Biomarker Development on Alcohol Addiction Using EEG

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Abstract. Alcohol addiction is harmful to society, economy and personal health. Alcohol addiction treatments intend to help addicted individuals reduce and stop compulsive alcohol use. Using biomarker, the clinicians could determine if drugs are having a desirable effect much earlier and given in correct dose for treatment. This paper will provide an up-to-date review of the state of the art in biomarker development for alcohol addiction treatment using electroencephalography (EEG) including EEG methodologies and their applications.

Keywords: Biomarker, alcohol addiction, EEG, predict.

1 Introduction

Alcohol addiction is characterized by an increased tolerance and physical dependence on alcohol that affect individual's ability to control alcohol consumption safely and cause withdraw symptoms once stop drinking. The harmful use of alcohol results in approximately 2.5 million deaths each year [1]. Alcohol damages almost every organ in the body, including the brain.

The harmful effects of alcohol addiction may be reduced through treatment policies. Biomarkers could help increase treatment efficiency by 1) combining with other screening tools (CAGE, MINI, …) to identify individuals with alcohol-related problems or who are at risk, 2) identifying the subset of abstainers at highest risk for relapse [2-3] and 3) evaluating new medications or behavioral interventions by giving outcome measures in earlier stage. Electroencephalography (EEG) is a non-invasive technique that detects electrical impulses in the brain due to neuronal activity using electrodes placed on the patient's scalp. EEG and related methodologies offer the promise of new biomarker for alcohol addiction treatment.

2 EEG Methodology and Alcoholism

Over the last decade, there has been a rapid development of EEG study on the harmful effect of alcohol addiction to brain. EEG may be recorded with the

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continuous electroencephalogram (EEG) or with the event-related brain potential (ERP) during cognitive and sensory tasks. The study of ERPs with new method of time frequency domain analysis, have revealed the phenomenon of event-related oscillation (ERO) which provide greater utility in understanding brain function than the traditional ERP.

2.1 Electroencephalogram (EEG)

Resting EEG is frequency-dependent, spontaneous and continuous neural activity during a restful or specific mental state. EEG signal can be decomposed into bands with different frequencies reflecting various types of brain activities, most commonly: delta (0-3.5 Hz), theta (4-7.5 Hz), alpha (8-12.5 Hz), beta (13-28.5 Hz) and gamma (> 29 Hz). In several studies, fast bands like alpha, beta, and gamma could be divided into sub-bands [2-4].

Many studies have shown higher tonic theta power in alcoholics than respective matched controls, and also in heavy drinkers compared to light drinkers and non-alcohol subjects. The elevated theta reflects a deficiency in the information-processing capacity of the central nervous system (CNS). By comparing 307 alcohol-dependent (AD) subjects with 307 alcohol control (AC) subjects in eyes closed state, Rangaswamy [5] found the result of an increase theta at all scalp loci, prominent at the central and parietal in male, and at the parietal in female. Moreover by using mental rehearsal tasks for testing frontal activities, Bruin et al [6] stated that heavy drinkers had more synchronization in the theta band than light drinkers during an eyes-closed condition. On the contrary, there are other studies reporting decreased slow bands activity (delta, theta) in their alcoholic patients [2], [4], [7]. Evaluating EEG relative power, Bauer [3] showed a slight increase in theta power in relapse-prone and no different found in abstinent-prone compared with non-alcohol control subjects after 6 months monitoring. Some other studies also showed a significant decrease in theta power over frontal regions associated with cortical atrophy when compared detoxified patients with controls [4], [7] . These results and conclusions were not consistent with each other's about the changes in theta power. However, the methodology and participant recruited criteria (alcoholics vs. detoxified patients) used by these studies are different. So it may be an indicator of the recovery of alcoholics. The relationship between theta power and the developing of alcoholism and, state-related condition need more investigation. Anyway, changing in resting theta did not seem to be present in the offspring of alcoholics, which may indicate a state-dependent condition.

Alpha rhythm was also found different between abstainers (the ones who keep stopping alcohol consumption after receiving treatment) and relapsers (abstainers who fall into addicted in alcohol again). The alpha rhythm is the predominant EEG rhythm in the relaxed alert state. Decrease in alpha activity in alcoholics is indicative of a deficiency in retrieving information from memory, and in attention. It is obtained both with eyes-open and eyes-closed, especially in the eyes-closed condition over the occipital regions. Ehlers and Phillips [8-9] suggested that alcohol dependence was associated with lower spectral power in the alpha frequency range. However, in their

studies, low voltage alpha was recorded to be exited in both alcoholics and controls, and there was no significant different between controls and alcoholics. Winterer [2] and Bauer [3] also showed especially less frontocentral alpha activity in relapsers compared with abstainers.

One of the robust and consistent resting EEG findings in alcoholism is the increased beta band activity in alcoholics and their high-risk offspring. Increased beta power in the EEG of alcoholics, particularly the increased fast beta (>20Hz) in the relapsers, has been well documented [2-4], [7], [10]. The increased beta power in the resting EEG may be an electrophysiological index of the imbalance in the excitation–inhibition homeostasis in the cortex. The quantitative EEG (QEEG) and relapse classification studies of detoxified alcohol-dependent patients as compared with normal controls [2] showed good predict ability of beta band power with correct classification rates of 83-85% using multilayer perception neuronal network (NN) with one layer 2-20 neurons [2] and 74,3% using logistic regression [3]. However, Winterer's study showed poor specificity with just 60-73% correct abstainers' classification. In contrast, Bauer's study showed improved specificity (85%) but poor sensitivity and (61%). Beta band predictive needs more studies and replications with different methods to improve its predictive rate, especially in medication treatment. The resting EEG beta power [11] also proved that it was more heritable and closer to gene action than clinical diagnosis (e.g. alcohol dependence).

These findings indicate that resting EEG is very promising state biomarker for future studies that can help in alcohol addiction treatment by predicting relapse patients.

2.2 Event-Related Potential (ERP)

ERPs are time-locked voltage fluctuations in the brain in response to a sensory, motor, or cognitive event. They are extracted from a set of EEG trial epochs by means of filtering and signal averaging. Early components with latency less than 100ms reflect sensory processes and contain small amplitude, while later components with larger amplitude reflect higher cognitive computations.

Most ERP studies in investigating the electrophysiological deficits in alcoholics and individuals at risk focused on the large positive P300 or P3 component that occurs between 300ms and 700ms after a 'significant' stimulus and is not related to its physical features. The lower amplitude of P3 components are related with the inefficient allocation of resources during neural processing and underlying CNS hyper excitability in alcoholics and individuals at risk. Many studies [12-16] showed that waveform of P3 to task-relevant target stimuli (P3b) are of significantly lower voltage and more delayed latency in abstinent alcoholics than in non-alcoholics, particularly over parietal regions. P3 deficit occurs in both visual and auditory tasks, but more consistent for visual tasks. Suresh [16] indicated that lower P3 amplitude presented under effect of alcohol in both genders for auditory oddball task, but more significant in male patients. Kamarajan [15] showed that alcoholics manifested low amplitude P3b components to not only target (Go) stimuli, but also to rare non-target (NoGo) stimuli, and there is less different between these two conditions in alcoholics.

Porjesz's studies suggested that low P3 voltages might not be reversible, but precede alcoholism, or recover more slowly after long abstinent periods [17]. Porjesz and colleagues also noted that alcoholics who were members of Alcoholics Anonymous still manifest low P3 amplitudes after extremely prolonged abstinent (3-10 years). However, 63.9% of the participants were correctly classified by Li Wan et al. [18] using P3 as the first predictor in the discrimination function. The result indicated that there was different in P3b between relapsers and abstainers. Thus, the P3 amplitude can be taken as a marker of risk and provides excellent endophenotype for genetic studies.

The P300 response can be divided into two subcomponents based on differing in task and subject-state correlates, latency, topography on the scalp and generating structure: P3a and P3b. P3a is recorded in response to novel non-target stimuli and has more frontal-central distribution with latency from 220-280ms. It is thought to reflect the initial signal evaluation. Posteriorly distributed P3b has a longer latency 300-700ms and is evoked by the rare target stimuli. Marinkovic et al. [13] reported about the decrease of P3a following a low dose of alcohol. The study also indicated that alcohol had a greater reducing effect on P3a amplitude to unattended rare stimuli than to P3b with attended rare stimuli. The result suggested P3a as a potential screening tool for alcohol dependent. Anderson [19] examined P3a amplitude as a direct predictor of treatment success for substance dependence. By using discriminant function analysis, he confirmed that P3a amplitude was a robust predictor of treatment completion, and more sensitive than other measures including substance abuse severity.

Stimulus processing is not a simple cognitive process of P300 but is composed of different stages with electrophysiological correlates; for example, perception level with P100 and N170, attention level with N200, and decision level with P300. The P300 is functionally linked to decisional processes and cognitive processing before activating the motor response, which is deficient in alcoholics. There are other ERP measures that can differentiate alcohol addictions from controls such as Mismatch negativity (MMN) and Brain-stem auditory-evoked potential (BAEP). Marco [20] reported about the deficit in P50 auditory sensory gating in abstinent chronic alcoholics. Curtin [21] indicated the relationship between alcohol and cognitive function from the reduced N450 and a more tonic, negative slow wave (NSW) associate with behavioral impairment resulted from failure in cognitive control function in alcohol consumption. More investigating about the early impairments in ERP signal may help to reveal the reason of deficit observed in cognitive processing of alcoholic patients.

2.3 Event-Related Oscillation (ERO)

For the classical approach to the study of ERP, ongoing EEG is treated as 'noise', in which the ERP signal is embedded. The ongoing oscillation is canceled out when extracting ERP by performing average, which results in the loss of critical information about variability upon single trials in neural activity.

New studies in time-frequency domain suggested that ERP represent the composition of electrical neural activities that evoked from multiple sources in the brain, and consist of superimposed event-related oscillation (ERO) of different spectral EEG bands that are related to sensory and cognitive processing. ERO can be divided into the same bands as spontaneous resting EEG, but with different reflection of brain function. Fast frequencies correspond to synchronization of groups of neurons in local areas, whereas slow frequencies are involved in larger distances synchronization.

Several studies have demonstrated that P3 responses are primarily the outcome of theta and delta oscillations elicited during cognitive processing of stimuli [22-27]. Jones et al. [27] indicated that frontally focused theta band activity (4–5 Hz) and a posterior distributed delta band activity constitute the P300 ERP waveform. The theta component formed the N200 and the early part of the P300 wave, and the delta component formed the main part of the P300 wave. These delta and theta EROs were derived from several cognitive paradigms, including the oddball task, Go/NoGo task, and a gambling task, to study alcoholism and related clinical conditions. Evoked delta and theta power were found to be significantly decreased among alcoholics compared with control subjects when processing the target stimuli in a visual oddball [26], [28] and Go/NoGo paradigm [23-24]. Fein et al. [25] found that the long-term abstinent alcoholics (LTAAs) showed a significantly larger theta ERS to the target stimulus compared with the non-alcoholic controls (NACs). Fein et al. [28] continued showing that theta ERS was larger in both short-term abstinent alcoholics (STAA) and LTAA compared to controls. The magnitude of the enhancement in STAA was greater than in LTAA. The significant different between long term and short term abstinence may be the indicator of brain function recovery from alcohol consumption. Significantly lower evoked delta ERO power, total delta and theta ERO power in LTAA provide an alternative and comparable representation of the reduced P3b amplitude for assessing recovery progress or relapse prediction. About the inherited risk of abusing alcohol, Rangaswamy [29] founded the decrease of total theta power and total evoked delta power for visual targets in high risk alcoholism's offspring.

Rangaswamy [29] and Ajayan [30] highlighted the evoked gamma. The responding suppression of gamma band activity to target stimuli observed in the frontal region of alcoholics may be associated with cognitive processes [30]. Based on the early phase-locked gamma oscillation during visual perception and the difference in gamma band energies, Ramaswamy [31-32] proposed evoked gamma as a screening tool and confirmed with accuracy of 91.12% using multilayer perceptron NN.

3 Discussion

In clinical practice using EEG, there are few reports about early relapse detecting method for alcoholic addiction treatment. Resting EEGs and ERPs components have been studied for predicting patients with high risk of relapse but the accuracy is still not accurate enough for clinical practice. The new EEG phenomenon (evoked theta, evoked delta, induced theta ERS, gamma oscillation) of EROs may be candidate for assessing treatment progress.

Following the review, there is still no study about the association between a deficit in gamma band and the duration of abstinent and its ability for discriminating between relapsers and abstainers.

Regarding the induce theta ERS, its differences between alcoholic and control groups have not been well defined [28]. Induced theta activity tends to increase with increased memory load and/or allocation of attention to task demands [33][30].

From these problems we can hypothesize:

1. The new sensitive and specific EEG biomarker will help increase treatment efficiency and to determine if drugs have a desirable effect much earlier.
2. Induce theta promises a "state marker" by showing different between abstain-prone and relapse-prone.
3. Delineating induced theta ERS effects in alcoholics appears to be the nature and modality of the discrimination task.

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References

1. World Health Organization, Global status report on alcohol and health. World Health Organization, Geneva, Switzerland (2011)
2. Winterer, G., Klöppel, B., Heinz, A., Ziller, M., Dufeu, P., Schmidt, L.G., Herrmann, W.M.: Quantitative EEG (QEEG) predicts relapse in patients with chronic alcoholism and points to a frontally pronounced cerebral disturbance. Psychiatry Research 78(1-2), 101–113 (1998)
3. Bauer, L.O.: Predicting relapse to alcohol and drug abuse via quantitative electro encephalography. Neuropsychopharmacology 25(3), 332–340 (2001)
4. Saletu-Zyhlarz, G.M., Arnold, O., Anderer, P., Oberndorfer, S., Walter, H., Lesch, O.M., Böning, J., Saletu, B.: Differences in Brain Function Between Relapsing and Abstaining Alcohol-Dependent Patients, Evaluated by Eeg Mapping. Alcohol and Alcoholism 39(3), 233–240 (2004)
5. Rangaswamy, M., Porjesz, B., Chorlian, D.B., Choi, K., Jones, K.A., Wang, K., Rohrbaugh, J., O'Connor, S., Kuperman, S., Reich, T., Begleiter, H.: Theta Power in the EEG of Alcoholics. Alcoholism: Clinical and Experimental Research 27(4), 607–615 (2003)
6. de Bruin, E.A., Bijl, S., Stam, C.J., Böcker, K.B., Leon Kenemans, J., Verbaten, M.N.: Abnormal EEG synchronisation in heavily drinking students. Clinical Neurophysiology 115(9), 2048–2055 (2004)
7. Coutin-Churchman, P., Moreno, R., Añez, Y., Vergara, F.: Clinical correlates of quantitative EEG alterations in alcoholic patients. Clinical Neurophysiology 117(4), 740–751 (2006)
8. Ehlers, C.L., Phillips, E., Schuckit, M.A.: EEG alpha variants and alpha power in Hispanic American and white non-Hispanic American young adults with a family history of alcohol dependence. Alcohol 33(2), 99–106 (2004)
9. Ehlers, C.L., Phillips, E.: Association of EEG alpha variants and alpha power with alcohol dependence in Mexican American young adults. Alcohol 41(1), 13–20 (2007)

10. Rangaswamy, M., Porjesz, B., Chorlian, D.B., Wang, K., Jones, K.A., Bauer, L.O., Rohrbaugh, J., O'Connor, S.J., Kuperman, S., Reich, T., Begleiter, H.: Beta power in the EEG of alcoholics. Biological Psychiatry 52(8), 831–842 (2002)
11. Rangaswamy, M., Porjesz, B., Chorlian, D.B., Wang, K., Jones, K.A., Kuperman, S., Rohrbaugh, J., O'Connor, S.J., Bauer, L.O., Reich, T., Begleiter, H.: Resting EEG in offspring of male alcoholics: beta frequencies. International Journal of Psychophysiology 51(3), 239–251 (2004)
12. Costa, L., Bauer, L., Kuperman, S., Porjesz, B., O'Connor, S., Hesselbrock, V., Rohrbaugh, J., Begleiter, H.: Frontal P300 decrements, alcohol dependence, and antisocial personality disorder. Biological Psychiatry 47(12), 1064–1071 (2000)
13. Marinkovic, K., Halgren, E., Maltzman, I.: Arousal-related P3a to novel auditory stimuli is abolished by a moderately low alcohol dose. Alcohol and Alcoholism 36(6), 529–539 (2001)
14. Maurage, P., Campanella, S., Philippot, P., de Timary, P., Constant, E., Gauthier, S., Miccichè, M.-L., Kornreich, C., Hanak, C., Noel, X., Verbanck, P.: Alcoholism leads to early perceptive alterations, independently of comorbid depressed state: An ERP study. Neurophysiologie Clinique/Clinical Neurophysiology 38(2), 83–97 (2008)
15. Kamarajan, C., Porjesz, B., Jones, K.A., Choi, K., Chorlian, D.B., Padmanabhapillai, A., Rangaswamy, M., Stimus, A.T., Begleiter, H.: Alcoholism is a disinhibitory disorder: neurophysiological evidence from a Go/No-Go task. Biological Psychology 69(3), 353–373 (2005)
16. Suresh, S., Porjesz, B., Chorlian, D.B., Choi, K., Jones, K.A., Wang, K., Stimus, A., Begleiter, H.: Auditory P3 in Female Alcoholics. Alcoholism: Clinical and Experimental Research 27(7), 1064–1074 (2003)
17. Porjesz, B., Begleiter, H.: Human brain electrophysiology and alcoholism, pp. 139–182. Plenum Press (1985)
18. Wan, L., Baldridge, R.M., Colby, A.M., Stanford, M.S.: Association of P3 amplitude to treatment completion in substance dependent individuals. Psychiatry Research 177(1-2), 223–227 (2010)
19. Anderson, N.E., Baldridge, R.M., Stanford, M.S.: P3a amplitude predicts successful treatment program completion in substance-dependent individuals. Subst Use Misuse 46(5), 669–677 (2011)
20. Marco, J., Fuentemilla, L., Grau, C.: Auditory sensory gating deficit in abstinent chronic alcoholics. Neuroscience Letters 375(3), 174–177 (2005)
21. Curtin, J.J., Fairchild, B.A.: Alcohol and cognitive control: Implications for regulation of behavior during response conflict. Journal of Abnormal Psychology 112(3), 424–436 (2003)
22. Krause, C.M., Aromäki, A., Sillanmäki, L., Åström, T., Alanko, K., Salonen, E., Peltola, O.: Alcohol-induced alterations in ERD/ERS during an auditory memory task. Alcohol 26(3), 145–153 (2002)
23. Kamarajan, C., Porjesz, B., Jones, K.A., Choi, K., Chorlian, D.B., Padmanabhapillai, A., Rangaswamy, M., Stimus, A.T., Begleiter, H.: The role of brain oscillations as functional correlates of cognitive systems: a study of frontal inhibitory control in alcoholism. International Journal of Psychophysiology 51(2), 155–180 (2004)
24. Kamarajan, C., Porjesz, B., Jones, K., Chorlian, D., Padmanabhapillai, A., Rangaswamy, M., Stimus, A., Begleiter, H.: Event-Related Oscillations in Offspring of Alcoholics: Neurocognitive Disinhibition as a Risk for Alcoholism. Biological Psychiatry 59(7), 625–634 (2006)

25. Andrew, C., Fein, G.: Induced theta oscillations as biomarkers for alcoholism. Clinical Neurophysiology 121(3), 350–358 (2010)
26. Rangaswamy, M., Porjesz, B.: From event-related potential to oscillations: genetic diathesis in brain (dys) function and alcohol dependence. Alcohol Research & Health (September 2008)
27. Jones, K.A., Porjesz, B., Chorlian, D., Rangaswamy, M., Kamarajan, C., Padmanabhapillai, A., Stimus, A., Begleiter, H.: S-transform time-frequency analysis of P300 reveals deficits in individuals diagnosed with alcoholism. Clinical Neurophysiology 117(10), 2128–2143 (2006)
28. Gilmore, C.S., Fein, G.: Theta event-related synchronization is a biomarker for a morbid effect of alcoholism on the brain that partially resolve with extended abstinence. Brain and Behavior 2(6), 796–805 (2012)
29. Rangaswamy, M., Jones, K.A., Porjesz, B., Chorlian, D.B., Padmanabhapillai, A., Kamarajan, C., Kuperman, S., Rohrbaugh, J., O'Connor, S.J., Bauer, L.O., Schuckit, M.A., Begleiter, H.: Delta and theta oscillations as risk markers in adolescent offspring of alcoholics. International Journal of Psychophysiology 63(1), 3–15 (2007)
30. Padmanabhapillai, A., Porjesz, B., Ranganathan, M., Jones, K.A., Chorlian, D.B., Tang, Y., Kamarajan, C., Rangaswamy, M., Stimus, A., Begleiter, H.: Suppression of early evoked gamma band response in male alcoholics during a visual oddball task. International Journal of Psychophysiology 60(1), 15–26 (2006)
31. Sharmilakanna, Ramaswamy, P.: Neural Network Classification of Alcohol Abusers Using Power in Gamma Band Frequency of VEP Signals. Multimedia Cyberscape Journal 1 (2003)
32. Ramaswamy, P.: Screening for Chronic Alcoholic Subjects Using Multiple Gamma Band EEG: A Pilot Study. JCS&T 7(2), 182–185 (2007)
33. Krause, C.M., Sillanmäki, L., Koivisto, M., Saarela, C., Häggqvist, A., Laine, M., Hämäläinen, H.: The effects of memory load on event-related EEG desynchronization and synchronization. Clinical Neurophysiology 111(11), 2071–2078 (2000)