Research Article

Highly Variable Breathing Rate, Regardless of Sleep Quality, is a Marker of Neuropsychophysiological Stress

Amrita Pal[1*], Taylor Kuhn[2]

[1]UCLA School of Nursing, Los Angeles, California, USA

[2]Department of Psychiatry and Biobehavioral Sciences, University of California Los Angeles, USA

*Corresponding Author: Amrita Pal, UCLA School of Nursing, 700 Tiverton Ave, Los Angeles, CA 90095–1702, USA

Citation: Amrita Pal, Taylor Kuhn. Highly Variable Breathing Rate, Regardless of Sleep Quality, is a Marker of Neuropsychophysiological Stress. Journal of Psychiatry and Psychiatric Disorders 6 (2022): 168-177.

Abstract

Introduction: Breathing rate variability (BRV) is known to be higher during psychophysically stressed states especially when accompanied by sleep deprivation. Additionally, spontaneous neuronal activity estimated with fractional amplitude of low-frequency fluctuations (fALFF) is higher at the occipital cortex during sleep deprivation. The ability to take deep breaths or sighs may counter some of these negative impacts. We tested this hypothesis in two groups from an HCP dataset showing tapered rhythmic breath patterns (burst) vs deep breath.

Methods: Demographics for the deep breath group were [(n=21, 5 males) age 29±4 years, systolic BP 121±13 mmHg, BMI 26±5 kg/m2] vs. burst group [(n=21, 14 males) 30±4 years, systolic BP 128±14 mmHg, 28±6 kg/m2], both groups had similar Pittsburgh Sleep Quality Index (PSQI) 5±3, Adult Self Report (ASR) raw scores for anxiety-attention-aggression problems were higher by 2 points in burst group. From the resting state data, BRV and fALFF were calculated and correlated, followed by group differences in fALFF with BRV as co-variate.

Results: Burst group showed higher BRV (4±3 breaths per minute or bpm) compared to deep-breath group (3±3 bpm). Only in the burst group, BRV positively correlated with BMI (r = 0.5, p<0.05).

fALFF correlated with BRV at the lateral ventricles, p<0.05 corrected for multiple comparisons. With BRV as co-variate, the burst group showed significantly higher fALFF activity compared to the deep-breath at the visual and somatosensory cluster.

Discussion: Individuals with ability to take deep breaths showed improved psycho-neuro-physiological states, irrespective of sleep quality.

Keywords: fALFF; Breathing; Resting state; Sleep deprivation

1. Introduction

In otherwise healthy participants, insufficient sleep is associated with breathing problems and poor overall health [1]. We want to investigate if breathing patterns could predict stress states irrespective of sleep quality. Human Connectome Project (HCP) had been vastly utilized to help the research community understand how our physiological states vary with the mental and neural states and vice-versa in non-pathological populations. One aspect of interest was post-hoc phenotyping of results from published HCP studies on the correlation of differences in breathing patterns with behavior and neuroimaging. Lynch et al. 2020 [2] had established that with different breathing patterns one may find indirect links to sleep-disordered breathing and associated psycho-neuro-physiological markers. The authors employed an algorithm on HCP data and identified groups of 21 subjects with deep breaths and another 21 subjects with burst type breathing. Recently, the link between higher breathing rate variability (BRV) and OSA was established in Pal et al. 2021 [3]; as well as, the link between resting-state

spontaneous neuronal fluctuations at low-frequency and physiologically stressed state was established in Sarma et al., 2021 [4]. Therefore, BRV was further utilized in characterizing the breathing patterns in the groups identified in Lynch et al. 2020.

Neural markers of slow frequency oscillations of resting-state functional Magnetic Resonance Imaging (fMRI) data, specifically the fractional amplitude of low-frequency fluctuations (fALFF) [5, 6] was chosen for correlation with BRV. fALFF could potentially reveal the autonomic state since higher low-frequency oscillations were commonly associated with higher sympathetic activation [4]. Furthermore, the sleep deprivation state in the deep breath and the burst groups were determined using Pittsburgh Sleep Quality Index (PSQI) scores as it is known that sleep quality can change breathing patterns especially in pathological conditions like OSA [7]. The PSQI score was 5 (indicating insufficient sleep) in both the deep breath and the burst groups indicating any differences in breathing pattern was probably not due to differences in sleep quality but owing to markers of differences in breathing patterns at rest. In some fMRI studies, it has been shown that higher BRV was common when the participant was drowsy [8], thus it was important to consider the PSQI scores. We know that typically the ability to take deep breaths is associated with improved emotional regulation and physiological states [9]. Since the burst group in the Lynch et a. al paper showed worse blood pressure, BMI and anxiety-aggression-attention scores compared to the deep breath group, therefore, we anticipated that the more pathologically higher BRV at rest would be observed in the burst group over the deep breath-taking group.

Lynch et al. 2020 already pointed out that the breathing pattern present in the more pathological breathing pattern group called burst was more prevalent in males compared to females. We also know that pathological sleep-disordered breathing was more common in males [10], so we expect that the burst group would have a more pathological higher BRV compared to the deep breath-taking group. Additionally, the psycho-physiological markers were better in the deep breath group compared to the burst group [2], further supporting the hypothesis that breathing states could alter the emotional and physiological states.

Sleep states often correlate with low-frequency cerebrospinal fluid oscillations, specifically, breathing coupled hemodynamic and CSF low-frequency oscillations that indicate sleep/wakefulness states during resting state [11], thus we anticipate that BRV would correlate with low-frequency vascular oscillations at the ventricles. Taken together, we wanted to assess if the specific breathing pattern quantified by the BRV variable would correlate with neuronal fALFF data and if BRV was factored out as a co-variate, the differences in the fALFF data in the two groups would reflect the signatures of improved psychophysiological states.

Sleep deprivation is known to impair selective attention and is associated with visual cortex attenuated activation [12]. Specifically, with sleep deprivation, higher ALFF activity is known to occur at the visual cortex, left sensorimotor cortex and fusiform gyrus [13]. We anticipate that the signatures of sleep deprivation reflected by higher fALFF activity in the above brain regions would be more

apparent in the burst group rather than the deep breath group even though the PSQI scores were similar in the two groups. This would be aligned with our hypothesis that the ability take deep breaths can counter the effects of sleep deprivation. Given the burst group was predicted to have poor chemoreflex control [2], we anticipate that this group's breathing pattern will correlate with poor sleep deprivation states compared with the deep breath group even though the PSQI was similar in both groups.

2. Methods

We utilized the datasets identified in Lynch et. al from the Human Connectome Project. Specifically, we utilized the participants who showed deep breath and burst patterns in their resting state breathing. During the entire 15 minutes of HCP data, we calculated BR, absolute BRV (Interquartile range of BR which will be referred to as BRV from now in this paper), and relative BRV%.

Further, we estimated the PSQI scores from the HCP dataset along with other psychophysiological variables of BMI, age, systolic blood pressure (BP), diastolic BP, anxiety-attention-aggression (Adult Self-Report or ASR raw scores [14]), via descriptive statistics of Mean±Standard Deviation to characterize the states in the two groups of burst and deep-breath. Further, we correlated these measures with BRV using Pearson correlation in MS Excel functions. The ASR scoring criterion used in the HCP data collection can be found in https://www.humanconnectome.org/storage/app/medi a/documentation/LS2.0/LS_2.0_Release_Appendix_2 .pdf, and the scores reflect the psychopathology in the adults.

The HCP resting-state fMRI dataset was originally acquired and preprocessed as per the overview article focused on the progress made during the first half of the 5-year project in refining the methods for data acquisition and analysis [15]. Conversion of DICOM files NIFTI format was carried out using the dcm2nii utility. This utility is a component of the MRIcron suite of tools developed by Chris Rorden (http://www.nitrc.org/projects/mricron/). The HCP MRI data pre-processing pipelines were primarily built using tools from FSL and FreeSurfer, the minimally preprocessed data were utilized for the current study [16].

fALFF was estimated from the simultaneous resting-state MRI data collected in the two groups, burst and deep breath using the "DPABI: Data Processing & Analysis" software package [17]. In the software package, the time series was first converted to the frequency domain using a Fast Fourier Transform, and the averaged square root of the power spectrum for the predefined typical frequency interval 0.01–0.08 Hz. We applied a bandpass filter ranging from 0.01 to 0.08 Hz to all f-ALFF analyses. fALFF data was calculated from the minimally preprocessed resting-state fMRI data filtered that was smoothed. f-ALFF measures the power within the low frequency (0.01–0.08 Hz) divided by the total power in the entire detectable frequency range to represent the relative contribution of low-frequency oscillations

[18]. We inputted the z score signals (prefixed with z-fALFFmap) outputted from DPABI [17], for subsequent statistical analysis with statistical parametric mapping (SPM) v12 package [19]. We correlated both BR and BRV with fALFF in both groups. Clusters of rs-fMRI differences are overlaid on anatomical backgrounds for visualization. Correction for multiple comparisons was performed with cluster thresholding, which consists of two stages. After thresholding with an uncorrected threshold of $p < 0.001$ and minimum cluster size of 3, clusters are each thresholded based on family-wise error (FWE) correction at $p < 0.05$. Then using BRV as a co-variate in the SPM model we identified the brain regions showing significantly different fALFF in the two groups burst and deep breath. The significance level of contrasts was set to $p < 0.05$ with FWE correction with cluster size greater than or equal to 3.

3. Results

In Table 1, we list the group differences in the deep-breath and the burst for all psychophysiological variables. The PSQI scores in the burst and deep breath groups were not significantly different (Table 1). The nature of the correlation between BR and BRV as well as relative BR with BRV reflect that the breathing pattern in the burst group compared to the deep breathing group is not entirely explained by the breathing rate. The BRV in the burst group was higher than the deep breath group.
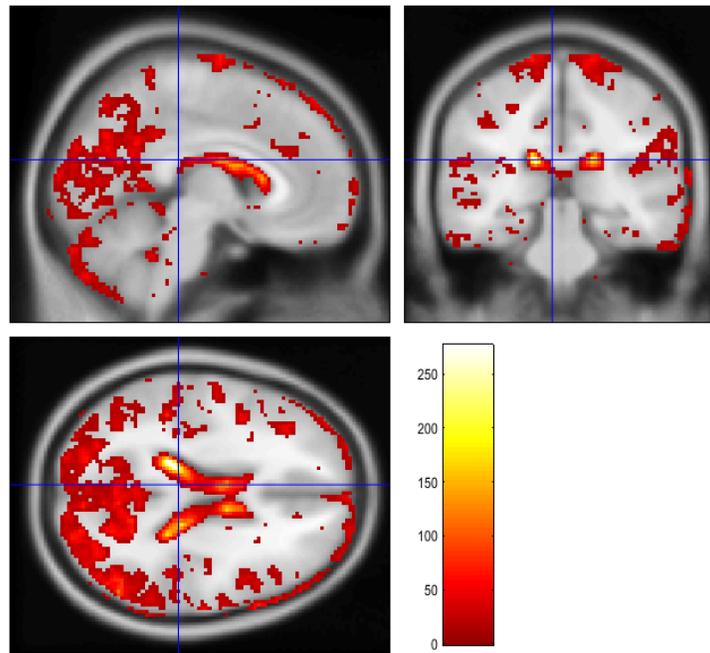
Figure 1: Brain regions showing fALFF correlation with BRV in all subjects at the cerebrospinal fluid (CSF) ventricles. Color bar indicates t-statistics.
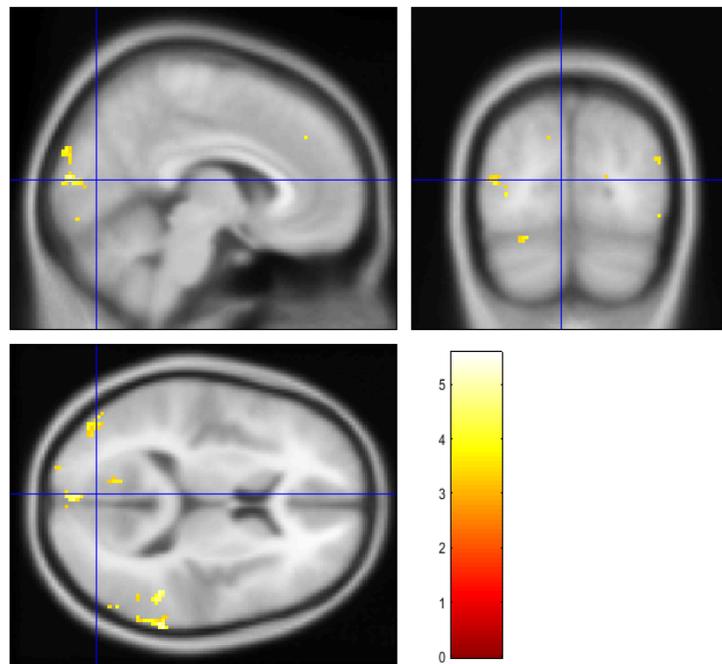

Figure 2: With BRV as covariate, higher fALFF activity in burst compared to deep breath group at the visual and somatosensory regions. Color bar indicates t-statistics.

The burst group showed higher BMI, higher blood pressure compared to the deep breath group (Table 1). Only BMI correlated with BRV in the burst group, not the deep breath group. From the HCP data, we reported the anxiety-attention-aggression ASR raw scores which were higher in the burst compared to the deep breath group (Table 1). We found significant correlation between BRV and the fALFF at the ventricles of the brain for both subjects in the burst (n=21) and deep breath (n=21) groups (Figure 1). No correlation was found between BR and fALFF. Additionally, after keeping BRV as co-variate in the SPM model, we found significantly higher fALFF at the visual and somatosensory cortex in the burst compared to the deep breath group (Figure 2). Differences in BMI, mean arterial blood pressure, anxiety, aggression, and attention were not statistically significantly different between burst and deep breath groups.

4. Discussion

We observed higher BRV in the burst compared to the deep breath group. This was expected given the breathing pattern of the burst group visually matched with apneic groups as conducted in previous studies [2, 3]. Additionally, BMI correlated with BRV only in the burst group. Also, BP and anxiety-aggression-attention problems were higher in the burst group (Table 1). These findings potentially point to a more pathological autonomic state in the burst group, also

indicated in the Lynch et al. 2020 paper [2]. In our study, we additionally found that the individuals in the burst group had similar PSQI scores as the deep breath group. Therefore, overall sleep quality did not appear to be the driving factor in these differences.

As anticipated, we found that the BRV correlated with the fALFF in both groups at the cerebrospinal ventricles. This result corresponds to the earlier findings of vascular origins of low-frequency oscillations in the cerebrospinal fluids that were coupled with breathing [11, 20]. It is interesting to note that BRV but not BR correlated with fALFF. That could mean that in the future, it may be better to consider BRV for physiological state analysis rather than BR, a suggestion made by other studies as well [21].

The correlation between BRV instead of BR with fALFF suggested that the coupling was between the respiratory fluctuations rather than the respiratory rate along with the spontaneous neuronal fluctuations, especially at the fourth ventricles. In other words, respiratory physiology was driving the movement of the glymphatic system, and a change in the autonomic state could change the glymphatic function [22]. The implications of the findings are that altering the biomarker of BRV, one can confirm changes in the neurophysiological state.

Summary statistics: Mean±std. dev, Correlation with BRV (Pearson R)	Deep breath (5 males, n=21)	Burst (14 males, n=21)
Breathing rate (BR) (breaths per minute or bpm)	14±7, 0.57*	18±3, 0.2
Absolute Breathing rate variability (BRV) (bpm)	3±3	4±3
Relative BRV (%)	24±14, 0.78*	24±18, 0.97*
Age (years)	29±4, -0.02	30±4, 0.03
BMI (kg/m^2)	26±5, -0.27	28±6, 0.50*
Systolic blood pressure (BP) (mmHg)	121±13, -0.14	128±14, 0.16
Diastolic BP (mmHg)	74±11, -0.31	76±9, 0.04
Anxiety	5±5, -0.09	7±7, -0.16
Attention	5±4, -0.03	7±4, -0.06
Aggression	3±3, -0.12	5±2, 0.29
Pittsburg Sleep Quality Index (PSQI)	5±3, -0.26	5±3, -0.03

Table 1: Psychophysiological characteristics of the deep breath vs. burst groups.

Additionally, we found that by including BRV as a co-variate, higher fALFF activity was found in the visual and somatosensory cortex in the burst compared to the deep breath group. In previous studies, higher ALFF activity in this region was associated with sleep deprivation states [12-13]. Together with the sleep quality scores not differing between the deep breath and burst groups, we interpret these findings to indicate that the differences in breathing patterns during the resting state reflected in the higher spontaneous neuronal activity in the visual and somatosensory cortex, in the default mode network regions. The higher default mode network activity could be associated with mind-wandering and difficulty in paying attention [22] in addition to sleep deprivation problems [5, 12-13]. These findings together with the higher ASR raw scores for anxiety-aggression-attention problems, higher blood pressure and higher BMI in the burst group compared to the deep breath group, reinforce that patterns of sleep deprivation become more obvious in the fALFF neural patterns when adjusted for the higher BRV in the burst group compared to the deep breath group. Our findings imply that during wake, if an individual is able to practice more deep breathing patterns (as in the deep breath group) then their neural pattern will be different than individuals who are unable to regulate their breathing pattern by taking sighs as in the burst group.

The limitations of this study were that there were only 21 people in each of the burst and deep breath groups. Future studies should design experiments where participants take deep breaths vs. shallow breaths with higher BRV during the test period. The signatures of breathing patterns obtained from the Lynch study [2] could be utilized to design future experiments. Moreover, in future experiments, the sleep quality

should be controlled for in participants. In this particular study, we happened to find two groups that had similar PSQI scores. The other limitation of this particular study is that it was done on relatively healthy individuals in the HCP cohort, and the differences between burst and deep breath groups in BMI, blood pressure, ASR scores were not statistically significantly different. Future studies should account for the effects in populations known to have higher BRV like OSA.

Overall these findings suggest that, deep breathing is associated with better cognitive and emotional states measured via both psychophysiological states as well as neural signatures associated with improved physiological states. Moreover, breathing pattern reflected particularly by BRV, may be a marker for, and mediator of, overall health in an individual. It is interesting that although, the subjective sleep quality PSQI scores did not vary in the two groups but the differences in BRV could indicate differences in neural states. These findings support that volitionally taking long, deep breaths during wake, as in meditation or diaphragmatic breathing practices, could help alter neural signatures, associated with psychophysiological states mediating arousal, anxiety, and attentional networks. It is also possible that such beneficial effects of deep breathing will hold even in individuals with mild sleep deprivation [23], and improve the overall quality of life in otherwise healthy populations like in the HCP cohort. In order to evaluate and determine clinically meaningful interventions, it is important to test these predictions considering different deep breathing techniques that utilize mouth vs. nostril breathing [24]. In conclusion, our study finds that involuntary deep breaths correlate

with altered resting-state fALFF dynamics and improved psychophysiological states, which may hold true with voluntary deep breath practices as in Zaccaro et al., 2018 [25].

Acknowledgments

Ethical Approval

All authors have seen and approved the manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.
The manuscript does not report on a clinical trial.

Significance

This study finds that differences in breathing pattern even with similar sleep quality reflect differences in neuro-psycho-physiological states. Particularly, the group that showed the ability to take deep breaths or sighs had a lower breathing rate variability as opposed to the burst group having signatures of apneic

breathing. The burst group was also associated with neural signatures of sleep deprivation with higher low frequency neuronal fluctuations at the visual and somatosensory cortex, had higher BMI, mean arterial blood pressure, higher anxiety-aggression-attention problems.

References

1. Chattu VK, Manzar MD, Kumary S, et al. The Global Problem of Insufficient Sleep and Its Serious Public Health Implications. Healthcare (Basel, Switzerland) 7 (2018): 1.

2. Lynch CJ, et al. Prevalent and sex-biased breathing patterns modify functional connectivity MRI in young adults. Nature Communications 11 (2020): 5290.

3. Pal A, et al. Breathing rate variability in obstructive sleep apnea during wakefulness. J Clin Sleep Med (2021).

4. Sarma MK, Pal A, Keller MA, et al. White matter of perinatally HIV infected older youths shows low frequency fluctuations that may reflect glial cycling. Sci Rep 11 (2021).

5. Dai XJ, et al. Long-term total sleep deprivation decreases the default spontaneous activity and connectivity pattern in healthy male subjects: a resting-state fMRI study. Neuropsychiatric disease and treatment 11 (2015): 761-772.

6. Wang L, et al. Sleep deprivation disturbed regional brain activity in healthy subjects: evidence from a functional magnetic resonance-imaging study. Neuropsychiatric disease and treatment 12 (2016): 801-807.

7. Macey PM, Woo MA, Kumar R, et al. Relationship between obstructive sleep apnea severity and sleep, depression and anxiety symptoms in newly-diagnosed patients. PLoS One 5 (2010): e10211.

8. Soon CS, Vinogradova K, Ong JL, et al. Respiratory, cardiac, EEG, BOLD signals and functional connectivity over multiple microsleep episodes. NeuroImage 237 (2021): 118129.

9. Vlemincx E, Taelman J, Van Diest I, et al. Take a deep breath: the relief effect of spontaneous and instructed sighs. Physiol Behav 101 (2010): 67-73.

10. Franklin KA, Lindberg E. Obstructive sleep apnea is a common disorder in the population-a review on the epidemiology of sleep apnea. J Thorac Dis 7 (2015): 1311-1322.

11. Fultz NE, et al. Coupled electrophysiological, hemodynamic, and cerebrospinal fluid oscillations in human sleep. Science (New York, N.Y.) 366 (2019): 628-631.

12. Poh JH, Chee MWL. Degradation of neural representations in higher visual cortex by sleep deprivation. Scientific reports 7 (2017): 45532-45532.

13. Zeng B, et al. Altered Percent Amplitude of Fluctuation in Healthy Subjects After 36 h Sleep Deprivation. Frontiers in Neurology (2021).

14. Achenbach TM, Ivanova MY, Rescorla LA. Empirically based assessment and taxonomy of psychopathology for ages 1½–90+ years: Developmental, multi-informant, and multicultural findings. Comprehensive Psychiatry 79 (2017): 4-18.

15. David C. Van Essen, Stephen M. Smith, Deanna M. Barch, Timothy E.J. Behrens, Essa Yacoub, Kamil Ugurbil, for the WU-Minn HCP Consortium. (2013). The WU-Minn Human Connectome Project: An overview. NeuroImage 80 (2013): 62-79.

16. Matthew F Glasser, Stamatios N Sotiropoulos, J Anthony Wilson, et al. The minimal preprocessing pipelines for the Human Connectome Project. Neuroimage 80 (2013): 105-124.

17. Yan CG, Wang XD, Zuo XN, et al. DPABI: Data Processing & Analysis for (Resting-State) Brain Imaging. Neuroinformatics 14 (2016): 339-351.

18. Lv H, et al. Resting-State Functional MRI: Everything That Nonexperts Have Always Wanted to Know. Am J Neuroradiol 39 (2018): 1390-1399.

19. Friston KJ. Statistical parametric mapping : the analysis of functional brain images. (Elsevier/Academic Press (2007).

20. Attarpour A, Ward J, Chen JJ. Vascular origins of low-frequency oscillations in the cerebrospinal fluid signal in resting-state fMRI: Interpretation using photoplethysmography. Hum Brain Mapp 42 (2021): 2606-2622.

21. Soni R, Muniyandi M. Breath Rate Variability: A Novel Measure to Study the Meditation Effects. Int J Yoga 12 (2019): 45-54.

22. Hablitz, L.M. and M. Nedergaard, The Glymphatic System: A Novel Component of Fundamental Neurobiology. J Neurosci 41 (2021): 7698-7711.

23. Brandman T, Malach R, SimonyE. The surprising role of the default mode network in naturalistic perception. Communications Biology 4 (2021): 79.

24. Jerath R, Beveridge C, Barnes VA. Self-Regulation of Breathing as an Adjunctive Treatment of Insomnia. Frontiers in psychiatry 9 (2019): 780-780.

25. Jiang Y, et al. Effectiveness of breathing through nasal and oral routes in unconscious apneic adult human subjects: a prospective randomized crossover trial. Anesthesiology 115 (2011): 129-35.

26. Zaccaro A, et al. How Breath-Control Can Change Your Life: A Systematic Review on Psycho-Physiological Correlates of Slow Breathing. Frontiers in human neuroscience 12 (2018): 353-353.