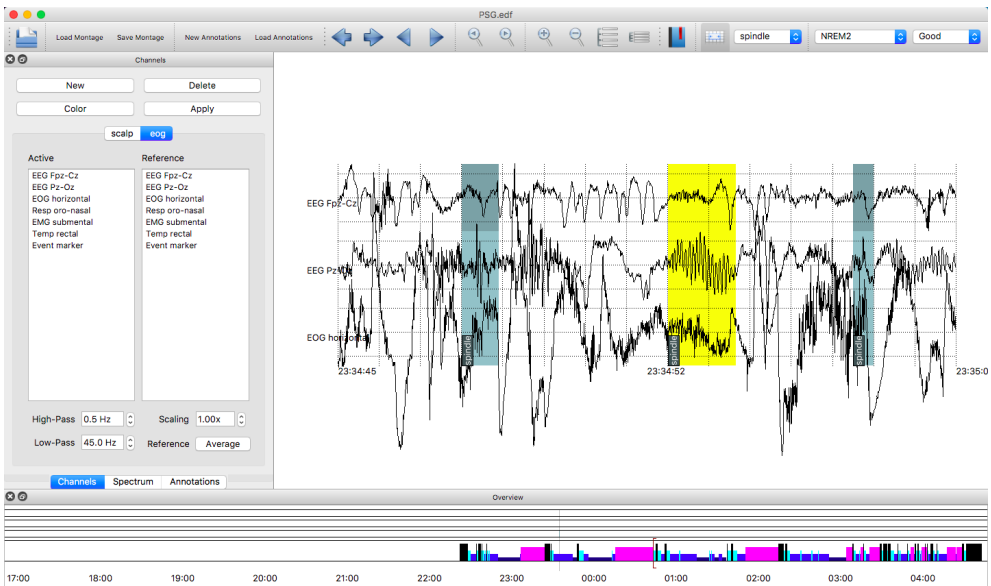

Fig. 1. A screenshot of the graphical user interface of Wonambi. Examples of automatically detected spindles are highlighted on the EEG trace

Decreased NREM sigma, delta, and beta oscillations in a Transgenic mouse with learning and memory impairments

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Keywords: TG mice, learning and memory impairment, EEG, Sleep spindle (Sigma)

Sleep spindles are distinct brain oscillations (which corresponds to Sigma waves) with a frequency band of 12–16Hz. This oscillation has been associated with neural plasticity that supports learning and memory. In the present study, we determined whether transgenic mice overexpressing a ‘hepatic-related’ protein with learning and memory impairments would

exhibit altered sleep spindles. Towards this, we made transgenic mice with overexpressed 'hepatic-related' protein and examined their behaviors in Y-maze, novel object recognition, and Barnes maze tests. We also employed an EEG power spectral analysis during the NREM state to measure their brain wave activities. Results revealed that the trangenic mice showed decreased spontaneous alternations in the Y-maze test and investigation time in the novel object recognition test. Barnes maze test also showed increased primary latency and primary errors during the four-day acquisition in the transgenic mice. Futhermore, EEG analysis revealed that the transgenic mice exhibited lower sigma (12–16Hz), delta (0–3.99Hz) and beta (15–30Hz) wave activity than the wild type. These findings suggest that the EEG changes observed may play a role in the learning and memory of the transgenic mice overexpressing the'hepatic-related' protein.

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Sleep spindles and general intelligence: a meta-analysis

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Keywords: sleep spindles, general cognitive ability, meta-analysis

The existence of a general intelligence which influences a wide variety of demographic and biological outcomes is one of the most well-replicated finding of psychology. Despite its statistical salience, the neurobiological underpinnings of general intelligence remain elusive, with few well-replicated associations, mostly consisting of a modest positive correlation between IQ and head size, brain size, neural efficiency, reaction time measures and genetic markers. Their association with cognitive ability is now also routinely mentioned in the scientific discussion of sleep spindles. Numerous studies have been published on the topic, with various methodologies and results. In this study we present a systematic meta-analysis of the extant literature on the topic.

Most of the studies in the meta-analysis (k = 21, total N = 870) were conducted in small samples (median N = 27). There is widespread evidence for publication bias in the literature, with small, frequently cited studies reporting the largest effect sizes which are not replicated by larger studies. It was a frequent practice not to report non-significant effect sizes in the papers and instead focus on the discussion of other cognitive measures which did reach a

significant association with sleep spindle measures. Some authors of small, non-significant studies did not respond to requests of effect sizes, making the sampling of unpublished studies incomplete.

We found evidence for a modest positive association (rslow = 0.12, rfast = 0.144, both $p < 0.001$) between cognitive ability and slow and fast sleep spindle amplitude which persisted beyond the effects of publication bias. There was no well-replicated relationship between sleep spindle density, duration and frequency, either in fast or slow spindles. Heterogeneity between effect sizes was not substantial after excluding the smallest studies: that is, effect sizes were similar regardless of different spindle detection methods, IQ measures or the lack of distinguishing slow and fast spindles in the analyses. The effect sizes are not significantly moderated by the mean age of subjects and the proportion of females in the sample.

This meta-analysis provides evidence of a true, replicable association between sleep spindle amplitude and general intelligence, adding this measure to the short list of the established neurobiological correlates of IQ. Sleep spindle amplitude, a proxy for the strength and efficiency of thalamocortical connections, accounts for a small but significant proportion of the variance in IQ scores. The purported associations between other spindle measures and IQ were unsupported, most likely also because sleep spindle amplitude shows the strongest convergent validity across detection methods. It is recommended that future studies having access to both sleep spindle and psychological measures report all effect sizes at least in detailed supplementary tables, regardless of their sign and significance, that datasets be pooled across research groups for more statistical power, and that at least a basic agreement of spindle detection and classification criteria be reached in the research community.

Acknowledgments
PPU was supported by the ÚNKP-17-4 New National Excellence Programme of the Ministry of Human Capacities.

Modulation of spindle activity through the alterations of intrathalamic connections – a modelling study.

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Keywords: burst, computational model, GABA-B IPSP, nucleus reticularis thalami

The cellular mechanism of spindle oscillations involves complex interactions between intrinsic neuronal firing properties and multiple types of synaptic receptors. Inhibition from nucleus reticularis thalami (NRT) cells has a critical role in the generation of spindle activity, it de-inactivates T-type Ca2+ channels, hence enables burst firing in thalamocortical (TC) neurons. NRT cells activate both GABA-A and GABA-B receptors in TC cells. Postsynaptic GABA-B receptor mediated slow IPSPs have been shown to control the frequency of spindles (Ulrich et al. 2017), their amplitude steeply increases with the length of NRT bursts, and

their marked increase can transform spindles to spike and wave discharges, the hallmark activity of absence epilepsy. In our previous modelling study (Bús et al, 2018) we have shown that the divergence of reticulothalamic input modulated spindle length and synchrony among NRT cells. Here we investigated how changes in intrathalamic connections affect GABA-B IPSPs, and how their alteration is involved in the changes of spindle characteristics.

We extended the model of Destexhe et al. (1994; 1996) to a network of 21 NRT and 63 TC cells. TC cells where not interconnected, while some of the NRT cells received GABA-A input from other NRT cells. The divergence of inputs from NRT to TC was larger than from TC to NRT (Lam and Sherman, 2005) and the connection between TC and NRT cells showed only a minimal amount of reciprocity. With the alteration of the connection pattern, by changing the number and strength of the NRT to TC connections we induced long bursts in some of the TC cells. The overal effect of these bursts depended on the synchrony of the NRT firing. Increase in the divergence of NRT to TC input distrupt the spindle oscillation especially when NRT firing was less synchronous.

According to our study the connection pattern might change the impact of certain channelopathies and therefore play a role in the manifestation of pathological conditions.

Acknowledgments

The research was supported by the grant EFOP-3.6.1- 16-2016- 00001 (“Complex improvement of research capacities and services at Eszterházy Károly University”).

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Developmental changes of sleep spindles and slow wave-spindle coupling from childhood to adolescence – a longitudinal study

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Keywords: spindles, development, longitudinal, memory consolidation, slow wave-spindle coupling

Sleep spindles are well known to support sleep-dependent memory consolidation and are related to general cognitive abilities. Even though sleep spindles are very stable within the individual, they show strong developmental changes from childhood to adolescence. The aim of our longitudinal study was to investigate whether these developmental spindle changes impact memory consolidation and cognitive abilities. Ambulatory polysomnographies was recorded during four nights for each of the 34 healthy subjects (24 female). Subjects were tested at two developmental stages: The first two nights were recorded during childhood (age range 8–11 years) and the second two nights were recorded during adolescence (age range 14–18 years). Subjects performed a declarative word-pair associate task and cognitive abilities were assessed by the Wechsler Intelligence Scale. We found that slow spindle density (11–13 Hz) was dominant during childhood; whereas fast spindles density (13–15 Hz) became more prominent at centroparietal electrodes during adolescence only. A result that might suggest that mature spindle topography develops throughout puberty. Not only the learning related increases in fast spindle density were positively associated to sleep-dependent memory consolidation but also developmental fast spindle density increases correlated with the improvement in memory consolidation across the two longitudinal measurements. Only the developmental changes of slow spindles were positively linked to general cognitive abilities. As slow waves temporally group spindles and undergo similar drastic developmental changes, our upcoming analyses will investigate the dynamics of slow wave-spindle coupling during childhood and adolescence.

Acknowledgments
This study was funded by the Austrian Science Fund (T397-B02, P25000) and the Jacobs Foundation (JS1112H). M. H. is associated with and financially supported by the Doctoral College “Imaging the Mind” (Austrian Science Fund W1233).

Different dynamic coupling between sleep spindles and down- and up-states of slow waves in human SWS

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Keywords: slow wave sleep, sleep spindles, slow waves, cortical up- and down state, coupling

Co-existent sleep spindles and slow waves in human sleep have been identified for both down- and up-cortical states and have been associated with offline information processing (Mölle and Born, 2011). Here we explored if the temporal synchronization between slow waves and spindle activity during the down- and up-states of slow wave sleep (SWS) in humans was modulated differentially by pre-sleep functional activations. We activated either the left or the right hemisphere before sleep by using a lateralized variant of serial response time task (SRTT). The stability and timing of coupling between positive (up-state) and negative (down-state) phases of slow waves and fast sleep spindle activity were quantified (Yordanova, Kirov, Verleger, and Kolev, 2017). As reported previously (Mölle and Born, 2011), fast spindle activity was temporally synchronized with both positive and negative slow half waves. Synchronization was laterally asymmetric after learning, corresponding to hemisphere-specific activations before sleep. However, as shown in Fig. 1, the down-state was associated with decoupling, whereas the up-state was associated with increased coupling of fast spindle activity over the pre-activated hemisphere. These observations provide original evidence that (1) the temporal grouping of fast spindles by slow waves is a dynamic property of human SWS modulated by functional pre-sleep activation patterns, and (2) fast spindles synchronized with cortical down- and up-states may be functionally distinct.

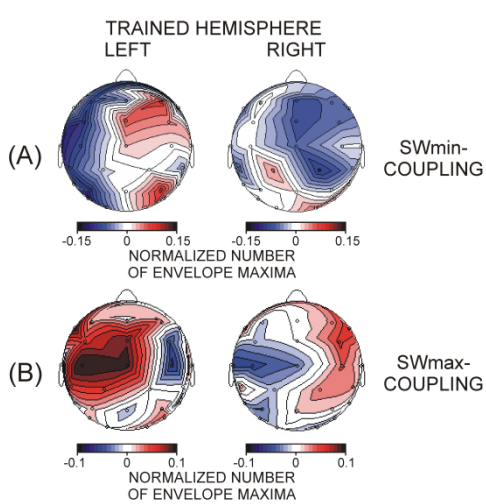

Fig. 1. Functional asymmetry between the trained and untrained hemispheres. Difference values of coupling between the learning and non-learning night are presented. (A) Coupling between negative slow half wave (SWmin, down-state) and fast spindle activity. (B) Coupling between positive slow half wave (SWmax, up-state) and fast spindle activity. Maps present the lateral asymmetry for each trained hemisphere (left and right).

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Long-term evolution of absence epilepsy in Long-Evans

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It is long known that older Long-Evans rats are showing the electrophysiological and behavioural symptoms of thalamocortical (absence) epilepsy, in the form of spontaneously emerging, rapidly generalizing, synchronous spike-and-wave (SW) episodes, but still there are many questions about the exact ictogenesis of this particular strain. Therefore the goal of this study was to explore the long-term evolution of absence epileptic seizures in Long-Evans rats.

First, we performed chronic recordings of cortical local field potential from the parietal cortex of ageing rats during spontaneous waking and sleep, to show the course of ictogenesis from a virtually seizure-free condition to chronic epilepsy. We characterized how aging affects the cortical appearance of the hallmark oscillations of the thalamocortical circuitry. We found that epileptic seizures become more synchronous progressively with ageing and cortical areas distant from the putative cortical focus become more entrained in seizure activity.

Second, in order to understand how the out-of-the focus areas can surpass seizure propagation in young, but not in older rats, we recorded unit activity and local field potential to investigate how different areas of cortex respond to intracortical stimulation. We found that cortical stimulation can differentially drive different cortical areas into physiological and pathological oscillations in an age- and state-dependent manner. Our results indicate that ageing affects local cortical circuits which may contribute to the development of global absence seizures in Long-Evans rats.

This work was supported by EU-FP7-ERC-2013-Starting grant (No.337075), the 'Momentum' Program of the Hungarian Academy of Sciences (LP2013-62), and the GINOP (2.3.2-15-2016-00018) and EFOP (3.6.1-16-2016-00008) grants.

Schizotypal traits are associated with sleep spindles and REM in adolescence

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Keywords: neural development, individual differences, creativity

Research suggests an association between schizophrenia and a decrease in sleep spindle activity, as well as a change in sleep architecture. It is unknown how the continuum of psychotic symptoms relates to different features in the sleep EEG. We set out to examine how sleep architecture and stage 2 spindle activity are associated with schizotypy in a healthy adolescent population. The participants in our study (n = 176, 61% girls) came from a community-based cohort. Schizotypal traits were evaluated using The Schizotypal Personality Scale (STA) in early adolescence (mean age 12.3 years, SD = 0.5) and the participants underwent ambulatory overnight polysomnography at mean age 16.9 years (SD =0.1). Sleep was scored in 30-second epochs into stages 1, 2, 3, and rapid eye movement (REM) sleep. Stage 2 spindles were detected using an automated algorithm. Spindle analyses from Central and Frontal derivations included spindle duration and density for slow (10–13 Hz) and fast (13–16 Hz) ranges. Covariates included sex and age. Those with highest STA scores had higher percentage of REM (B = 2.07 [95% CI 0.17, 4.0]; p = 0.03) than those with lowest scores. Those with highest scores had shorter spindle duration as derived from the frontal regions, slow oscillation range (B = –0.04 [95% CI –0.07, –0.01]; p = 0.023) than those with lowest scores. We conclude that high levels of schizotypy characteristics measured in early adolescence may associate with distinguished features of sleep architecture, namely with spindle morphology and higher proportion of REM sleep.

Timing and phase of closed-loop acoustic stimulation predicts the enhancement of slow oscillations but not the efficiency of spindles in young and aged adults.

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Keywords: closed-loop stimulation, auditory stimulation, fast spindles, slow oscillation phase

Auditory closed-loop stimulation during deep sleep is a promising technique for enhancing the impact of sleep on cognition by locally boosting the amplitude of ongoing slow oscillations (SOs: 0.5–Hz) and sleep spindle activity (12–16Hz) in both young and older adults [1], [2]. Nevertheless, as the neural mechanisms involved in the cortical response to phase-locked stimuli are not fully understood, the optimal placement of sound stimulus remains to be determined, as do the effects of the acoustic stimulus on sleep spindles [3], [4]. In this exploratory work, we evaluate the distinctive response of SOs and spindles to acoustic stimuli falling at different phases of the slow oscillation, and different timings with respect to the slow oscillation peak.

We analysed the EEG of twenty-one young subjects and ten participants aged over fifty who underwent closed-loop sham and sound stimulation during slow wave sleep (SWS) on two independent nights. SOs and spindles were automatically detected when they meet defined time and amplitude criteria. Stimulus efficiency was determined by measuring five SOs measures (RMS energy, peak to peak voltage, slope, trough and peak amplitudes) and six spindles parameters (central frequency, duration, number of oscillations, amplitude, symmetry and RMS energy) of individual events depending on the auditory stimulus timing relative to the maximum SO peak and the corresponding SO phase computed using the Hilbert transform.

We found strong effects of the phase and the timing of stimulation for SOs energy and amplitude in both young and older subjects ($p < 0.0001$ for Kluskal-Wallis test), indicating greatest enhancement in SOs when stimulation occurred ~200ms before the maximal peak but, 0 to $\pi/3$ radians after the maximal phase of the positive wave deflection and ($p < 0.01$ corrected for multiple comparisons), which may originate a two-peaked positive wave. On the other hand, the phase of stimulation did not predict the outcome of spindle measures in either young or older participants. Furthermore, although spindle activity was significantly enhanced by closed-loop auditory stimulation, only the amplitude of detected spindles was influenced by the stimulus timing in young adults ($p = 0.0242$) and phase/timing effects were not observed in older participants.

Our findings suggest that the degree to which closed-loop auditory stimulation can synchronize cortico-cortical networks that have the potential to engage larger neural populations

may depend strongly upon both the timing of the stimulation with respect to the slow oscillation peak and the phase of SOs. Conversely, the increment of fast spindle activity during close-loop auditory stimulation might not be directly mediated by the phase of the stimulus, but may perhaps relate instead to the readiness of the cortico-thalamic loop for spindle initiation. The rigorous analysis of phase and timing of auditory stimulation during SWS may pave the way for further manipulation of sleep patterns, facilitating a better understanding of sleep and associated phenomena.

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The relationship between sleep spindles and cognitive performance following sleep restriction and sleep extension in adolescents.

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Keywords: Sleep Spindles, Adolescents, Cognition, Sleep Restriction

Sleep spindles have been shown to correlate with cognitive performance in adult samples (Fogel & Smith, 2011) and increasingly in adolescents (Geiger et al., 2013; Bodizs et al., 2014; Hoedlmoser et al., 2014), however it is unclear whether sleep loss has an impact on this relationship. Adolescents typically restrict their sleep during weekdays and experience detriments to aspects of academic achievement (Chaput et al., 2016), and an analysis of sleep spindle activity and cognitive performance in the context of experimental sleep restriction may elucidate a mechanism through which this occurs.

34 adolescents attended a 10-day laboratory study where they received 5 consecutive nights of either 5hrs, 7.5hrs or 10hrs of sleep opportunity, with 2 baseline and 2 recovery nights of 10 hrs' sleep opportunity before and after the experimental phase. Cognitive variables examined were: working memory (operation span task), fluid intelligence (letter sets and number series tasks) and attention (psychomotor vigilance task).

At baseline for the full sample, fluid intelligence was positively correlated with fast spindle density ($r = .34$) and trended toward significance with fast spindle duration ($r = .26$) and slow spindle amplitude ($r = .23$). Working memory and attention did not show significant relationships with spindle characteristics at baseline. The change in spindle parameters was

not consistently associated with change in cognitive performance across sleep restriction. Although correlations did not reach significance, there were consistent small relationships between working memory improvements and increased density of fast spindles in all conditions (5hr: r = .29; 7.5hr: r =.19; 10hr: r =.40), and increased slow spindle amplitude for the two sleep restriction conditions (5hr: r = .27; 7.5hr: r = .26). Improvements in fluid intelligence (Letter Sets task only) significantly related to increased density of fast spindles in the 5hr condition (r = .61) and increased amplitude of slow spindles in the 7.5hr condition (r = .84).

Sleep spindles show both static and dynamic associations with some measures of cognitive performance in adolescents. Implications for the underlying mechanism will be discussed, along with futher analysis of cognitive variables.

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Deficits in Sleep Spindle Characteristics in Progressive Supranuclear Palsy vs. Healthy Controls

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Background and Significance: Progressive Supranuclear Palsy (PSP) is a neurodegenerative disease characterized by profound and progressive deterioration of motor and cognitive function. The affected neuroanatomy overlaps with brain regions associated with sleep-wake regulation, including the brainstem and thalamus. While our previous work describes several sleep-wake characteristics of PSP, the effect of disease on sleep spindles has not be examined. Based on the neuroanatomy of degeneration in PSP, we hypothesize that stage 2 (N2) sleep spindles will be reduced in PSP relative to controls, in terms of their number, amplitude, duration, and density. *Methods:* 19 PSP and 16 healthy, elderly age-matched controls underwent one night of polysomnography in the sleep laboratory. An automated spindle detection

algorithm developed by Tononi and colleagues, with slight modifications to amplitude and onset/offset thresholds to increase sensitivity in our sample, was applied to the average of the C3 and C4 signals to measure spindle characteristics in N2 sleep. The Wilcoxon rank sum test was used to assess group differences and all p-values were corrected for multiple comparisons with a false-discovery rate procedure. *Results:* One PSP subject was excluded due to absence of N2 sleep, and one control subject was excluded due to poor signal quality, therefore data on 18 PSP and 15 healthy controls were analyzed for sleep spindles. PSP, relative to controls, was associated with reduced spindle number ($z = 2.86$, $p = 0.004$), reduced peak amplitude ($z = 2.37$, $p = 0.018$) and integrated amplitude ($z = 2.513$, $p = 0.012$), reduced spindle duration ($z = 2.37$, $p = .018$), and reduced spindle density ($z = 2.22$, $p = 0.026$). *Conclusions:* These preliminary analyses indicate a deficit in number and quality of sleep spindles in PSP relative to healthy control subjects. These findings are consistent with the neuroanatomy of degeneration in PSP. Given the important role spindles are thought to play in memory as well as other aspects of cognition, these findings suggest one mechanism through which the disease impacts cognition and the normal functions of sleep.

"Sleep" spindles during wakefulness in the hippocampal formation

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Introduction. In humans, spindles are classically defined as waxing-and-waning 10–16Hz oscillations lasting 0.5–2s (Gibbs 1950). Sleep spindles are the electroencephalographic hallmarks of non-rapid eye movement (NREM) sleep believed to mediate many sleep-related functions from memory consolidation to cortical development. Hippocampal sleep spindles are known but less examined phenomenon, their significance and possible relation to epileptic activity is still unclear (Frauscher 2015). Recent data indicate the presence of sleep spindle-like events in epilepsy patients in wakefulness too (Gelinas, 2016). *Patients and methods*. We have retrospectively analyzed the EEG records of 20 patients with focal epilepsy who underwent video-EEG with implanted FO electrodes for presurgical evaluation. Waking spindles were examined during non-activated wakefulness (the first hour after awakening in the morning) and during one hour long learning tasks. Visual and also automated spindle detection was performed, using an individually adjusted method (IAM) for measuring spindle characteristics (amplitude, duration, frequency range and prevalence). The frequency and morphology features of waking and sleep spindles during NREM sleep were compared. Furthermore the association between waking spindles and interictal spikes, seizure-onset zone and MRI lesions were also analyzed. *Preliminary results*. Based on visual inspection, 13 of 20 patients have beta-range sleep spindle-like waxing-waning oscillations during wakefulness in the FO electrodes. Waking spindles tend to be more frequent during a learning task compared to non-active wakefulness. Based on oscillation frequency they are in a higher range compared to the respective individuals' sleep spindles. The waking spindles may occur on either and on both sides, but among patients with mesiotemporal epilepsy, they tend to

be on the seizure-onset side. *Conclusion.* We found waking beta-range sleep spindle-shaped oscillations in the foramen ovale electrodes detecting the activity of the hippocampal formation. It is unclear whether these oscillations are physiological (Iyama et al 1992; Frauscher 2015) or represent the epileptic process (Sullivan et al 2014; Malow et al 1999).

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Acknowledgment

Our research was supported by the National Brain Research Program (KTIA_NAP_13-1-2013-0001, 2017-1.2.1-NKP-2017-00002) and MET Hungary Ltd.

There are no conflicts to disclose.

Characterising sleep spindles and electroencephalography activity in sheep *(Ovis aries)*

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Keywords: spindles, Huntington's disease, neurological disorder, automated detection, sheep

Spindle activity can be used to define both normal and abnormal brain function. Alterations in spindle characteristics have been reported in Huntington's disease (HD), a progressive adult-onset neurodegenerative disease. Neurodegeneration in HD starts in the basal ganglia and cortex. It progresses relentlessly and severely impacts brain function. As well as the characteristic motor and cognitive symptoms1, patients suffer from sleep and electroencephalographic abnormalities1,2. We have been using sheep as large animal models of HD. With their large brains, human-like basal ganglia anatomy, and long life, sheep are proving to be a promising model species for studying the brain. Novel methods for monitoring multichannel electroencephalogram (EEG), electromyogram (EMG) and ocular activity (electrooculogram, EOG) in unrestrained sheep have been developed previously by our lab3.

Here we present data from neurophysiological recordings made from 8 channel EEG in normal sheep. EEG electrodes were implanted subdurally, and EEG was collected by telemetry using an MCS advanced wireless system (W2100-HS16, Multichannel Systems Gmbh, Germany). Simultaneous recordings were made from 8 sheep with a sampling frequency of 1 kHz. The EEGs were analysed with a particular focus on characterising sleep spindles. Here we examine the diversity of spindle characteristics in sheep, and ask how they differ from those in humans. We compare automated spindle detection methods (swa-matlab toolbox4) with detections made both by an expert visual scorer and an in-house automated detection algorithm coded in MATLAB. As well, we catalogue other characteristic waveforms such as sleep stages, epileptiform activity, and K-complexes from the sheep EEG. With these analyses, we hope to establish a comprehensive baseline set of sleep neurophysiological parameters in normal sheep that can be used for making detailed comparisons with EEGs recorded from a transgenic line of HD sheep5.

Acknowledgments
This work was funded by CHDI Inc.

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Reassessment of cortical spindles in rodents: characteristics and underlying physiology

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Keywords: cortical spindles, rat, dendrites, EEG, LFP

Progress in our understanding of the function of cortical spindles has been hindered by two main obstacles: a lack of consensus on the characteristics of spindles within and across species and their underlying physiology (reviewed in [1]). In this study, we show that insight

to the latter question may help inform the former and develop new approaches to study spindles' functions. We recently provided the first evidence for a physiological link of EEG spindle power (sigma: 9-16 Hz) specific to dendritic activity synchronisation in the rodent cortex [2]. Interestingly, dendritic activity synchronisation also correlated with higher frequencies in the beta range (16-30 Hz) which were themselves strongly correlated with sigma power. These observations raised the intriguing possibility of a wider frequency band associated with spindles in the rodent cortex [2]. Since spindles in rodents are difficult to detect in the EEG, we tested this hypothesis using cortical LFP recordings in head-fixed sleeping rats.

We visually detected 2219 spindle events recorded from 57 locations (depth range: 823-2343µm) in the somatosensory cortex of adult rats (n = 4). Our results confirm that the frequency range of cortical spindles is larger than the sigma band (min. = 10 Hz; max. = 25 Hz) and centred on 16-17 Hz (Frequency (± s.e.m.) = 16.8 ± 0.19 Hz). Importantly, 2/3 of the spindles display frequencies above 16 Hz. A power spectral analysis of the NREM LFP signal confirms an increased power in the 10-20 Hz range, peaking at 16 Hz. Finally, a more detailed analysis of spindle characteristics revealed that the duration of spindles (min. = 0.13s; max. = 2.54s) was predictive of their frequency in an inverse relationship; the shorter the spindle, the higher its frequency (r = –0.34, P = 7.97E-62, n = 2219).

Here we provide evidence that spindles in the rat cortex are not restricted to the traditional sigma band used in most studies and extend to faster frequencies (i.e. 25 Hz) as recently suggested by others [3]. It follows that the study of spindles in the rodent model, at least in relation to cortical functions, may benefit from an updated definition of EEG spindles characteristics. Finally, if dendritic activity synchronisation represents the neurophysiological correlate of sleep spindles, our results also propose that variability in dendritic electrogenesis may explain the variability in spindles characteristics across individuals, species and brain areas.

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4 Hz rhythmic precursors of sleep spindles in rat EEG

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Keywords: absence epilepsy, EEG, time-frequency analysis, continuous wavelet transform

Continous wavelet tansform is the basic methodology for automatic detection of EEG rhythmic events (e.g. sleep spindles), for quantifiyng the time-varying structure of sleep EEG etc. This method provides exact information about intrinsic frequency of sleep spindles which is an important characteristic of thalamocortical network activity. Previously we found low-frequency (< 9 Hz) subdominant frequency components in 30-70 % of sleep spindels in WAG/Rij rats [1].

Recently using the same technique we found slow wave rhythmic activity 1-3 s before the onset of 44.5 % of sleep spindles in Wistar rats and 55.7 % in WAG/Rij rats. The mean frequency of these rhythmic precursors of sleep spindles was 3.9 Hz in Wistar rats and 4.2 Hz in WAG/Rij rats.

In general, almost half of sleep spindles in two rat strains were followed by ~ 4 Hz slow waves, which showed negative orientation, therefore ~ 4 Hz precursors of sleep spindles in rats may be associated with cortical down state.

Acknowledgments
This study was financially supported by the Russian Foundation for Basic Research (grant 16-04-00275).

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Individual slow wave morphology is a marker of ageing

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Keywords: slow wave, ageing, LASSO regression,

Slow wave activity is a hallmark of deep NREM sleep which reflects a synchronized onset and cessation of cortical neuronal firing and which is strongly reduced with ageing. Gross slow wave activity can be assessed by several summary variables, such as the number of waves, mean wave amplitude or delta power. However, the shape of the slow wave is characterized by a stereotypical morphology, similar to evoked potentials, which may be more strongly related to physiological parameters such as ageing than amplitude or slopes which are lower-resolution descriptions of the wave shape. We recorded full-night polysomnography in 160 subjects (age 17–69) and detected slow waves using three different methods with 75 uV and 140 uV peak-to-peak thresholds and a dynamic threshold, respectively. We triggered all slow waves to the maximum negative deflection and averaged the mean EEG of the electrodes F3 and F4 1–1 sec before and after these deflection points to obtain an individual average slow wave of each subject. We also calculated the individual average slow wave amplitude, average ascending and descending slope steepness and the total number of slow waves (summary parameters). We investigated if entering the individual slow wave morphology (with one variable at each EEG sampling point) in a least-square regression predicting age would yield additional accuracy beyond the effects of the summary parameters. We used LASSO regression in order to select a limited subset of non-redundant predictors from the highly correlated and underdetermined original subset of predictors. Wave amplitude at multiple time points emerged as independent predictors of age in all models, beyond the effects of summary parameters. Younger subjects were characterized by more rapid and more prominent deflections on both the descending and ascending slope of slow waves. Our results suggest that the fine-resolution individual morphology of the slow wave is a more sensitive marker of ageing than summary parameters, and it may yield increased prediction accuracy as a clinical biomarker of age-related cognitive decline.

Acknowledgments
Péter P. Ujma was supported by the ÚNKP-17-4 New National Excellence Programme of the Ministry of Human Capacities.

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List of References here, if applicable. References should follow the style provided in the Instructions for Authors of the Sleep Spindles & Cortical Up States: A Multidisciplinary Journal.

REM sleep microstates: a high density EEG study of phasic and tonic REM sleep

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Keywords: REM sleep, EEG power, high alpha, beta, gamma oscillations

In contrast with traditional views, evidence has been accumulating that Rapid-Eye-Movement (REM) sleep, much like non-REM sleep, consists of distinct microstates. During REM sleep, short phasic periods with rapid eye movements alternate with longer tonic periods during which the eyes hardly move. Some studies have already investigated these microstates and found that they differ in oscillatory activity (Simor, Gombos, Szakadát, Sándor & Bódizs, 2016), awakening thresholds (Ermis, Krakow & Voss, 2010), subjective experience (Molinari & Foulkes, 1969) and connectivity within and between neural networks (Wehrle et al., 2007; Chow et al., 2013). Neverteheless, much research is still needed to unravel the exact characteristics and more specifically, the topographical aspects of REM sleep microstates. The current study aimed to investigate these microstates in more detail, by collecting and analyzing nocturnal high density EEG data on 128 channels from eighteen young, healthy adults. Eye-movement artifacts were removed using Independent Component Analysis, and surface Laplacian transformation was applied to the data to increase spatial resolution. Subsequently, frequency analysis was performed to analyze the power spectra of phasic and tonic REM sleep segments from nighttime sleep recordings. Our results replicated and extended previous findings, pointing towards higher gamma and lower beta and high alpha power in phasic compared to tonic REM sleep. Whereas the high alpha difference was located in central sites only, beta power was lower in both anterior and central sites, and gamma power was elevated in all regions (anterior, central and posterior) in phasic compared tonic REM sleep. Widespread gamma activity has been speculated to reflect increased sensory and emotional processing (Jouny, Chapotot & Merica, 2000; Müller, Gruber & Keil, 2000), which can be associated with the vivid, emotional dream images found to be present in phasic REM sleep (Molinari & Foulkes, 1969). In contrast, the elevated high alpha and beta activity found in tonic REM is thought to be related to the relatively increased sensitivity to external sensory input (Simor et al., 2016), and the mentalizing, thought-like dream processes found in tonic REM (Molinari & Foulkes, 1969). The current results thus provide further support for the notion that REM sleep consists of structurally and functionally distinct microstates. Since REM sleep has been associated with many psychological processes and disorders (e.g. emotional memory consolidation, dreaming, depression, PTSD, Germain, 2012; Nishida, Pearsall, Buckner, & Walker, 2008), exploring the neurophysiological background of tonic and phasic REM sleep could lead to important new insights.

Acknowledgments
The Project was supported BY the ÚNKP-17-4 New National Excellence Program of the Ministry of Human Capacities and by the Hungarian Scientific Research Fund (NKFI NK 104481) of the National Research, Development and Innovation Office.

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The role of sleep spindles in overnight verbal memory consolidation in temporal lobe epilepsy patients

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Keywords: epilepsy, declarativelearning, memoryconsolidation.

Introduction. Declarative memory performance and hippocampal functioning are highly associated. Learning induced memory consolidation results in an increased coupling between mesial temporal lobe, thalamus and frontal areas during sleep, resulting in the increase of sleep spindles and slow wave sleep. Our aim was to investigate the modulatory effect of learning on sleep spindles in temporal lobe epilepsy (TLE) patients and to see whether the as-

sociation between declarative memory consolidation and sleep parameters are altered for this population. *Methods.* We administered three modified versions of the Rey Auditory Verbal Learning Task to TLE patients (n=21) on three consecutive evenings undergoing video-EEG monitoring. Delayed recall was measured 30 minutes after learning, memory retention was measured in the following morning. Sleep stages were detected manually, sleep spindles were detected with an automated threshold-cutting method based on individually adjusted slow and fast sleep spindle frequency values. Our analysis focused on two main aspects of-learning and sleep-dependent memory-consolidation: trait-like relationship between sleep spindles, learning and memory consolidation; and the possible long-term consequences of epilepsy on learning and memory consolidation. For the first analysis, we correlated average (all learning nights included) fast and slow sleep spindle density, duration and amplitude to average learning performance and retention rates (all learning nights). To estimate the long-term consequence of epilepsy on sleep spindles, we correlated the number of years spent with epilepsy syndrome with sleep spindle parameters. *Results.* Learning performance (number of words recalled per learning trials) showed a positive correlation with IQ, and a negative correlation with years spent with epilepsy syndrome. Furthermore, learning scores correlated positively with slow spindle duration and density mainly at frontal and temporal electrode sites. Average slow sleep spindle amplitude correlated positively with memory retention scores. Also, years spent with epilepsy syndrome correlated positively with fast sleep spindle density and fast sleep spindle duration at frontal electrode sites.Online learning scores showed positive correlation with slow spindle duration, density and amplitude, and a negative correlation with fast spindle density and duration. On the contrary, memory retention scores showed a negative relationship with slow spindle density, duration and amplitude. *Conclusions.* Our results indicate that learning and overnight memory consolidation related sleep spindles are compromised by the pathological processes of TLE. Years spent with epilepsy syndrome and IQ have important impacts on verbal learning performance. Learning correlated positively with slow spindle duration and density at frontal and temporal electrode sites. Slow sleep spindle amplitude correlated with overnight memory retention, indicating that similarly to the healthy population, sleep spindles have some role in memory consolidation processes for TLE patients as well, however these processes seem to be impaired, most probably in the fast sleep spindle frequency range. The correlation between years spent with epilepsy syndrome and fast spindle parameters might explain the shift towards slow sleep spindle amplitude (instead of fast) in the role of memory consolidation processes.

Acknowledgments
KTIA_NAP_13-1-201

A spindle detection algorithm that emulates human sleep spindle scoring

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Keywords: spindle, algorithm, event detection, performance evaluation

Sleep spindles are defined in the AASM Manual for Scoring Sleep as "A train of distinct waves with frequency 11–16 Hz (most commonly 12–14 Hz) with a duration >0.5 seconds, usually maximal in amplitude using central derivations" (1). For human clinical polysomnography, the visual scoring of sleep spindles by human experts is generally considered the gold standard, but it is time-consuming, costly and can introduce inter/ra-scorer bias. Automated spindle detection methods are efficient and reproducible, but are not well correlated with human scoring (2). Typically, automated detectors find large numbers of false positives ('hidden spindles') relative to human scorers. While it is plausible that the false positives are biologically meaningful, these 'hidden spindles' present several problems, including: i) lack of gold standard for 'hidden spindles'; ii) lack of agreement between automated detectors for 'hidden spindles'; iii) 'hidden spindles' can be found throughout NREM, REM and wake, and therefore no longer are consistent with the original concept of the sleep spindle. To reduce the problem of 'hidden spindles', we have developed an automated spindle detector ('A7') that emulates how a human scores spindles. The 'A7' detector relies on the correlation/covariation of the sigma band-passed signal to the original broadband filtered (0.3–30Hz) EEG signal. To test the performance of the detector, we compared it against a gold standard spindle dataset derived from the consensus of a crowd-sourced group of human experts. The by-event performance of the 'A7' spindle detector was similar to individual experts (f1 score: 0.70 vs 0.67) against the consensus of a group of human experts (2). This was 0.17 points higher than other spindle detectors we tested. The 'A7' detector is designed to emulate human spindle scoring by minimizing the number of 'hidden spindles' detected and thereby detecting spindles that have the highest signal/noise ratio. We provide an open-source implementation of this detector for further use and testing.

Acknowledgments
Funding for this work was provided by the Chaire Pfizer, Bristol-Myers Squibb, SmithKline Beecham, Eli Lilly en psychopharmacologie de l' Université de Montréal, the Centre de Recherche Hôpital du Sacré-Coeur de Montréal, and the Canadian Institutes of Health Research (CIHR).

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SpiSOP – Spindles, Slow Oscillations, Power density and fast replication of basic sleep EEG analyses in one tool

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Keywords: sleep spindles, slow waves, EEG, polysomnography, power spectral density, sleep scoring, replication crisis

Replicating comprehensive sleep EEG analyses is a challenge. Even expensive, time consuming and specialized proprietary software solutions have no edge to cut into the prevailing conflicts found in reports on the function of hallmark sleep EEG phenomena. I present 'SpiSOP' (RRID:SCR_015673, www.spisop.org), a FieldTrip-based (RRID:SCR_004849), open-source, parallel computing tool that quickly pipelines comprehensive sleep EEG analyses of large sleep datasets and facilitates methodological exchange. It supports pre- and reprocessing, assisted manual sleep scoring and a comprehensive analysis of sleep EEG and associated features as a basis for advanced sleep studies. SpiSOP automatically detects and reports properties of rapid eye movements, (fast and slow) sleep spindles, slow oscillations, their co-occurrence and aids the search of sleep stage matching 'non-events'. Power and energy density spectra or frequency bands can be reported as well. All analyses consider automatized or manual exclusion of sleep-EEG-typical artefactual epochs and work on multiple channels, sleep stages or their combinations. The algorithms have flexible standard parameters that support replication of most basic sleep features as they are commonly reported in current sleep and memory research. SpiSOP does not require a Matlab license or programming skills. A complete standard sleep EEG analysis can be set up, adapted and started within minutes and the setup immediately shared to others for replication on their datasets. This represents a first step in analyzing large sleep data quanta across researchers, studies, designs, tasks and species. I thus hope SpiSOP will facilitate our understanding of the Dynamics, Networks and Associations of sleep EEG phenomena, the 'DNA' of sleep.

Associations between EEG cross-frequency coupling during sleep and declarative learning in healthy older adults: A pilot study

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Keywords: sleep, brain oscillations, cross-frequency coupling, memory

Introduction. Learning and memory consolidation processes may be mediated by a spontaneous synchronization of neuronal oscillations known as cross-frequency coupling (CFC)1, 2. Coupling of neuronal oscillations (e.g. spindles and slow oscillations) is observed in both awake and asleep EEG recordings. Associations between increased CFC during sleep (especially REM sleep) and learning are found in animals and adult humans, but similar studies have rarely been conducted in older adult humans. The aim of this pilot study was to explore this knowledge gap by examining CFC during sleep in relation to learning and declarative (word-pair) memory performance in healthy older adults. Hypotheses. First, CFC measured during NREM and REM sleep would increase after learning within-subjects, relative to a non-learning baseline. Second, greater CFC during sleep after learning would be positively associated with better memory recall performance across subjects. *Methods.* 16 healthy older adults (age = 67.7 ± 5.59 years; 13 female) were recruited from the community, following a preliminary assessment using a semi-structured interview, cognitive screening (MMSE, MoCA), and self-report questionnaires about sleep and mood. Eligible older adults completed a baseline polysomnography to rule-out severe sleep apnea, followed by seven days of ambulatory monitoring using actigraphy and a daily sleep diary. A second polysomnography recording was performed at least one week later. During the second visit, participants completed a word-pair associates task (40 word-pairs), with an immediate (pre-sleep) recall period shortly after learning, and a delayed (post-sleep) recall shortly after waking from sleep the next morning. Phase-amplitude CFC was quantified using the modulation index3 from frontal (Fz) and central (Cz or C3) EEG data between delta (1–4Hz) and sigma (11–16Hz; adapted) bands during NREM sleep (NREM2, NREM3, NREM2/3) in the first sleep cycle, and between delta (1.5–3Hz) [or theta (4–7Hz)] and gamma (50–100Hz) bands during total REM sleep. Statistical analyses included within-subjects ANOVA models to compare the extent of CFC observed during sleep between the two sleep study nights, and linear regression to examine associations among CFC and word-pair recall performance. *Results.* Better delayed word-pair recall performance was positively associated with greater CFC (i.e., a

higher modulation index), in NREM2/3 sleep measured on the second night. A higher delayed word-pair performance was also positively associated with a greater relative increase in CFC between the first and second overnights during NREM2/3 sleep, and during REM sleep. Moreover, greater word-pair performance stability between immediate and delayed recall conditions was positively associated with greater relative increases in CFC during REM sleep between the two sleep recording nights. *Conclusion.* These results contribute to accumulating evidence which suggests that CFC during sleep may reflect a neural mechanism underlying offline memory consolidation for newly learned declarative information. This study also provides novel evidence for relations between CFC during sleep and declarative learning in healthy older adults.

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Dynamic coupling between slow waves and sleep spindles depends differently on NREM sleep stages (SWS and S2)

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Keywords: slow wave sleep, S2 stage of sleep, NREM sleep, slow oscillation, sleep spindles, coupling

The temporal associations between sleep spindles and slow oscillations (SO) during NREM sleep have been viewed as a mechanism for offline memory consolidation (Mölle and Born, 2011; Demanuele, Bartsch, Baran, Khan, Vangel et al., 2017). Here we explored if the temporal synchronization between SO and fast spindle activity depends differentially on specific stages during NREM sleep, slow wave sleep (SWS) and S2 stage of sleep. We compared the stability of coupling and power of SO-coupled fast spindle activity between SWS and S2 in a non-learning night and learning night preceded by training of a lateralized variant of serial response time task (SRTT) in which either the right or the left hemisphere was activated. The stability and timing of coupling between negative phases of SO and fast sleep spindle activity were quantified during SWS and S2 (Yordanova, Kirov, Verleger, and Kolev, 2017).

In the non-learning night, SO-coupled fast-spindle power was significantly larger during S2 relative to SWS ($p < 0.0001$) and was more pronounced over the left hemisphere in the two sleep stages ($p < 0.001$). On the opposite, the coupling of fast-spindle activity with the

cortical down state was substantially stronger during SWS as compared to S2 ($p < 0.001$). The lateral asymmetry of coupling in SWS (L > R) was different from that in S2 (R > L). Evaluating the effects of pre-sleep training indicated that the functional reactivity of SO-coupled fast spindle activity also differed between the SWS and S2 stages. Only during S2, the power of SO-coupled fast spindle activity increased over the hemisphere contra-lateral and decreased over the hemisphere ipsi-lateral to the side of pre-sleep training. In contrast, only during SWS, were there contra-lateral vs. ipsi-lateral effects of pre-sleep training on the strength of coupling between SO and fast spindle activity.

The results provide evidence for the differential functional characteristics of SO-coupled fast spindle activity during SWS and S2 stages of NREM sleep, implying specific roles for these two stages in offline information processing.

Acknowledgments

This work was supported by funding granted to RV by the Deutsche Forschungsgemeinschaft within the Collaborative Research Center "Plasticity and Sleep" SFB 654, project A02.

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