Enhancing or depressing memories, while deepening sleep, by EEG-guided neurostimulation

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determine if this daytime sleepiness was related with a modification of the kinetics of sleep pressure buildup.

**Materials and methods:** 8 drug-free sleepy adult ADHD patients (mean age = 39.9 ± 11 years, 2 males) and 7 matched (sex, age and chronotype) healthy volunteers have been recruited. To be included in the study, sleepy ADHD patients should have a mean sleep latency 4±40 minutes MWT < 20 min. For four days prior to the study, participants were asked to maintain regular bedtimes and wake-up times according to their individual usual preferences (checked by actimetry and PSG). All volunteers underwent a 36-h of extended wakefulness in "constant routine" protocol. Karolinska drowsiness test (KDT) and MWT were repeated every 4hr. Sleep pressure was evaluated by theta-alpha (6-9Hz) band of EEG during KDT. Frontal power theta-alpha frequency (PTAF) was calculated after an automatic artifact rejection. Kinetics of sleep pressure buildup was defined by asymptote and time constant assessed by saturating exponential function.

A mixed linear model taking into account age, gender and score of Morning/Evening questionnaire of Horne and Ostberg was used to compare MWT sleep latency in both groups over time. The same model was used to compare the asymptote and the time constant.

**Results:** Total sleep time did not differ between the two groups before the CR at the actimetry and at the PSG. At the first MWT measurement, ADHD patients presented a significantly lower sleep latency than healthy controls (p<0.012). This difference remained constant over the 9 measurements. No significant difference was found between groups for time constant and asymptote.

**Conclusions:** While MWT sleep latencies during the extended wakefulness are shorter in ADHD patients than healthy subjects, the kinetics of sleep pressure buildup is not different. The difficulty to remain awake during soporific circumstances in some ADHD patients is not explained by an alteration of homeostatic sleep process. This difficulty to remain awake may be related to a reduction of wake promoting signal and/or a primary disorder of vigilance/tonic alertness.

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**Insomnia**

**PSYCHOSOCIAL INTERVENTION FOR DISCONTINUING BENZODIAZEPINE HYNOTICS IN PATIENTS WITH CHRONIC INSOMNIA: A SYSTEMATIC REVIEW AND META-ANALYSIS**

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**Introduction:** Long-term benzodiazepine (BZD) use is not recommended in the treatment of chronic insomnia because of the disadvantages of long-term BZD use such as cognitive decline, risk of fall, and development of dependence. Psychosocial interventions, particularly cognitive behavioral therapy for insomnia (CBT-I), are recommended in the clinical guidelines of chronic insomnia and are considered as a potential treatment option for discontinuing BZDs. The aim of this systematic review and meta-analysis was to clarify whether psychosocial interventions are effective for discontinuing BZD hypnotics in patients with chronic insomnia.

**Materials and methods:** A literature search of major electronic databases was conducted up to July 2018. We searched the electronic databases of PubMed, Cochrane Central Register of Controlled Trials, and Embase for reports of randomized-controlled trials (RCTs) using appropriate subject headings and search syntaxes, which were relevant to each resource. Two researchers independently selected relevant publications, extracted data, and evaluated methodological quality according to the Cochrane risk of bias assessment. We used Cochrane Collaboration Review Manager software (RevMan 5.3) for statistical analysis.

**Results:** Eight RCTs, all of which evaluated CBT-I, were included in this review, and meta-analyses were performed. The results indicated that short-term (<3 months) CBT-I plus gradual tapering was more effective than gradual tapering alone for discontinuing BZDs hypnotics (risk ratio: 1.68, 95% confidence interval [CI]: 1.19 - 2.39, p=0.003) and for improving insomnia symptoms (g: -0.69, 95% CI: -1.09 - -0.28, p=0.0009). However, the long-term (12 months) efficacy of CBT-I for discontinuing BZDs was not significant (risk ratio: 1.67, 95% CI: 0.91 - 3.07, p=0.10).

**Conclusions:** The results of this review suggest that CBT-I is effective for discontinuing BZD hypnotics as well as improving insomnia symptoms in the short-term (<3 months). However, the effects of CBT-I for discontinuing BZDs in the long-term (12 months) did not reach statistical significance (p=0.10). Further studies with larger samples and appropriate evaluations will be needed to clarify the efficacy of CBT-I for discontinuing BZD hypnotics in the long-term.

**Other**

**RELATION BETWEEN SLEEP QUALITY AND DAILY PHYSICAL ACTIVITY IN CHRONIC SCHIZOPHRENIA PATIENTS**

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**Introduction:** In a general terms, sleep disorders are often seen as a precursor to the onset of symptoms and symptoms of psychiatric disorder. Activity amount during the daytime contributes to sleep-wake rhythm synchronization. An increase in sedentary time and a decrease in Moderate to Vigorous Physical Activity (MVPA) may impair sleep quality. Therefore, is the activity (sedentary behavior time or MVPA) of patients with chronic schizophrenia related to objective sleep index?

**Purpose:** The purpose of this study was to examine the correlations among objective sleep variables and daily physical activity in schizophrenia patients.

**Design:** Research study.

**Materials and methods:** Twenty schizophrenia patients (twelve men and eight women, mean age: 59.0 ± 9.8yrs) constituted sixteen inpatient and four outpatient. We evaluated 24-hour objective sleep variables and daily physical activity for one week. Total sleep time (TST), Sleep efficiency (SE) and waking after sleep onset (WASO) were determined by wrist actigraph. Daily physical activity was assessed by three-dimensional accelerometer. All subjects for this study were recruited following authorization by the Ethics Committees of the College of Nursing Art and Science, University of Hyogo.

**Results:** The grand mean of total sedentary behavior time, total sedentary bout, Moderate to Vigorous Physical Activity (MVPA) and METs Rate were 695 ± 104min, 121.7 ± 42.6min, 46 ± 41min and 1.1 ± 0.1METs. The sedentary behavior (behavior below 1.5 MET during wakefulness) account for about 70% of wakefulness, thus schizophrenia patient’s activity was generally low Met. TST, SE and WASO were 6h58m ± 47m, 85.0 ± 6.0 % and 46.3 ± 27.3 min, respectively. MVPA was significantly positive correlated with SE (r = 0.536, p<0.05), negative correlated with WASO (r = -0.580, p<0.01). The sedentary behavior was significantly correlated with SE (r = -0.592, p<0.01) and WASO (r = 0.503, p<0.05).

**Conclusions:** Our results suggest that sleep quality in schizophrenia patients may be more effectively improved by increasing the MVPA or reducing the sedentary behavior.

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**Memory**

**ENHANCING OR DEPRESSING MEMORIES, WHILE DEEPENING SLEEP, BY EEG-GUIDED NEUROSTIMULATION**

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**Introduction:** Over recent years we have developed a pioneering technique that allows us to interact with the sleeping brain in real-time. An automated loop, involving real-time modeling and prediction of electrophysiological brain signals, targets stimuli to specific patterns in ongoing brain activity. This sophisticated form of manipulation, termed closed-loop neurostimulation (CLNS), enables innovative experimentation and exciting applications.
Materials and methods: We used CLSN to test the hypothesis that sleep-related memory reactivation and consolidation are specifically linked to the depolarized phase of slow oscillations (SO’s). Participants were exposed to a foreign vocabulary-learning task in the evening and tested for vocabulary acquisition the next morning. During sleep, memory reactivation was induced through subtle, auditory presentation of foreign words, locked to a specific phase of the slow oscillation.

Results: Using this approach, we showed that the alignment of memory cues to the SO depolarising slope enhances memory for cued vocabulary items. Conversely, cues targeted to the down-going slope promote forgetting. Moreover, subtle auditory stimuli locked to SO zero-crossings can boost the slow oscillation dynamic, inducing long SO trains that effectively increase the duration and percentage of deep sleep across the night.

Conclusions: These results provide strong evidence for the notion that sleep-related memory consolidation occurs during the depolarised phase of slow oscillations. Moreover, they show that declarative memory traces can be either enhanced or suppressed during sleep, depending on the precise alignment of reactivating cues to specific neural activity patterns. Finally, we show for the first time that sleep, as whole, can be deepened using intermittent, SO phase-locked sound stimulation during NREM sleep.

These findings provide important insights into sleep-related memory reprocessing and point the way to possible applications of CLSN in the treatment of sleep problems and disorders involving maladaptive memories, such as PTSD, phobia and addiction.

Psychiatric Disorders Affecting Sleep/Wake
THE SPECTRAL FINGERPRINT OF SLEEP PROBLEMS IN POST-TRAUMATIC STRESS DISORDER

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Background: Sleep problems are a core feature of post-traumatic stress disorder (PTSD). However, a robust objective measure for the sleep disturbance in patients has yet to be found.

Methods: The current study assessed EEG power across a wide frequency range and multiple scalp locations, in matched trauma-exposed individuals with and without PTSD, during rapid eye movement (REM) and non-REM (NREM) sleep. In addition, a full polysomnographical evaluation was performed, including sleep staging and assessment of respiratory function, limb movements and heart rate. The occurrence of sleep disorders was also assessed.

Results: In PTSD patients, NREM sleep shows a substantial loss of slow oscillation power and increased higher frequency activity compared to controls. The change is most pronounced in right-frontal brain areas and correlates with insomnia. PTSD REM sleep shows a large power shift in the opposite direction, with increased slow oscillation power in occipital areas, which is strongly related to nightmare activity and to lesser extent with insomnia. These pronounced spectral changes occur in the context of severe subjective sleep problems, increased occurrence of various sleep disorders and modest changes in sleep macrostructure.

Conclusions: This is the first study to show pronounced changes in EEG spectral topologies during both NREM and REM sleep in PTSD. Importantly, the observed power changes reflect the hallmark of PTSD sleep problems: insomnia and nightmares and may thus be specific for PTSD. A spectral index derived from these data distinguishes patients from controls with high effect size, bearing promise as a candidate biomarker.

Sleep Breathing Disorders
ASSOCIATION BETWEEN INFANT SLEEP DISORDERED BREATHING AND EXTERNALIZING BEHAVIORAL TRAJECTORIES IN EARLY CHILDHOOD

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Introduction: Childhood sleep disordered breathing (SDB) is associated with increased behavior problems such as ADHD. SDB in infancy may be associated with persistent behavior problems throughout childhood. The primary objective of this study is to determine the association between SDB symptoms at age two years and externalizing behavioral trajectories in early childhood.

Materials and methods: Data from 679 infants participating in the Edmonton sub-cohort of the CHILD birth cohort study were used to examine association between infant SDB symptoms and longitudinal behavior trajectories. SDB was determined using the Pediatric Sleep Questionnaire (PSQ; a positive PSQ score >0.33) administered at two years of age. Behavior was assessed using the parent-reported Child Behavior Checklist (CBCL; Mean T-score of 50, SD=10) annually between age 2 and 5 years. Higher scores on the CBCL indicate increased behavior problems. The STATA Proc Traj group-based trajectory analysis was used to identify CBCL externalizing behavioral trajectories between two and five years of age. Participants had to have at least one time-point assessed in order to be included in the analysis. Trajectory analyses identified three independent externalizing behavior groups: children with high-persistent externalizing behavior problems (18.1%; mean T-score = 57, SD=4.2), children with low-risk externalizing behavior symptoms (52.3%; mean T-score = 45, SD=4.0) and children with no significant externalizing behavior symptoms (29.6%; mean T-score = 34, SD=3.0). The trajectory analysis provides the probability of each individual being included in the highest behavioral trajectory group. Multiple regression was used to examine the absolute risk of being assigned to the high-persistent externalizing behavior problem trajectory group.

Results: In adjusted analysis, SDB symptoms at two years of age were associated with a 28% absolute increased risk of being assigned to the high-persistent externalizing behavior problem group. In the same analysis, children whose mothers had SDB had a 5% absolute increased risk of developing persistent externalizing behavior problems. Similarly, children whose mothers had a history of asthma had a 6% absolute increased risk of developing persistent externalizing behavior problems. Household smoke exposure was associated with a 12% increased absolute risk of developing persistent externalizing behavior problems. Finally, quality of parent-child relationship (2% absolute risk) and infant language problems (1% absolute risk) were significantly associated with developing persistent externalizing behavior problems. There was no significant association between sleep duration and developing persistent externalizing behavior problems.

Conclusions: This analysis of data identified three externalizing behavioral trajectory groups using data from a population-based cohort. We identified that infants with SDB symptoms are at increased risk for persistently high externalizing behavior problems. These results suggest that SDB symptoms during infancy may have adverse consequences for significant behavior problems. These findings highlight the need to screen and refer young children with SDB and behavioral difficulties to reduce risk for later mental health problems.

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Sleep Breathing Disorders
EFFECT OF NOCTURNAL OXYGEN TREATMENT ON OBSTRUCTIVE SLEEP APNEA/HYPOPNEA SYNDROME IN HIGHLANDERS: RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLINDED TRIAL

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