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BREATHING PATTERN ESTIMATED BY BREATHING RATE VARIABILITY CORRELATED WITH AMPLITUDE OF LOW FREQUENCY RESTING STATE MRI FLUCTUATIONS MAY PREDICT SLEEP QUALITY

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Introduction: We recently showed that people with obstructive sleep apnea (OSA) have higher breathing rate (BR) variability (BRV) in population (Pal et al. 2021)1. Simultaneously, Lynch et al. 20202 had assessed impaired breathing in the resting state healthy Human Connectome Dataset, and identified 21 people in each of the three groups of breathing patterns: eupnea (clean), sighs (deep breath) and suspected apnea breathing pattern (burst). During resting state functional MRI recordings, increased amplitude of low frequency fluctuations (ALFF) were found within areas related to hyperarousal such as the midbrain and bilateral extra-nucleus, whereas decreased ALFF were found within areas associated with memory and attention involving the parietal and occipital lobule and others; furthermore, the altered ALFF was associated with sleep efficiency (Ran et al. 20173). Could altered breathing pattern reflect an altered spontaneous neuronal activity state measured by fractional ALFF (fALFF) and associated psycho-physiological markers of sleep quality? Our goal was to characterize BRV and fALFF from the resting state HCP data in the three breathing pattern groups identified in Lynch et al. 2020 along with their psycho-physiological states including sleep quality measured by Pittsburg Sleep Quality Index (PSQI).

Methods: In the three groups (n=21 X 3), clean group (6 males) age (mean±std. dev) 29±4 years, deep breath group (5 males) 29±4 years, burst group (14 males) 30±4 years - we calculated BR, absolute BRV (Interquartile range of BR) and relative BRV% from 15 minutes of resting state respiration belt data; and, fALFF from the minimally preprocessed resting state fMRI data filtered at 0.1-0.08 Hz and smoothed. We correlated fALFF with BR, BRV. Additionally, in the three groups, we report the mean±stdev of PSQI, BMI, systolic and diastolic blood pressure (BP), self-reported anxiety, attention problem, aggression scores along with their correlations with the absolute BRV.

Results: Absolute BRV was lower in deep breath group 3±3 breaths per minute (bpm) compared to clean (4±2 bpm) and burst (4±3 bpm) groups. BR was also lower in deep breath 14±7 bpm and correlated with BRV at Pearson R = 0.57 ($p<0.05$), compared to 18±2 bpm, R = -0.51 ($p<0.05$) in clean group and 18±3 bpm, R = 0.2 in burst group. In the deep breath group, the relative change in BRV 24±14%, correlated less with absolute BRV R = 0.78 ($p<0.05$) compared to the clean 24±13%, R = 0.98 ($p<0.05$) and burst groups 24±18%, R = 0.97 ($p<0.05$) indicating some voluntary sighs in the deep breath group as also validated by visual data inspection. The sleep quality (lower PSQI better sleep quality) was best in the clean 4±2 points, compared to both deep breath 5±3 and burst groups 5±3. Improved psychophysiological state in the clean and deep breath group compared to burst group was indicated by the systolic BP (121±12, 121±13 and 128±14 mmHg), BMI (25±5, 26±5, 28±6 kg/m2), anxiety (5±5, 5±5, 7±7)/attention problems (5±3, 5±4, 7±4)/aggression (3±2, 3±3, 5±2) scores in clean, deep breath and burst groups respectively. Only in the burst group, higher BRV correlated with higher BMI (R = 0.5, $p<0.05$). fALFF correlated with BRV ($p<0.05$, FWE corrected), not BR in all three groups at the cerebrospinal fluid (CSF) ventricles. With BRV as co-variate, burst group showed higher fALFF activity ($p<0.001$, uncorrected) compared to both clean and deep breath groups at the visual and somatosensory regions. Additionally, fALFF at the central executive network (CEN) was higher ($p<0.001$, uncorrected) for both clean and deep breath groups compared to burst. Interestingly, the clean group as well as the burst group had higher right somatosensory fALFF activity compared to deep breath group, that corresponded to the lower BRV in deep breath group.

Conclusion: Higher fALFF activity of burst compared to clean and deep breath groups in the visual and somatosensory regions were associated with sleep deprivation states (Dai et al., 20124; Wang et al., 20165 , Ran et al. 20173). Higher CEN fALFF activity indicating better sleep and physiological states (Zeighami et al., 20216, Ran et al. 20173) were found in the clean and deep breath groups compared to burst. Higher right somatosensory fALFF activity in the clean and burst groups compared to deep breath indicating higher breathing related movements in the groups having higher BR and BRV (clean and burst) compared to the deep breath group. The fALFF results are consistent with the indication of breathing coupled hemodynamic and CSF low-frequency oscillations that indicate sleep/wakefulness states during resting state (Fultz 20197). Overall, our study supports that BRV could be a potential indicator of psychophysiology, and taking sighs or deep breaths could potentially improve some psycho-neurophysiological states but not necessarily sleep quality. As indicated earlier by Lynch et al. 20202, males report more burst breathing pattern while females report more deep breathing pattern indicating the ability to take deep breaths may counteract potential sleep disordered breathing problems.

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0146

SEVOFLURANE PRECONDITIONING PROMOTES SLEEP REINTEGRATION FROM LIPOPOLYSACCHARIDE INDUCED SHATTERED SLEEP

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Introduction: Anesthesia and sleep partially share neural circuits, yet little is known regarding the effect of anesthetics on sleep. Anesthetic agents exhibit a variety of biological effects concomitant with anesthesia. Sevoflurane, one of the wildly used volatile anesthetics, is known to increase the survival of sepsis model mice. Systemic inflammation like sepsis increases the inflammatory mediators in the brain affecting sleep dynamics with increase in NREM and decrease in REM. We hypothesized that sevoflurane preconditioning positively impacts disturbed sleep caused by systemic inflammation.

Methods: We conducted a prospective, randomized laboratory investigation in C57BL/6J mice. A mouse model of lipopolysaccharide (LPS)-induced systemic inflammation was employed to investigate the effects of sevoflurane on sleep recovery. We evaluated symptoms recovery through electroencephalography/electromyography (EEG/EMG) and histological studies. The mice were exposed to 2% sevoflurane before and after peritoneal injection of LPS. The EEG and EMG were recorded for 24 h after the procedure. Brain tissue was harvested after the sevoflurane/LPS procedure and was immunostained using individual antibodies against choline acetyltransferase (ChAT) and Fos.[YI1] We quantitatively analyzed the ChAT-positive and ChAT/Fos double-positive cells

in the pedunculopontine tegmental nucleus and laterodorsal tegmental nucleus (PPTg/LDTg).

Results: Compared to control mice, mice preconditioned with sevoflurane but not post-conditioned showed a significant recuperation in rapid eye movement (REM) sleep and waking time during EEG recording following the LPS challenge. They also demonstrated shorter REM latency and restored theta power, indicating an early recovery from LPS-altered sleep. The bouts of REM episodes were retained with sevoflurane preconditioning. The number of ChAT/Fos double-positive cells in the PPTg/LDTg decreased by LPS challenge. However, group with sevoflurane preconditioning followed by LPS challenge showed higher number of activated neurons, restoring physiological degree of activation.

Conclusion: Compared to control mice, mice preconditioned with sevoflurane but not post-conditioned showed a significant recuperation in rapid eye movement (REM) sleep and waking time during EEG recording following the LPS challenge. They also demonstrated shorter REM latency and restored theta power, indicating an early recovery from LPS-altered sleep. The bouts of REM episodes were retained with sevoflurane preconditioning. The number of ChAT/Fos double-positive cells in the PPTg/LDTg decreased by LPS challenge. However, group with sevoflurane preconditioning followed by LPS challenge showed higher number of activated neurons, restoring physiological degree of activation.

Support (If Any):

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ELECTROPHYSIOLOGIC LOCALIZATION OF PATHOLOGICAL BRAIN TISSUE IS ACCOMPLISHED WITH INTRACRANIAL SLEEP STAGING

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Introduction: Low Frequency brain rhythms facilitate communication across large spatial regions in the brain and high frequency rhythms are thought to signify local processing among nearby assemblies. A heavily investigated mode by which these low frequency and high frequency phenomenon interact is Phase-Amplitude Coupling)PAC). This phenomenon has recently shown promise as a novel electrophysiologic biomarker, in a number of neurologic diseases. In 10 patients undergoing phase-2 monitoring for the evaluation of surgical resection and in whom temporal depth electrodes were implanted, we investigated electrophysiologic relationships of PAC in epileptogenic (seizure onset zone or SOZ) and non-epileptogenic tissue (non-SOZ). That this biomarker can differentiate pathologic from non-pathologic brain and has been established with ictal and pre-ictal data, but less so with interictal data. Here we show that this biomarker can differentiate interictally. We also show PAC activity is related to interictal epileptiform discharges and high frequency activity. Importantly, we also show a differential level of PAC in slow-wave-sleep from NREM1-2 and awake. And finally we show that localization of pathologic tissue sensitivity and specificity is optimal when utilizing beta or alpha phase onto high-gamma or Ripple with knowledge of the sleep stage. Illustrating some of the physiologic nature of this biomarker in human epilepsy will provide a basis for understanding the mechanism of neurologic disease and normal physiology of brain communication, details which are at this point ready to be utilized in neurotechnological therapies to treat and understand both.

Methods: Per Institutional Review Board protocol, 10 patients who were under evaluation for resective surgery for MRE at Mayo Clinic in Rochester MN were included in this study. IRB approved the study and necessary consenting procedures were followed prior to any data acquisition. All subjects had bilaterally placed intracranial depth electrodes with usually 8 contacts. In some cases not all contacts could be used for data acquisition (hardware or recording problems). 6 Subjects of this cohort had scalp and EMG recordings concurrently placed for the purposes of sleep scoring. Subject recordings were ignored for POD-1 as anesthetics were dissipating. Subjects then stayed in the ICU ranging from 3-12 days before explanation.Pathological tissue identified as seizure onset zone (SOZ) was determined from phase II monitoring and determined by a trained neurologist. Sleep staging was done with expert-in-the-loop semi automated methods described elsewhere but overseen by a trained neurologist. Behavioral state was determined with scalp EEG signals and verified by a neurologist board certified in sleep medicine. All EEG recordings were bandpass filtered 0.3-75Hz and 60Hz notch filtered for scoring. Visual sleep scoring was in accordance with standard methods with modification for replacing the electrooculogram (EOG) recording with FP1, FP2, FPZ scalp electrodes. Wakefulness was determined by the presence of eye blinks visualized in fronto-parietal scalp leads, accompanied by posteriorly dominant alpha rhythms (8 - 12 Hz) comprising >50% of the epoch. Slow-wave sleep (N3) was scored when high-voltage (>75 uV) delta (0.5 - 3 Hz) frequency scalp EEG activity was present in at least 20% of the epoch (i.e., at least 6 s within a 30 s epoch) in the frontal derivations using conventional International 10-20 System electrode placements (FP1, FP2, FZ, F3, F4, CZ, C3, C4, O1, O2, and Oz). Phase Amplitude Coupling with Coherency Angle CFC. A Hanning taper n points is the length of the sliding time window. Next, the coherency CFC(fmodulating,fmodulated) was estimated between signal {Xt} and the estimate of the time-course of power{Pt(fmodulated)} for a given frequency fmodulating. The coherence was the absolute value of the CFC . The phase difference between the signal at fmodualting and the power at fmodulated is given by the angle of the coherency arg(CFC). In this case $_{\gamma}$ refer to a 1024 points Hanning window and * to the complex conjugate. This allowed us to characterize the phase-to-power cross-frequency interaction with respect to f and fmodulated sensor by sensor. The spike detection algorithm was utlized to evaluated successive 1 minute blocks of iEEG and removes artifact channels. Individual channels were defined as average slope greater than 10 SD outside of mean slopes of all channels. Second, iEEG was bandpass filtered 20-50Hz to identify possible spikes, where a sharp discharge must last between 20-70ms. Absolute amplitudes of peaks greater than 4SD of channel mean amplitude were noted as potential spike locations for further consideration. Third, raw iEEG was bandpass filtered (2nd order Butterworth) 1-35Hz. A scaling factor is determined by finding a value that will bring the median of all channel amplitudes to 70uV. All channels are multiplied by this scaling factor. Once the data have been scaled, the amplitude and slope of each half-wave of the potential spikes identified previously in step 2 are calculated and the values are compared to static thresholds (Total amplitude of both half-waves > 600μV, slope of each half-wave > 7μV/ms, duration of each half-wave > 10ms). Potential spikes with half-waves that exceed these thresholds are marked as interictal spikes.HFOs were detected using a Hilbert transform-based method, as previously reported. Here, the discrete time series is transformed into an analytic signal, where the real part is the original signal, and the imaginary part is the Hilbert transform of the original, x(t).

Results: Holding constant the frequency for amplitude to include all high activity (30-175Hz), beta is the best localizing (not statistically significant from alpha) band. Holding the frequency for phase,