

EEG Brain Synchronization in Epileptic Patients During Sleep

Samaneh Baghbani, Jonathan-F Baril, Marcus Ng¹

¹*Epileptologist (MD, FRCPC), University of Manitoba*

INTRODUCTION

Brain synchronization occurs when different areas of the brain work simultaneously and communicate together. However, if there is over-synchronization of the brain, then this can lead to the medical condition of epilepsy, which is defined as the tendency to recurrent unprovoked seizures. Cortical hyper-synchronization facilitates spatial and temporal summation of aberrant neuronal activity into epileptiform discharges and seizures.

On visual electroencephalographic (EEG) analysis, brain synchronization also varies in different stages of sleep with high synchronization observed during NREM (non-rapid eye movement) sleep and high desynchronization observed in REM (rapid eye movement) sleep.¹⁻³ However, it has only been recently recognized that brain synchronization variations may influence observed changes in seizure susceptibility through different sleep stages in epileptic patients.¹⁻³ Specifically, seizures and epileptiform discharges have been observed to worsen during NREM but improve in REM sleep.^{1, 4-14} A recent study has attempted to quantify the degree of EEG synchronization in a particular sleep stage per frequency band of brain activity in nonepileptic persons.¹⁵

We hypothesize that there are measurable EEG brain synchronization changes in epileptic patients during sleep. Brain synchronization can be inferred by

calculating statistical interdependencies among signals in coupled neuronal systems. These dependencies can then be analysed using quantitative EEG measures. This study aims to identify brain synchronization changes in epileptic subjects during REM and NREM sleep by using EEG spectral analysis.

METHODS

EEG signals were continuously recorded over 48 hours (two nights) from 76 high density electrodes in the 10-10 EEG electrode configuration on three patients admitted to the University of Manitoba Health Sciences Centre Epilepsy Monitoring Unit. Each 10 second EEG epoch was manually sleep staged (i.e. NREM1, NREM2, NREM3, REM) and then filtered into four frequency bands (i.e. fast alpha and beta bands, slow theta and delta bands) using MATLAB software. To examine synchronization, we assessed the connectivity metrics of cross-correlation (XCOR), multivariate phase synchronization (MPS), and imaginary coherence (IC).

Each metric generated a 76x76 dependency matrix of 5,700 normalized synchronization elements between electrode pairs (ignoring diagonal auto-dependency values). For a single subject, there was a separate matrix for each respective metric, sleep stage, frequency band, and night of recording. We then subtracted REM matrix elements from

each corresponding NREM matrix element to generate a "change-matrix".

Positive-valued change-matrix elements represented electrode pairs with greater desynchronization in REM sleep (and simultaneous greater synchronization in NREM sleep). We represented desynchronization as the proportion of positive-valued elements in a change-matrix. A value of 0.5 represents chance (equal synchrony between REM and NREM sleep), less than 0.5 represents maximal desynchronization in NREM sleep, and more than 0.5 represents maximal REM sleep desynchrony.

RESULTS

We calculated EEG synchronization metric values for 1,231,200 change-matrix elements from 2,462,400 total matrix elements. REM sleep was the most desynchronized state for 674,253 change-matrix elements (54.8%) and 116 change-matrices (53.7%). This finding held consistent when compared between recording nights (range 54% to 55.5%), individuals (range 54.3% to 55.5%), and slow and fast frequency bands (range 52.9% to 54.9%).

Table 1 demonstrates that REM sleep was consistently the most desynchronized state when compared to NREM1 sleep (average 66.3%). This finding held consistent when compared between recording nights (range 66% to 66.7%), individuals (range 65.5% to 67%), slow and fast frequency bands (range 66% to 66.7%), and across all connectivity metrics (range 55.1% to 87.1%).

In contrast, REM sleep was more desynchronized than NREM2 sleep for an average 48.9% of total change-matrix elements (range 47.1% to 50.4% across

connectivity metrics), and for an average 49% of total change-matrix elements in NREM3 sleep (range 47.5% to 50% across connectivity metrics).

Table 1: Proportion of Normalized Positive-Valued Change-Matrix EEG Synchronization Metric Elements. Values greater than 0.5 represent maximal EEG brain desynchronization in REM sleep.

		Night 1			Night 2			
		SUB 1	SUB 2	SUB 3	SUB 1	SUB 2	SUB 3	
XCOR	Alpha	NREM1 & REM	0.5	0.61	0.57	0.51	0.6	0.5
		NREM2 & REM	0.48	0.46	0.47	0.44	0.47	0.46
		NREM3 & REM	0.48	0.52	0.48	0.46	0.48	0.48
	Beta	NREM1 & REM	0.56	0.61	0.64	0.55	0.61	0.56
		NREM2 & REM	0.47	0.5	0.51	0.49	0.45	0.51
		NREM3 & REM	0.48	0.5	0.43	0.47	0.5	0.5
	Theta	NREM1 & REM	0.49	0.59	0.53	0.5	0.57	0.51
		NREM2 & REM	0.46	0.45	0.46	0.42	0.46	0.49
		NREM3 & REM	0.43	0.46	0.49	0.39	0.46	0.48
Delta	NREM1 & REM	0.5	0.55	0.51	0.54	0.54	0.59	
	NREM2 & REM	0.44	0.51	0.49	0.5	0.47	0.45	
	NREM3 & REM	0.45	0.51	0.48	0.48	0.52	0.46	
MPS	Alpha	NREM1 & REM	0.58	0.56	0.56	0.58	0.56	0.57
		NREM2 & REM	0.45	0.5	0.47	0.43	0.51	0.51
		NREM3 & REM	0.44	0.51	0.5	0.39	0.5	0.47
	Beta	NREM1 & REM	0.58	0.56	0.58	0.58	0.58	0.57
		NREM2 & REM	0.49	0.54	0.55	0.55	0.47	0.45
		NREM3 & REM	0.53	0.51	0.52	0.56	0.52	0.48
	Theta	NREM1 & REM	0.58	0.57	0.56	0.58	0.57	0.58
		NREM2 & REM	0.48	0.48	0.65	0.44	0.57	0.42
		NREM3 & REM	0.56	0.51	0.64	0.46	0.61	0.5
	Delta	NREM1 & REM	0.57	0.57	0.56	0.56	0.46	0.58
		NREM2 & REM	0.51	0.52	0.65	0.41	0.38	0.41
		NREM3 & REM	0.55	0.5	0.64	0.38	0.37	0.36
IC	Alpha	NREM1 & REM	0.92	0.88	0.95	0.97	0.87	0.81
		NREM2 & REM	0.54	0.44	0.53	0.56	0.51	0.51
		NREM3 & REM	0.55	0.38	0.46	0.55	0.5	0.46
	Beta	NREM1 & REM	0.84	0.81	0.79	0.9	0.81	0.77
		NREM2 & REM	0.48	0.46	0.53	0.49	0.52	0.55
		NREM3 & REM	0.5	0.46	0.5	0.49	0.47	0.55
	Theta	NREM1 & REM	0.89	0.74	0.91	0.94	0.68	0.86
		NREM2 & REM	0.49	0.52	0.53	0.5	0.5	0.48
		NREM3 & REM	0.52	0.51	0.48	0.52	0.51	0.46
	Delta	NREM1 & REM	0.92	0.9	0.97	0.94	0.91	0.94
		NREM2 & REM	0.45	0.51	0.5	0.47	0.49	0.53
		NREM3 & REM	0.47	0.5	0.52	0.49	0.52	0.52

Desynchronization values were most robust using the IC connectivity metric (average 62.4%, range 49.5% to 87.2%) compared to the XCOR (average 49.9%, range 47.1% to 55.2%) and MPS

(average 52%, range 49.3% to 56.7%) metrics. This distribution was consistent when compared between recording nights and individuals.

When comparing desynchronization between slow and fast bands during certain stages of sleep, levels of synchronization were similar for all NREM stages (i.e. average 66% for slow bands and 66.7% for fast bands in NREM1, 48.6% for slow bands and 49.3% for fast bands in NREM 2, 49.2% for slow bands and 48.8% for fast bands in NREM3).

DISCUSSION

Our preliminary findings show that REM sleep is the most desynchronized sleep state for consistently over 50% of high density EEG electrode pairings in epileptic patients over 48 hours of continuous EEG recording. Although the magnitude of this effect was modest (around 54%), it was highly consistent over 2,462,400 matrix elements with a very tight range (no more than 2%) even when controlled for variability between patients, different nights of recording, different frequency bands, and different connectivity metrics. Although all connectivity metrics more or less agreed with one another in this study, the IC connectivity metric was the most robust in elucidating synchronization changes.

Our preliminary finding that maximal desynchronization occurs in REM sleep appears driven by stage NREM1 sleep, which was the most synchronized state even when controlled for intra-patient variability, different nights of recording, and different connectivity metrics. Although NREM sleep is overall more synchronized on visual EEG analysis, the bulk of EEG synchrony is usually

appreciated during NREM3 (slow wave) sleep in the slow bands. Surprisingly, we did not find a robust difference between fast and slow bands in our study to date.

If our preliminary findings continue to hold true as we continue recruiting more patients and analysing data on additional patients already recruited, then this may speak to the importance of EEG brain synchronization changes during transitions between sleep states rather than the particular sleep states themselves *per se*. NREM1 sleep includes much of what is colloquially known as drowsiness, which marks the transition from wakefulness into sleep. It is possible that quantitative EEG synchronization changes too insensitive for the human eye to appreciate on visual analysis may play a much larger role in the spatial and temporal summation of abnormal neuronal activity into seizures and epilepsy than currently recognized at present.

ACKNOWLEDGEMENTS

We would like to thank the EEG technologists and Dr. Yankovsky at the University of Manitoba Health Sciences Centre Epilepsy Monitoring Unit for their invaluable assistance with this project.

REFERENCES

- [1] M. Ng, M. Pavlova "Why are seizures rare in rapid eye movement sleep? Review of the frequency of seizures in different sleep stages," *Epilepsy Res Treat*, 2013:932790.
- [2] M. N. Shouse, J. M. Siegel, M. F. Wu, R. Szymusiak, and A. R. Morrison, "Mechanisms of seizure suppression during rapid eye-movement (REM)

- sleep in cats," *Brain Research*, vol. 505, no. 2, pp. 271–282, 1989.
- [3] M. N. Shouse, P. R. Farber, and R. J. Staba, "Physiological basis: how NREM sleep components can promote and REM sleep components can suppress seizure discharge propagation," *Clinical Neurophysiology*, vol. 111, no. 2, pp. S9–S18, 2000.
- [4] R. A. Hrachovy, J. D. Frost, and P. Kellaway, "Sleep characteristics in infantile spasms," *Neurology*, vol. 31, no. 6, pp. 688–694, 1981.
- [5] R. Sakuraba, M. Iwasaki, E. Okumura, et al. "High frequency oscillations are less frequent but more specific to epileptogenicity during rapid eye movement sleep," *Clinical Neurophysiology*, vol.127, pp. 179-186, 2016.
- [6] AP. Bagshaw, J. Jacobs, P. LeVan et al. "Effect of sleep stage on interictal high-frequency oscillations recorded from depth macroelectrodes in patients with focal epilepsy," *Epilepsia*, vol. 50, pp.617-628, 2009.
- [7] Z. Clemens, J. Janszky, B. Clemens, A. Szucs, and P. Hal'asz, "Factors affecting spiking related to sleep and wake states in temporal lobe epilepsy (TLE)," *Seizure*, vol. 14, no. 1, pp. 52–57, 2005.
- [8] Z. Clemens, J. Janszky, A. Szucs, M. B'ek'esy, B. Clemens, and P. Hal'asz, "Interictal epileptic spiking during sleep and wakefulness in mesial temporal lobe epilepsy: a comparative study of scalp and foramen ovale electrodes," *Epilepsia*, vol. 44, no. 2, pp. 186–192, 2003.
- [9] F. Ferrillo, M. Beelke, F. De Carli et al., "Sleep-EEG modulation of interictal epileptiform discharges in adult partial epilepsy: a spectral analysis study," *Clinical Neurophysiology*, vol. 111, no. 5, pp. 916–923, 2000.
- [10] B. A. Malow, X. Lin, R. Kushwaha, and M. S. Aldrich, "Interictal spiking increases with sleep depth in temporal lobe epilepsy," *Epilepsia*, vol. 39, no. 12, pp. 1309–1316, 1998.
- [11] B. A. Malow, R. Kushwaha, X. Lin, K. J. Morton, and M. S. Aldrich, "Relationship of interictal epileptiform discharges to sleep depth in partial epilepsy," *Electroencephalography and Clinical Neurophysiology*, vol. 102, no. 1, pp. 20–26, 1997.
- [12] G. F. Rossi, G. Colicchio, P. Pola, and R. Roselli, "Sleep and epileptic activity," in *Epilepsy, Sleep and Sleep Deprivation*, R. Degen, Ed., pp. 35–46, Elsevier Science Publishers B.V., Amsterdam, The Netherlands, 1984.
- [13] G. F. Rossi, G. Colicchio, and P. Pola, "Interictal epileptic activity during sleep: a stereo-EEG study in patients with partial epilepsy," *Electroencephalography and Clinical Neurophysiology*, vol. 58, no. 2, pp. 97–106, 1984.
- [14] J. Montplaisir, M. Laverdière, and J.M. Saint-Hilaire, "Sleep and focal epilepsy: contribution of depth recording," in *Sleep and Epilepsy*, M. B. Serman, Ed., pp. 301–314, Academic Press, New York, NY, USA, 1982
- [15] C. Nayak, A. Bhowmik, P. D. Prasad, S. Pati, K. K. Choudhury , K. K. Majumdar, "Phase synchronization analysis of natural wake and sleep states in healthy individuals using a novel ensemble phase synchronization measure," *Clinical Neurophysiology*, Vol. 34 , pp. 77–83, 2017