Electro-Acupuncture (EA) as an Adjunct Therapy to Methadone Maintenance Treatment (MMT) in Heroin Addiction: A Study of 2D EEG Power Spectral Topography and Morlet Wavelet

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Abstract—**The present study investigates the efficiency of electro acupuncture (EA) as an adjunct therapy to methadone maintenance treatment (MMT) in heroin dependents. Time-frequency analysis, based on Morlet wavelet transform together with 2D spectral power topography were applied to demonstrate different brain dynamics in subjects being acupunctured as compared to controls. A significant decrease of delta activity in right hemisphere together with an increase of alpha activity in central areas was observed in subjects who underwent acupuncture which may indicate the modulatory effects of electro-acupuncture as a treatment to improve the conditions of opioid dependency.**

Keywords-electro acupuncture (EA); methadone maintenance treatment (MMT); Morlet wavelet; 2D power spectral topography

I. INTRODUCTION

The inadequate social status brings the potential of developing the drug addiction in many countries, including Malaysia, to highest rates today [1]. Methadone maintenance treatment (MMT) is currently the prime pharmacotherapy for treatment of addiction to opiates as the major drugs of abuse [2]. During MMT, employing long-acting opiates to fulfill the body needs of the addict, homeostasis is shifted from a natural baseline level to an elevated level (opioid saturation).

Although applying acupuncture in treating drug dependence has recently gained much interest in public, yet its efficiency in treating drug addiction remains controversial [3]. Acupuncture analgesia can be provoked by low-frequency stimulation of 2 or 4 Hz, or high-frequency stimulation of 100 or 200 Hz. The particular frequencies make the central nervous system to have different effects induced by peripheral electric stimulation. The studies of Electrical Acupuncture Stimulation (EAS) induced analgesia show that: (1) 2Hz stimulation provokes enkephalin to activate *mu- and delta-*opioid receptors while simulation of 100Hz discharges dynorphin connecting to kappa receptor [4-7]; (2) the analgesic effect induced by 2Hz stimulation is eliminated at the abrasion of arcuate nucleus (ARC) of hypothalamus [8] while it impairs the parabrachial nucleus (PBN) ; and (3) brain areas in specific pattern could not be stimulated by peripheral electric stimulation of 2 or 100Hz which is the same as in *c-fos*gene expression [4, 9].

The frequency modulation of the brain function is the core theory that shows the effects of the main mechanisms of the acupuncture [10] . There are short-term and long-term effects achieved by the mechanisms of the acupuncture [11]: (1) the short-term effect was provoked by frequency modulation of neuroplasticity and (2) the long-term effect was shown by neuroimaging that gene transformation of protein synthesis was presented in the specific brain activations [12, 13].

The cocaine-dependent individuals have been treated by acupuncture for drug dependence in several studies. In one of the biggest studies, that evaluated the auricular acupuncture, 620 cocaine dependent individuals were randomly selected in two groups, with a needle insertion control condition or a relaxation control condition, and it showed that there are no distinctions between the groups in cocaine use reduction or treatment retention [14].

Several studies have attempted to assess the effectiveness of acupuncture treatment used for opiate reduction, and some confirmed satisfactory results. In the study of heroin detoxification presented by Washburn *et al.*, randomly selected individuals were evaluated with auricular acupuncture or a placebo treatment. Increased attrition was presented in both groups, however, the auricular acupuncture treated individuals were more regularly appointed in the clinic in a longer time treatments [15].

In a different study it was reported that acupuncture was not successful to treat alcohol or opiate dependence. The

adjunctive acupuncture treatment was not efficient in alcohol consumption or alcohol craving outcomes [16]. It has been shown by Gossop *et al*. that the acupuncture treatment was less successful than standard methadone treatment during opiate detoxification [17].

EEG and acupuncture stimulation were evaluated with various effects, however, the particular assessment of acupuncture on heroin addict was not completely investigated. The modern EEG recording method, 2D high-resolution 19-ch EEG topographic mappings and Morlet wavelet, was used to estimate the acupuncture performance.

II. METHODOLOGY

A. Subjects

Three heroin dependent subjects from University Malaya Medical Center (UMMC) and one control subject under methadone treatment , aged 28.3 ± 6.5 years (mean ± SD), participated in the study. They were evaluated at the Psychiatry ward, UMMC. The inclusion criteria for this study were at least one year of documented regular heroin use or fulfilled Diagnostic Statistical Manual IV (DSM IV) for heroin dependence syndrome diagnosis. The criteria for exclusion were alcohol dependency or any other non-opiates substance dependence, presence of any acute psychiatric or neurological (major head trauma) or other physical (vascular pathology) diseases, history of allergy to methadone, or any other records of poly-substance dependence. Written consent was obtained from each subject according to the standards set by Declaration of Helsinki. The study was approved by the Ethics Committees at the University of Malaya Medical Center (Ethic Number: MEC 871.14).

B. Trial Design

This is an open-labeled randomized-control trial design comparing treatment group and controls who both received 30 minutes of acupuncture treatment per session for 6 months. The treatment group underwent electro-acupuncture stimulation of 1.1+ 80Hz at auricular point (Jerome point: ear lobe at the end of the helix), ST36 and SP6 whereas the controls received Sham electro-acupuncture (fixed to the device at the auricular points without increasing the intensity of the stimulation). During the first week, they received 5 sessions of acupuncture, in the second week, 2 sessions, and for the rest of the six months, only one session per week. Each subject underwent alcohol breath screening test, blood investigations for Human Immunodeficiency Virus (HIV), hepatitis B/C screening, and urine rapid drug test for illicit drug use (e.g. heroin, morphine, methadone, amphetamine type stimulant, cannabinoids, ketamine and benzodiazepine) to verify the absence of alcohol and other substance used prior to the baseline EEG measurement. Verbal statements collected from the subjects. Subjects underwent 6 minutes of EEG recording (three minutes with their eyes open and three minutes close) after each session of electro acupuncture in baseline, first, second, sixth, and twelfth week. For further analysis and comparison to controls, this study applied EEG signals recorded after the twelfth week of acupuncture. After the instruments were calibrated and the electrodes located on the scalp, subjects were comfortably positioned in a dimmed and electromagnetically shielded recording room while verbal instructions were explained to them. Subjects were instructed to look straight (even with their eyes closed) and have comfortable position without any movement.

C. EEG Recording

Nicolet EEG Diagnostics system (CareFusion Corporation, 3750 Torrey View Court, San Diego, CA 92130) was used to capture EEG activities. Cut-off frequency of 0.5Hz to 90Hz (with sampling rate of 256 Hz) was applied in the EEG amplifier. Prior to EEG recording impedance of all the electrodes was adjusted to the value less than 5 KΩ. Considering the technical limitations and to reduce the complexity of the analysis, EEG signals from 21electrodes (F7/8 .Fz . F3/4 . T7/8 . C5/6 . C3/4 .Cz . P7/8 . P3/4 .Pz .O1/2) were analyzed. 10/20 standard of the electrode placement was used with the Fpz as the Ground and Ear lobe as the reference. The 3D 19-ch montage with the nomenclature is illustrated in Fig.1. Bilateral EOG signals were recorded from the horizontal and vertical sites to monitor blinking and eye movements.

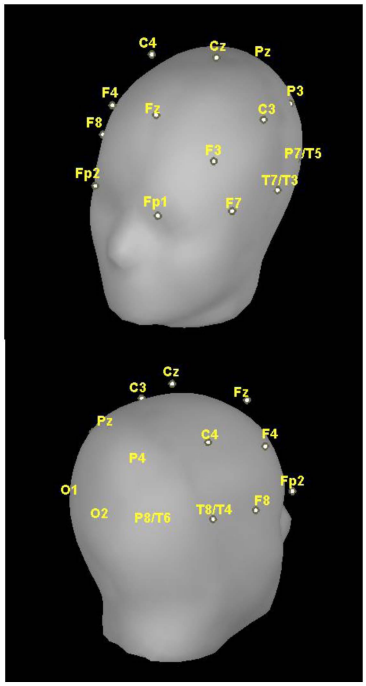

Figure 1. Superior-anterior view (Upper panel) and superior-posterior view (Lower panel) perspectives of the 19-ch EEG electrode nomenclature in 10/20 montage.

D. Data Processing

EEG data was filtered within 1-90 Hz using off-line band-pass filter while being subjected to 36 sec. epoching and artifact removal. Each 36 seconds of the EEG data was taken for further analysis. Epochs containing blinks, DC bias, and slow eye movement were eliminated as artifacts. The portion of EOG contamination of each scalp trace was also removed in the off-line analysis using AcqKnowledge 4.0 software (BIOPAC Systems Inc., Goleta, CA). Morlet Wavelet transform was applied to analyze time-frequency decomposition of each 36 seconds EEG data within Delta (1–4 Hz), Theta (5–7 Hz), Alpha (8–12 Hz), Beta (13–29 Hz), Gamma 1 (30–59 Hz), and Gamma 2 (60-90 Hz).

The six band powers of valid EEG epochs collected after the twelfth week of acupuncture were averaged in study subjects and compared to that of the control. Brainstorm 3.1 software [18] was applied to calculate the group averages and Power Spectral Density (PSD) maps of different conditions.

III. Results and Discussion

A. Time-Frequency Analysis

Initially absolute power values had been taken for normalization while spontaneous Morlet wavelet signals were measured per channel. As the next step, average of time-frequency results in three subjects were calculated and compared to that in control subject (Fig.2). Time-frequency analysis based on complex Morlet wavelets, centered between 1 and 4 Hz, was applied to detect maximal spectral power. It is worth to note the burst appearance of delta spontaneous oscillations under acupuncture condition as compared to methadone treatment (Fig.2).

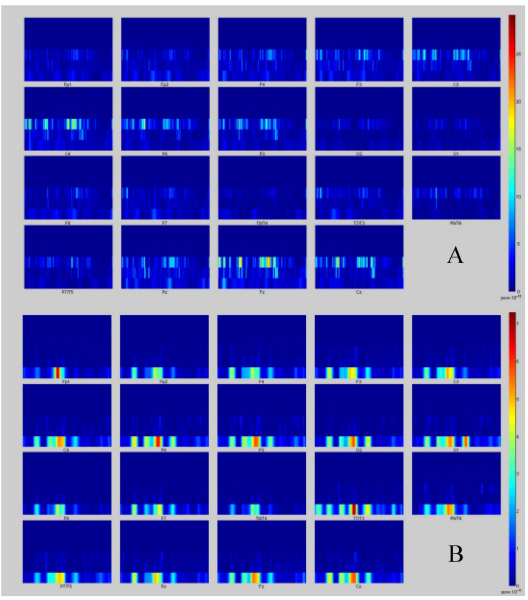

Figure 2. Power Spectrum of Acupunctured Subjects (A), and Controls (B)

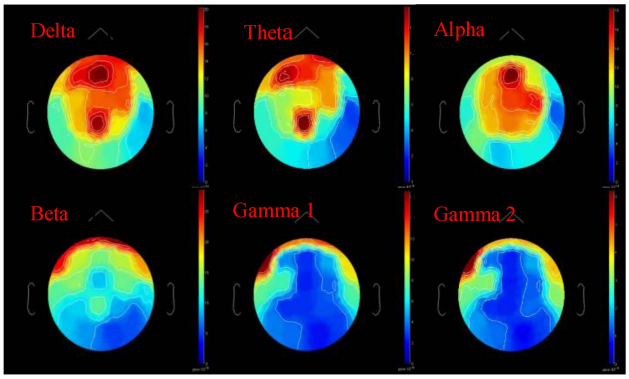

Figure 3. EEG power spectral topography of the three subjects after the twelfth week of acupuncture treatment.

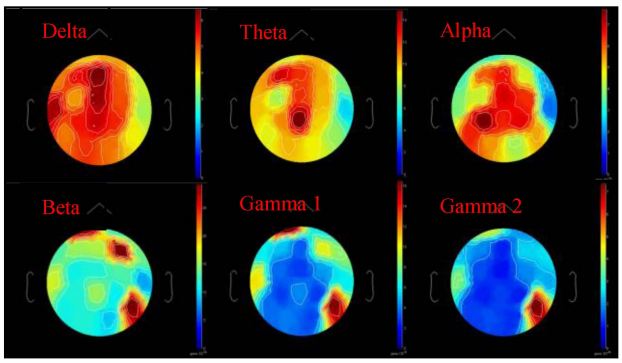

Figure 4. EEG power spectral topography of the control subject receiving MMT.

Time-frequency analysis following acupuncture at Jerome Point, ST36, and SP6 demonstrated (Fig.2): a) A decrease in delta spectral power observed in temporal areas (T4, T6, F8), b) An increase in alpha power values observed in central regions (Cz, C3, C4, Fz, F3, F4, P3, P4). These results revealed different patterns of oscillatory brain activities in subjects underwent acupuncture and in control subject. These changes in spectral power values were mainly confined to alpha and delta frequencies demonstrating conspicuously different brain dynamics in the subjects receiving acupuncture and the control.

B. 2D Power Spectral Topography

Power spectrum grand average of the three subjects after the twelfth week of acupuncture treatment (Fig.3) compared to control (Fig.4), along with their focal maximal scalp locations in each of the six frequency bands have been analyzed (Table1).

Table1. Comparison of the Maximal Average Activity between Three Acupunctured Subjects and the Control

Spectral Activity	Scalp Distribution of the Maximal AverageActivity in Three Subjects	Scalp Distribution of the Maximal Average Activity in the Control Subject
Delta	Frontal and parietal midline (Fz, Pz)	Frontal midline and bilateral temporal (Fz)
Theta	Left-frontal and parietal midline (F3, Pz)	Midline (Pz)
Alpha	Frontal–central midline(Fz)	Parietal- central (P3)
Beta	Prefrontal site on the top of both eyes (Fp2)	Frontal and the right posterior temporal (F4, P8/T6)
Gamma 1	Left lateral frontal lobe (F7)	Right posterior temporal (P8/T6)
Gamma 2	Left lateral frontal lobe (F7)	Right posterior temporal (P8/T6)

As compared to control, delta activity decreased in three acupunctured subjects (Fig.4) while alpha activity was observed to be highly diffused across central areas (Fig.3) [19, 20].

IV. CONCLUSION

To our knowledge, this is the first Morlet wavelet-based analysis which applies power spectral topography to investigate the efficiency of acupuncture as an adjunct treatment in MMT patients. Previous studies of Hui*et al*. and Wu *et al*. revealed the significant modulatory effects of acupuncture on the limbic system, paralimbic and subcortical gray structures [21-23] while studies in animals demonstrated the effects of amygdala high density opioid receptors on the pain threshold [24].

Decrease of delta band power in the temporal channels of ipsilateral hemisphere following acupuncture at Jerome Point, ST36 and SP6 may indicate the relation between homologous regions in opposite hemispheres[25, 26]. This may speculate the probability of existing delta band-limited power flow between these power-decreased and power-increased areas. On the other hand, the burst increase of alpha band power in central areas after acupuncture may derive from the increased amplitude in amygdala located deep within the middle gyrus of the cortex.

Altogether distinct band-limited power alterations observed in this study demonstrates the conspicuously differential brain activity following acupuncture suggesting the effectiveness of this therapy.

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REFERENCES

[1] J. A dworth, *Results from the 2007 National Survey on Drug Use and Health: National Findings*: DIANE Publishing, 2009.

[2] W. Van Den Brink and J. M. Van Ree, "Pharmacological treatments for heroin and cocaine addiction," *European Neuropsychopharmacology,* vol. 13, pp. 476-487, 2003.

[3] S. Birch, J. K. Hesselink, F. A. M. Jonkman, T. A. M. Hekker, and A. Bos, "Clinical research on acupuncture: part 1. What have reviews of the efficacy and safety of acupuncture told us so far?," *The Journal of Alternative and Complementary Medicine,* vol. 10, pp. 468-480, 2004.

[4] M. A. Hamza, P. F. White, H. E. Ahmed, and E. A. Ghoname, "Effect of the frequency of transcutaneous electrical nerve stimulation on the postoperative opioid analgesic requirement and recovery profile," *Anesthesiology,* vol. 91, p. 1232, 1999.

[5] L. Z. Wu, C. L. Cui, and J. S. Han, "Han's acupoint nerve stimulator (HANS) for the treatment of opiate withdrawal syndrome," *Chin J Pain Med,* vol. 1, pp. 30-38, 1995.

[6] W. U. L. Zhen, C. U. I. C. Lian, and H. Sheng, "Treatment on heroin addicts by four channel Han's acupoint nerve stimulator (HANS)," *Journal of Beijing Medical University,* 1999.

[7] L. WU, C. CUI, and J. HAN, "REDUCTION OF METHADONE DOSAGE AND RELIEF OF DEPRESSIONAND ANXIETY BY 2/100 Hz TENS FOR HEROIN DETOXIFICATION [J]," *Chinese Journal of Drug Dependence,* vol. 2, 2001.

[8] X. D. Shi, W. Ren, G. B. Wang, F. Luo, J. S. Han, and C. L. Cui, "Brain opioid-receptors are involved in mediating peripheral electric stimulation-induced inhibition of morphine conditioned place preference in rats," *Brain research,* vol. 981, pp. 23-29, 2003.

[9] C. L. Cui, L. Z. Wu, and F. Luo, "Acupuncture for the treatment of drug addiction," *Neurochemical research,* vol. 33, pp. 2013-2022, 2008.

[10] J. S. Han, "Acupuncture: neuropeptide release produced by electrical stimulation of different frequencies," *TRENDS in Neurosciences,* vol. 26, pp. 17-22, 2003.

[11] T. J. Kaptchuk, "Acupuncture: theory, efficacy, and practice," *Annals of internal medicine,* vol. 136, pp. 374-383, 2002.

[12] G. Biella, M. L. Sotgiu, G. Pellegata, E. Paulesu, I. Castiglioni, and F. Fazio, "Acupuncture produces central activations in pain regions," *Neuroimage,* vol. 14, pp. 60-66, 2001.

[13] Y. Uchida, A. Nishigori, D. Takeda, M. Ohshiro, Y. Ueda, M. Ohshima, and H. Kashiba, "Electroacupuncture induces the expression of Fos in rat dorsal horn via capsaicin-insensitive afferents," *Brain research,* vol. 978, pp. 136-140, 2003.

[14] A. Margolin, H. D. Kleber, S. K. Avants, J. Konefal, F. Gawin, E. Stark, J. Sorensen, E. Midkiff, E. Wells, and T. R. Jackson, "Acupuncture for the treatment of cocaine addiction," *JAMA: the journal of the American Medical Association,* vol. 287, pp. 55-63, 2002.

[15] A. M. Washburn, R. E. Fullilove, M. T. Fullilove, P. A. Keenan, B. McGee, K. A. Morris, J. L. Sorensen, and W. W. Clark, "Acupuncture heroin detoxification: a single-blind clinical trial," *Journal of Substance Abuse Treatment,* vol. 10, pp. 345-351, 1993.

[16] M. L. Bullock, T. J. Kiresuk, R. E. Sherman, S. K. Lenz, P. D. Culliton, T. A. Boucher, and C. J. Nolan, "A large randomized placebo controlled study of auricular acupuncture for alcohol dependence," *Journal of Substance Abuse Treatment,* vol. 22, pp. 71-77, 2002.

[17] M. Gossop, B. Bradley, J. Strang, and P. Connell, "The clinical effectiveness of electrostimulation vs oral methadone in managing opiate withdrawal," *The British Journal of Psychiatry,* vol. 144, pp. 203-208, 1984.

[18] F. Tadel, S. Baillet, J. C. Mosher, D. Pantazis, and R. M. Leahy, "Brainstorm: A user-friendly application for MEG/EEG analysis," *Computational intelligence and neuroscience,* vol. 2011, p. 879716, 2011.

[19] R. Hari and R. Salmelin, "Human cortical oscillations: a neuromagnetic view through the skull," *Trends in neurosciences,* vol. 20, pp. 44-49, 1997.

[20] J. Groß, J. Kujala, M. Hämäläinen, L. Timmermann, A. Schnitzler, and R. Salmelin, "Dynamic imaging of coherent sources: studying neural interactions in the human brain," *Proceedings of the National Academy of Sciences,* vol. 98, p. 694, 2001.

[21] K. K. S. Hui, J. Liu, N. Makris, R. L. Gollub, A. J. W. Chen, C. I Moore, D. N. Kennedy, B. R. Rosen, and K. K. Kwong, "Acupuncture modulates the limbic system and subcortical gray structures of the human brain: evidence from fMRI studies in normal subjects," *Human brain mapping,* vol. 9, pp. 13-25, 2000.

[22] K. K. S. Hui, J. Liu, O. Marina, V. Napadow, C. Haselgrove, K. K. Kwong, D. N. Kennedy, and N. Makris, "The integrated response of the human cerebro-cerebellar and limbic systems to acupuncture stimulation at ST 36 as evidenced by fMRI," *Neuroimage,* vol. 27, pp. 479-496, 2005.

[23] M. T. Wu, J. M. Sheen, K. H. Chuang, P. Yang, S. L. Chin, C. Y. Tsai, C. J. Chen, J. R. Liao, P. H. Lai, and K. A. Chu, "Neuronal specificity of acupuncture response: a fMRI study with electroacupuncture," *Neuroimage,* vol. 16, pp. 1028-1037, 2002.

[24] J. P. Aggleton, "The contribution of the amygdala to normal and abnormal emotional states," *Trends in neurosciences,* vol. 16, pp. 328-333, 1993.

[25] C. Stam, B. Jones, I. Manshanden, A. Van Cappellen van Walsum, T. Montez, J. Verbunt, J. De Munck, B. Van Dijk, H. Berendse, and P. Scheltens, "Magnetoencephalographic evaluation of resting-state functional connectivity in Alzheimer's disease," *Neuroimage,* vol. 32, pp. 1335-1344, 2006.

[26] Z. Liu, M. Fukunaga, J. A. De Zwart, and J. H. Duyn, "Large-scale spontaneous fluctuations and correlations in brain electrical activity observed with magnetoencephalography," *Neuroimage,* vol. 51, pp. 102-111, 2010.