35th Annual International Conference of the IEEE EMBS
Osaka, Japan, 3 - 7 July, 2013

Habituation of Steady-State Visual Evoked Potentials in response to High-Frequency Polychromatic Foveal Visual Stimulation*

Heng-Yuan Kuo, George C. Chiu, John K. Zao†, *Senior Member, IEEE*, Kuan-Lin Lai, Allen Gruber, Yu-Yi Chien, Ching-Chi Chou, Chih-Kai Lu, Wen-Hao Liu, Yu-Shan Huang, Albert C. Yang, Yijun Wang, Fang-Cheng Lin, Yi-Pai Huang, Shuu-Jiun Wang, Tzyy-Ping Jung, *Senior Member, IEEE*

Abstract— **In an attempt to develop safe and robust methods for monitoring migraineurs' brain states, we explores the feasibility of using white, red, green and blue LED lights flickering around their critical flicker fusion (CFF) frequencies as foveal visual stimuli for inducing steady-state visual evoked potentials (SSVEP) and causing discernible habituation trends. After comparing the habituation indices, the multi-scale entropies and the time dependent intrinsic correlations of their SSVEP signals, we reached a tentative conclusion that sharp red and white light pulses flickering barely above their CFF frequencies can replace commonly used 13Hz stimuli to effectively cause SSVEP habituation among normal subjects. Empirical results showed that consecutive short bursts of light can produce more consistent responses than a single prolonged stimulation. Since these high frequency stimuli do not run the risk of triggering migraine or seizure attacks, further tests of these stimuli on migraine patients are warranted in order to verify their effectiveness.**

I. INTRODUCTION

MIGRAINEURS were known to exhibit pre-ictal and inter-ictal abnormalities in their visual evoked potentials (VEP) when exposed to intermittent photic or visual stimulation [1,2].While normal subjects tend to produce VEP with gradually diminishing amplitudes under prolonged stimulation due to an effect known as the *habituation* of EEG arousal [3], migraineurs often produce VEP with increased amplitudes [4,5]. These abnormalities are regarded as a manifestation of *hyper-excitability* of the trigeminal pathways, a process often culminates to a migraine attack [6]. Consequently, transient PVEP induced by 1–5Hz pattern-reversal checkerboard patterns [7] and steady-state SSVEP induced by α-band photic/visual stimulation [8] are often used to monitor migraineurs' brain states for the sake of tracking patients' conditions or predicting imminent migraine attacks. Unfortunately, the intense α-band stimulation can inadvertently trigger migraine or seizure attacks. Hence, there is a fervent search for safe and robust methods for monitoring migraineurs' brain states.

Since 2012, we at the NCTU Brain Research Center and the UCSD Swartz Center for Computational Neuroscience have been studying human foveal SSVEP responses to polychromatic visual stimuli flashing above their critical flicker fusion (CFF) frequencies [9,10]. Our aim is to develop high frequency SSVEP applications by embedding these potentially imperceptible stimuli into visual displays and ambient lights. These high-frequency stimuli are much less annoying to their viewers as they do not flicker notably and are much safer to use because they do not run the risk of causing photo-epileptic seizure (PSE) or migraine attacks. This study focuses on foveal SSVEP habituation induced by high frequency and low duty cycle color LED lights. We tried to compare the effectiveness of these stimuli against that of the conventional 13Hz white light by studying the variation of habituation indices among normal subjects as they are exposed to continuous and bursty white/red/green/blue light pulses at 13, 32 and 40Hz. We also examined the effects of these stimuli towards the time synchronicity and complexity of SSVEP signals using multi-scale entropy (MSE) and time-dependent intrinsic correlation (TDIC) analysis. The rest of this paper is divided into four parts. The basic rationale of employing high-frequency polychromatic foveal visual stimuli was highlighted in Section II. Subjects, apparatus and procedures of the experiment were mentioned in Section III. Different analysis techniques and their results were described in Section IV. Conclusions were given in Section V.

II. RATIONALE

The main purpose of employing visual stimuli flashing above the CFF frequencies is to eliminate or at least reduce viewers' flickering sensation. Previous experiments demonstrated that it is possible to induce SSVEP with significant sideband signal-to-noise ratios using high-frequency stimuli without causing any discomfort to the viewers [11]. The use of polychromatic stimuli, on the other hand, was motivated by two reasons. First, color lights with lower CFF frequencies can induce stronger SSVEP responses without showing notable flickering. Thus, red and blue lights can be better stimuli as their CFF frequencies at approx. 30 and 35Hz respectively are lower than that of the white light [12]. Besides, polychromatic stimuli can be branded into color images more easily since images maintain their hue by combining different intensity of red/green/blue or RGB lights. As visual stimuli,

---

* This research was partially supported by the ATU Plan Phase II program under Taiwan Ministry of Education [Grant No.: 102W959] and the UST-UCSD International Center of Excellence in Advanced Bio-engineering program under Taiwan National Science Council I-RiCE Program [Grant No.: NSC-102-2911-I-009-101].

John K. Zao is with the Computer Science Department and the Biomedical Engineering Institute (phone: +886-936-814- 849; fax: +886-35-724-176; e-mail: jkzao@cs.nctu.edu.tw); Hen-Yuan Kuo, Cheng-Chi Chiu, Chih-Kai Lu, Wen-Hao Liu, Yu-Shan Huang are with the Computer Science Department (email: kuohengyuan@gmail.com, ccchiu46@pet.cs.nctu.edu.tw, mreltonlu@pet.cs.nctu.edu.tw, lwh0702@pet.cs.nctu.edu.tw, isable632021@pet.cs.nctu.edu.tw); Yu-Yi Chien, Ching-Chi Chou, Fang-Cheng Lin and Yi-Pai Huang are with the Photonics Department and the Display Institute (e-mail: yuyichien2543.eo99g@g2.nctu.edu.tw, chingchi.di00g@g2.nctu.edu.tw, fclin.eo93g@nctu.edu.tw); above authors are all affiliated with the National Chiao Tung University, Hsinchu, Taiwan.

Kuan-Lin Lai, Albert C. Yang and Shuu-Jiun Wang are with the Neurology Department, Taipei Veteran General Hospital, Taipei, Taiwan (email: laikuanlin@gmail.com, accyang@gmail.com, sjwang@vghtpe.gov.tw).

Allen Gruber and Tzyy-Ping Jung are affiliated with the Schwartz Center of Computational Neuroscience, University of California at San Diego (e-mail: wangyijun97@gmail.com, jungtp@gmail.com).

978-1-4577-0216-7/13/$26.00 ©2013 IEEE

RBG LED lights are far more superior to tungsten lamps, florescent lights or CRT displays. Not only that their intensity and waveforms can be precisely controlled, their *radiance spectra* [Figure 1] can also be tuned to match the *responsivity spectra* of cone photoreceptors [Figure 2]. Thus, they can generate time/frequency/color concentrated pulses for inducing maximal VEP responses. Finally, foveal stimulation may be more practical in many consumer applications, in which viewers use mostly their foveal vision. Moreover, the high concentration of cone photoreceptors may enhance viewers' foveal VEP responses towards color stimuli.

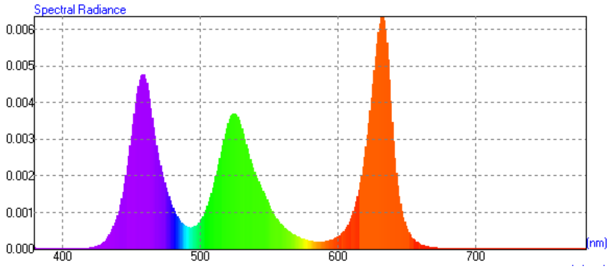


Figure 1: Spectral radiance of commercial R/G/B LED lights

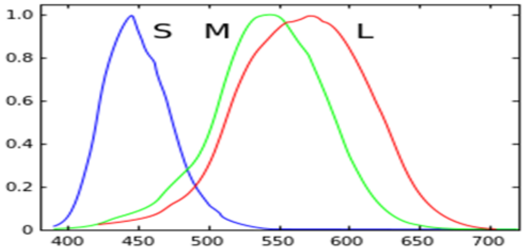


Figure 2: Normalized responsivity spectra of human cone photoreceptors

III. METHOD

A. Subjects

Six young healthy subjects (3M, 3F) age: 21–25 (μ=23.3, σ=1.2) participated in this experiment. All subjects have normal or corrected-to-normal vision with no vision impairment. Each subject was also confirmed to have no uncomfortable experience with flashing lights and no epileptic seizure in personal and family history. They were informed of the objectives, procedures and potential risks of the experiment and signed an informed consent form before participation.

B. Apparatus

The experiment was conducted in a darkened and radio-shielded room in order to minimize environmental contamination to the visual stimuli and the EEG signals.

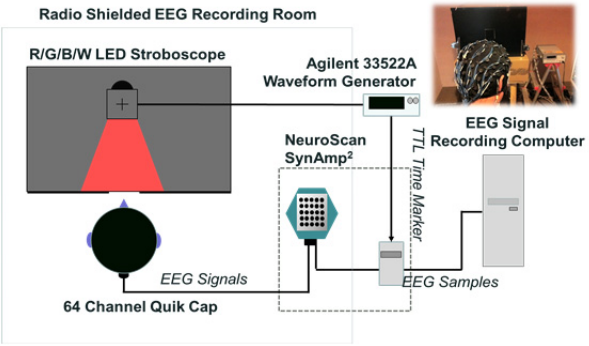
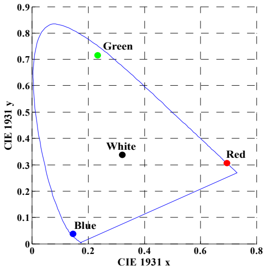


Figure 3: Equipment set-up for polychromatic SSVEP experiment



Chromaticity	**x**	**y**
Red	0.692	0.308
Green	0.232	0.718
Blue	0.144	0.039

Figure 4: CIE chromaticity gamut and coordinates of the RGB LED lights used in the experiment

Figure 3 shows the experiment set-up. We used commercial red/green/blue/white LEDs as the light sources. Their spectral radiance and CIE chromaticity were measured and displayed in Figure 4 and the associated table. Each set of color LED lights was mounted on a separate head piece that can be fitted onto a Monarch MVS 115/230 LED stroboscope. It was in turn driven by an Agilent 33210A waveform generator. To ensure uniform luminance, the light was projected through two diffusers onto a mylar-covered view screen erected 60cm in front of the subject. A 4.37cm circular hole was cut out on the screen to create a 5° circular stimulus pattern. EEG signals were captured using a 64-channel Quik-Cap plus a NeuroScan SynAmps^2 amplifier and recorded using a dual-core computer. The EEG electrodes were placed according to the International 10–20 system. A TTL-SYNC signal produced by the waveform generator was fed into the EEG recording system to supply the time marks synchronized to the light pulses.

C. Procedures

During the experiment, each subject was asked to sit in a comfortable chair, placed his/her head on a chin-rest and stared at the diffused light patterns appeared on the view screen. Two visual stimulation patterns with 153 cd/m^2 luminance, 20% duty cycles and 15/32/40Hz in frequencies were applied in each round of the experiment: (1) five 10sec bursts interlaced with 10sec rest periods and preceded with a 15sec baseline recording period were applied in accordance with the international guideline for using EEG in epilepsy diagnosis [13]; (2) a continuous 50sec stimulation preceded with a 15sec baseline period was also applied for comparison. The rounds were randomized for each subject so that overall results would not be biased by their ordering.

During signal preprocessing, interferences from out-of-band noise and in-band artifacts were removed from the EEG data steam by passing them through 1Hz–100Hz band-pass filtering, 4-to-1 down sampling, artifact epoch removal and ICA artifact component removal. Cleansed data were then subjected to marker-synchronized sample averaging with a 1sec sliding window to enhance time-locked SSVEP signals. All signal processing was performed using EEGLAB [14].

IV. RESULTS AND DISCUSSIONS

Since we conducted our experiment on healthy subjects, we cannot provide direct evidence whether polychromatic high-frequency visual stimuli may be effectively used as a migraineur monitoring tool. Nevertheless, we can compare subjects' SSVEP responses towards these new stimuli vs. the conventional 13Hz white stimulus. Whether the new stimuli could produce *similar* and *consistent* responses may serve as an indication of their *effectiveness* as a tool. As mentioned, we examined not only the *habituation* of subjects' SSVEP responses but also the *synchronicity* and the *complexity* of their responses under the influence of these visual stimuli.

A. Polychromatic HF-SSVEP Habituation

As the amplitudes of SSVEP responses vary among subjects and diminishes inverse proportionally to their stimulus frequency, we must employ the normalized *habituation index* H as an un-biased measurement. It is the ratio between the SSVEP spectral amplitude in a specific recording epoch vs. the one in the first epoch taken from a subject using a specific stimulus. Figure 4 and Figure 5 show the boxplots of SSVEP habituation indices at Oz among the six subjects in response to the aforesaid stimuli. Obviously, they vary significantly between the epochs and differ notably among the subjects. However, the responses towards *bursty white* and *blue stimuli* did show certain degree of *similarity* as their mid-range (25%-50%) H values at different frequencies overlap with one another. The responses towards *bursty/continuous white* and *bursty blue stimuli* also showed some *consistency* as their H values appear less dispersed.

We also examined the trends of variation among habituation indices. To do so, we calculated the differences between H values from 2nd and 4th epochs. Figure 6 shows the boxplot of these differences. In this case, the *red stimuli* stand out with the most *similar* and *consistent* variations whereas the *green* and *blue stimuli* show the least. In general, *bursty stimuli* tend to produce more *consistent* results than the continuous ones.

B. Signal Complexity and Synchronicity

We applied MSE and TDIC analysis to Fz and Oz signals reconstructed by combining the ICA components with signal power concentrated in frontal and occipital regions. Multi-scale entropy (MSE) [15] shows a series of sampled entropy values computed in progressive time scales. It offers a way to quantify intrinsic autocorrelation and signal complexity in multiple time scales. Whereas, time-dependent intrinsic correlation (TDIC) [16] is a novel method to estimate partial correlation among non-stationary signals based on ensemble empirical mode decomposition (EEMD).

Figure 7 displays the MSE profiles of SSVEP at Oz and Fz in response to continuous 13/32/40Hz red stimuli. Most profiles, esp. those of Oz, show the familiar "long-tail" shape indicating modest amount of multi-scale autocorrelation. Especially, the profiles of 32Hz stimuli resembled the 13Hz ones. Most notably, the $1/T$ profiles of a migraineur suspect are maintained between 13Hz and 32Hz. In comparison, the 40Hz stimuli lack of this effect.

Figure 8 shows the TDIC profiles between SSVEPs at Fz and Oz in response to continuous 13/32/40Hz red stimuli. It reveals that 32Hz red stimuli have compatible but weaker effects in enhancing EEG synchronicity between occipital and frontal regions when compared with the 13Hz stimuli. Again, the 40Hz stimuli lack of this synchronizing effect.

V. CONCLUSIONS

Our attempt to induce habituation and to affect synchronicity as well as complexity of EEG signals using high-frequency polychromatic visual stimuli represents a novel approach in brain-state monitoring and entrainment. The effectiveness of such an approach is far from certain as we have merely conducted an exploratory experiment on a few healthy subjects. Nonetheless, our preliminary results seem to suggest that sharp red and white LED light pulses flashing around critical flicker fusion frequencies may have the ability to induce notable SSVEP responses, cause discernible habituation trends and even affect the synchronicity and complexity of brain activities. These high-frequency stimuli may not be as effective as the conventional α-band stimuli in some cases. Nonetheless, they are less annoying and safer to use. Further investigation of their effectiveness is warranted.

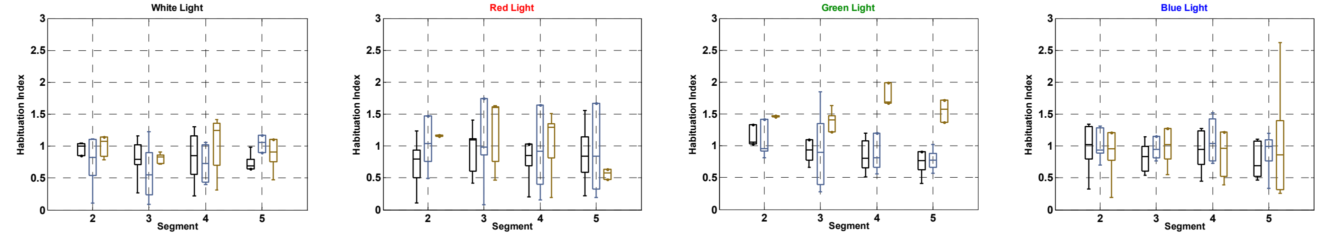


Figure 4: Habituation indices of SSVEP at Oz at 13Hz (black), 32Hz (navy) & 40Hz (karkki) under continuous white/red/green/blue stimulation

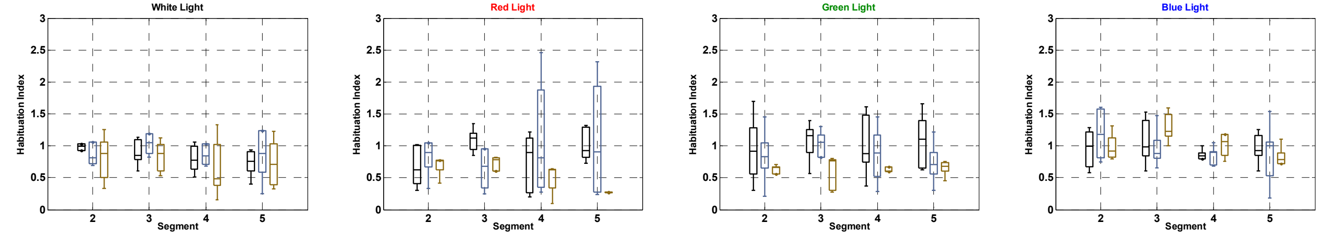


Figure 5: Habituation indices of SSVEP at Oz at 13Hz (black), 32Hz (navy) & 40Hz (karkki) under burst white/red/green/blue stimulation

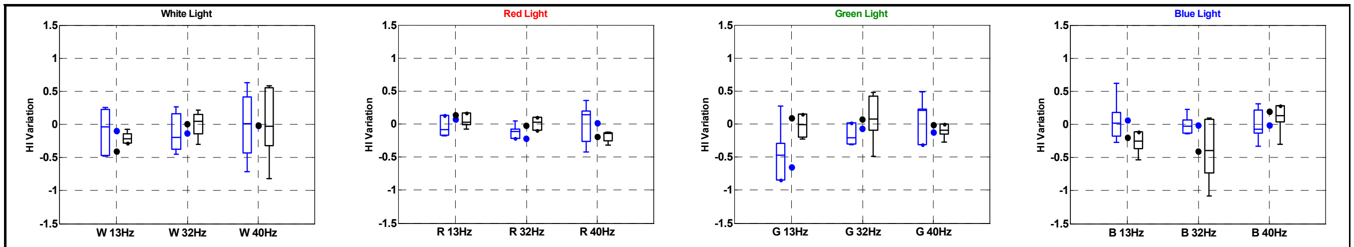


Figure 6: Trends of SSVEP habituation index variation at Oz under white/red/green/blue stimulation.

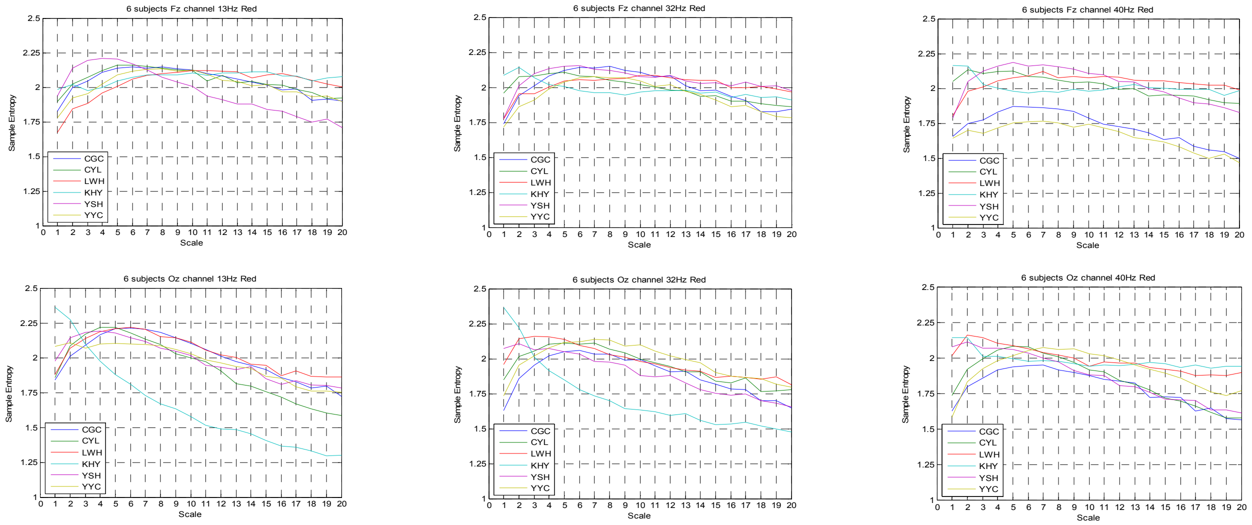


Figure 7: MSE profiles of SSVEP at Oz & Fz of six subjects under 13Hz, 32Hz & 40Hz continuous red stimulation

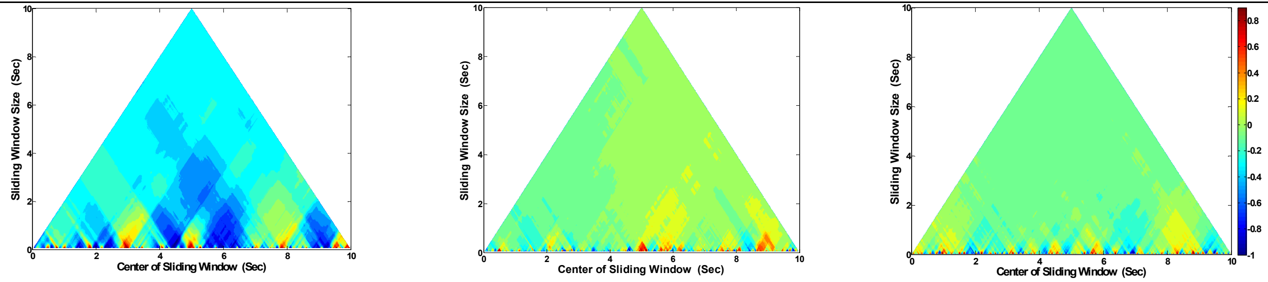


Figure 8: TDIC profiles of an individual's Fz-Oz correlation under continuous 32Hz red stimulation

REFERENCES

[1] F.L. Golla, A.L. Winter. "Analysis of cerebral response to flicker in patients complaining of episodic headache". *Electroencephalography Clinical Neurophysiology* 11:539-49, 1959.

[2] J.B. Lehtonen. "Visual evoked potentials for single flashes and flickering light in migraine". *Headache* 14:1-12, 1974.

[3] S. Sharpless, H. Jasper. "Habituation of the arousal reaction". *Brain*. 79:357–388, 1956.

[4] T. Nyrke, et al.. "Difference of steady-state visual evoked potentials in classic and common migraine". *Electroencephalography Clinical Neurophysiology* 73:185–294, 1989.

[5] F.M. Puca, et al. "Brain mapping in migraine: spontaneous activity and steady-state visual evoked potentials in migraine with and without aura". *Cephalalgia* 11:69-70, 1991.

[6] D. Pietrobon, J. Striessnig. "Neurobiology of migraine". *Nature Reviews Neuroscience*, 4(5), 386-398, 2003.

[7] K. Shibata, M. Osawa, M. Iwata. "Pattern-reversal visual evoked potentials in classic and common migraine." *J. neurological sciences* 145.2: 177-181, 1997.

[8] M. de Tommaso, et al. "Visually evoked phase synchronization changes of alpha rhythm in migraine: correlations with clinical features." *I. J. Psychophysiology* 57.3:203-210, 2005.

[9] F.C. Lin, J.K. Zao, K.C. Tu, et al. "An SNR analysis of high-frequency steady-state visual evoked potentials from foveal and extrafoveal regions of human retina", *EMBC-2012,* San Diego, USA, August 28 – September 1, 2012.

[10] J.K. Zao, et al. "Human steady-state visual evoked potentials induced by high-frequency polychromatic flickering stimuli", *IEEE BMBI-2012*, August 27, 2012.

[11] Y. Wang, et al. "Brain-computer interface based on high-frequency steady-state visual evoked potential." *IEEE Int'l Conf. on Neural Interface & Control*, May 26–28, 2005.

[12] S. Shady, et al. "Adaptation from invisible flicker", *PNAS* 101(14): 5170–5173, April 6, 2004

[13] R. Flink. "Guidelines for using EEG methodology in epilepsy diagnosis." *Acta Neurologica Scandinavica* 106.1:1-7, 2002.

[14] EEGLAB, http://sccn.ucsd.edu/wiki/EEGLAB.

[15] M. Costa, et al. "Multiscale entropy analysis of complex physiologic time series." *Phy. Review Ltrs* 89.6: 68102, 2002.

[16] X. Chen, Z. Wu, E.N. Huang. "Time-dependent intrinsic correlation based on empirical mode decomposition". *Adv. in Adaptive Data Analysis* 2.02: 233-265, 2010.