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Event-Related Oscillations in Alcoholism Research: A Review

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Abstract

Alcohol dependence is characterized as a multi-factorial disorder caused by a complex interaction between genetic and environmental liabilities across development. A variety of neurocognitive deficits/dysfunctions involving impairments in different brain regions and/or neural circuitries have been associated with chronic alcoholism, as well as with a predisposition to develop alcoholism. Several neurobiological and neurobehavioral approaches and methods of analyses have been used to understand the nature of these neurocognitive impairments/deficits in alcoholism. In the present review, we have examined relatively novel methods of analyses of the brain signals that are collectively referred to as event-related oscillations (EROs) and show promise to further our understanding of human brain dynamics while performing various tasks. These new measures of dynamic brain processes have exquisite temporal resolution and allow the study of neural networks underlying responses to sensory and cognitive events, thus providing a closer link to the physiology underlying them. Here, we have reviewed EROs in the study of alcoholism, their usefulness in understanding dynamical brain functions/dysfunctions associated with alcoholism as well as their utility as effective endophenotypes to identify and understand genes associated with both brain oscillations and alcoholism.

Keywords

Event-related oscillations (EROs); Event-related potentials (ERPs); Electroencephalogram (EEG); Alcoholism; Endophenotype; Genes; Cognitive function; Frontal lobes

Introduction

Brain dysfunction, especially the frontal lobe changes, associated with chronic alcoholism and a predisposition to develop alcoholism has been well documented by neurophysiological, neuroimaging, and neuropsychological studies (see Moselhy et al. [1] for a review). Over the decades, there has been compelling evidence for brain abnormalities in ‘nonamnesic’ chronic alcoholic patients as well as in their high-risk offspring from electrophysiological [2-12], neuroimaging [13-20], and a wide range of neuropsychological investigations [21-28].

Although neuroimaging methods, such as structural/functional MRI and PET have many advantages, including a higher level of spatial resolution, they offer relatively poor temporal resolution compared to electrophysiological methods, which offer excellent temporal resolution in the millisecond range [29,30]. This ability to record millisecond-by-millisecond brain signals with electrophysiological techniques is crucial for the

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understanding of subtle sensory/cognitive processing as they are occurring in the brain. Electrophysiological techniques have further advantages of being non-invasive, relatively inexpensive to implement, and can be used to study a large variety of cognitive processes/ brain functions; recently developed electrophysiological analytical techniques and methods allow for a better study of neural communication across different brain regions in normal [31-33] as well as pathological conditions [34-38], and provide subtle measures of neurocognitive (dys) function. More recent studies increasingly use localization techniques such as standardized low resolution brain electromagnetic tomography (sLORETA) to characterize specific activity patterns and communication across brain regions three-dimensionally and these methods have been implemented in many psychiatric disorders including alcoholism [9-11,39,40].

Alcoholism is a common, complex disorder with contributions from both genetic and environmental influences and their interactions [41]. The identification of suitable quantitative biological markers that are genetically transmitted could explicate the genetic factors involved in the etiology of alcoholism [42]. One successful approach has been the use of biological markers as “endophenotypes”, or intermediate phenotypes (measurable components, traits or variables along the pathway between disease and distal genotype, that are heritable, correlated with the illness, and are already present in those at risk prior to the onset of the illness [43]). In this regard, (electrophysiological measures such as electroencephalogram (EEG), event-related potentials (ERPs) and event-related oscillations (EROs) provide a rich source of potentially useful and powerful endophenotypes for alcoholism, as they meet these criteria, are quantitative, less complex and more proximal to gene function than traditional diagnoses, and represent important correlates of human information processing and cognition; hence they provide more power to localize and characterize disease susceptibility genes (cf. [42]).

Ongoing brain functioning in the form of electrophysiological activity can be recorded non-invasively using scalp electrodes. The German physiologist and psychiatrist Hans Berger (1873-1941) first recorded the human EEG in 1924 [44]. Scalp-recorded electrophysiological activity consists of three distinct methods: 1) EEG: frequency-dependent, spontaneous and continuous neural activity during a restful or specific mental state, 2) ERPs: time-locked, trial-averaged, and task-specific electrophysiological activity during a specific sensory/motor/cognitive event, and 3) EROs: time-frequency (TF) measures of brain electrical activity during a specific sensory/motor/cognitive event.

The human scalp EEG represents the ongoing electrophysiological signals in a continuous fashion, and can be recorded during several mental states: eyes-closed relaxed state, eyes-open steady state, meditation, hypnosis, sleep, coma, and other normal/altered states of consciousness [45]. Traditionally, EEG can be decomposed into different frequency bands, 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), and each of these bands are assumed to reflect different types of brain activity. One of the robust and consistent resting EEG findings in alcoholism is that alcoholics and their high-risk offspring show increased beta band activity [46-50].

While EEG records the ongoing electrical activity of the brain, ERPs are time-locked voltage fluctuations in the brain in response to a sensory, motor, or cognitive event, and are extracted from a set of EEG trial epochs by means of filtering and signal averaging [51]. The amplitude (or the voltage measure) of an ERP component has been related to the neural resources available to process a stimulus or event [52], while the latency (or the time measure with respect to the stimulus) reflects stimulus/event processing time. Further, each ERP component has been attributed to specific functions based on the type, modality, and cognitive specificity of the task employed. The most studied and popular ERP component is

the so-called P3 or P300, a large positive deflection that occurs between 300–700 ms after the stimulus onset and is related to its significance and not its physical features [53]. Across numerous ERP studies in alcoholism, the robust and consistent finding is that alcoholics and their high-risk offspring show reduced P3 amplitude across a variety of tasks and modalities (see [42,54] for reviews). Furthermore, the P3 component is highly heritable [55-59] and has proven to be useful as an endophenotypic marker of alcoholism. However, a reduction of P3 amplitude has not been found to be specific to alcoholism, but is also found in other related externalizing or disinhibitory disorders, such as substance use disorders (SUDs), conduct disorder (CD), antisocial personality disorder (ASPD), oppositional defiance disorder, (ODD), and attention deficit hyperactivity disorder (ADHD) [60,61]. In SUDs, reduced P3 amplitudes have been observed in individuals with dependence/abuse for tobacco [62], cocaine [63], cannabis [64,65], and 'ecstacy' or methylene-dioxy-methamphetamine (MDMA) [66]. Thus, reduced P3, while not specific to alcoholism, is a marker of alcoholism and related externalizing or disinhibitory disorders. However, the P3 component is not a unitary electrophysiological phenomenon elicited during cognitive processing; but emanates from multiple sources in the brain with contributions from frontal cortex (including anterior cingulate), parietal cortex, and hippocampus [7,67-71]; furthermore, it is primarily the outcome of event-related delta (concentrated more posteriorly) and theta (concentrated more anteriorly) oscillations [72-78]. Thus, because the EROs can analyze brain signals in terms of their constituent time-frequency components arising from various brain regions during sensory and cognitive events based on task conditions, they provide greater utility in understanding brain function than the traditional ERPs.

EROs as Measures of Cognitive Function

According to Basar et al. [79], selectively distributed delta, theta, alpha and gamma oscillatory systems act as resonant communication networks through large populations of neurons, with functional relations to cognitive and integrative functions. Relating to this view, ERP components are shown to be partially determined by the superposition of oscillatory responses of various frequencies [80-84] through phase synchronization or 'partial phase resetting' in response to specific stimulus event(s) [85-88]. According to the phase-resetting model, ERP components do not simply emerge from evoked, fixed latency-fixed polarity responses that are additive to and independent of ongoing EEG (i.e., 'additive model of ERP generation'), but instead, ERPs are generated by a superposition of ongoing EEG oscillations that reset their phases in response to sensory input (see Sauseng et al. [89] for a critical discussion of this debate). Generally, EROs are broadly categorized into either 'evoked' or 'induced'. Phase-aligned ERO signals (during the trials of cognitive events) are called 'evoked' or 'phase-locked' oscillations, while the (remaining) signals that become 'out-of-phase' across trials are termed 'induced' or 'non-phase-locked' oscillations [90]. The combination of both evoked and induced oscillatory power has been referred to as 'total' power [78]. Further, specific frequency bands within oscillatory responses have been attributed to underlie various cognitive processes [91-95], although the interpretation is often task-specific. For example, delta oscillations are thought to mediate signal detection and decision making (e.g., [91,96,97], while theta frequencies are linked with different cognitive processes, such as conscious awareness, recognition memory, episodic retrieval, and frontal inhibitory control [83,92,94,96,98,99]. The slow alpha rhythm (8-10 Hz) has been reported to modulate as a function of attentional demands [100-102], and fast alpha activity (10-12 Hz) has been shown to mediate semantic memory processes as well as stimulus-related aspects [92,101,103,104]. Further, it has been shown that oscillatory gamma responses are involved in visual perception, cognitive integrative function such as "binding," and frontal input during sensory processing (top-down processing) [93,96,105-107]. Furthermore, these event-related oscillatory rhythms have been shown to mediate neural communication; higher frequency oscillations are involved in more localized

neural networks, whereas the slower oscillations govern the long-range communication networks (e.g., posterior to anterior sites) [108-112].

EROs offer a few advantages over ERPs: (1) examining the oscillatory dynamics of EROs helps to dissect and subgroup the cognitive processes (e.g., [86,113]), especially for complex ERP components with multiple sources like P300, N400 etc. (2) correlated maps of brain regions for different cognitive processes can emerge from studying the cross frequency synchrony in EROs (e.g., [108,114,115]), (3) EROs can facilitate the understanding of how different cortical networks are integrated in response to an external stimulus and how information can be transferred between such circuits (e.g.,[87]), and (4) EROs allow for analysis of single trial epochs, which provide information about trial-by-trial variation in event-related brain dynamics, which is far superior to simple response averaging [116-119]. In a study from our lab, Chorlian et al. [120] demonstrated that single trial data enables both phase and amplitude information to be extracted and then compared across trials to determine whether amplitude or frequency modulation has occurred in bands of interest. The objective of the experiment was to produce the entrainment of alpha EEG activity by photic driving (through the use of a flashing background stimulus on which a non-flashing foreground stimulus appears), and to affect the entrainment by imposing an oddball task. Higher peak gamma amplitude was consistently observed during post-target-stimulus (300-750 ms) alpha suppression than at the time of maximum alpha activity during the immediate post-stimulus period. Further, the amplitude modulation of gamma (i.e., the amplitude envelope of the gamma activity) was at alpha frequency which was the frequency of entrainment). The authors suggested that there was an interaction between the alpha and gamma generating systems, in which gamma triggered alpha activity and was subsequently inhibited by it, thus producing the observed amplitude modulation. EROs have been used to understand not only normal cognitive processes but also neuro cognitive dysfunctions underlying psychopathological conditions and disorders that include alcoholism.

EROs and Alcoholism

As EROs represent the basic mechanisms of neural communication during cognitive tasks, they provide links to associative and integrative brain functions [121] that can be used to investigate normal brain function, as well as dysfunction in clinical and subclinical conditions. While relatively few studies have implemented EROs to study alcoholism, they have been used to examine several groups: 1) individuals affected with alcohol dependence, 2) unaffected offspring and relatives of alcoholics who are at high risk to develop alcoholism, 3) subjects under the direct effect of alcohol on the brain. Studies have examined several ERO measures including evoked, induced, and total power [122,123] in alcoholism [99,122,124-127]. Thus, EROs provide useful tool to investigate brain dysfunction in alcoholism, and to tease apart those that are a consequence of alcoholism, and those involved in a predisposition to develop alcoholism. Furthermore, they provide powerful quantitative endophenotypes that have successfully been used to identify genes.

Theta and delta EROs in alcoholics and high-risk individuals

Event-related delta activity is generated by cortico-cortical interactions [74], and is a product of the distributed network system of the brain [73,91] and involved in signal detection and decision making [73,91,96]. On the other hand, event-related theta oscillations are related to cortico-hippocampal [91,128] or frontolimbic interactions [83], and are associated with a complex set of cognitive processes including alertness, arousal or readiness [91], episodic encoding and retrieval processes [92,129], selective attention and short-term memory [73,130-132], error processing [133-135] and reward processing [136-139]. These delta and theta EROs have been derived from several cognitive paradigms, including the oddball task,

Go/NoGo task, and a gambling task, to study alcoholism and related clinical conditions, as discussed below.

Visual oddball task—The most commonly used paradigm to elicit the P3 component of the ERP is the oddball paradigm [140], in which a random sequence of stimuli is presented. The stimuli can be classified into one of two (or more) categories, and the task is to classify the stimuli, either by counting or by pressing a button to members of one category (usually called the 'target' stimuli) while ignoring the other category (referred as 'non-target' stimuli). The first study to investigate EROs in alcoholism using a visual oddball paradigm was reported by Jones et al. [78] from our laboratory. The authors used a time-frequency signal analysis method called the "S-transform" to decompose the event-related signals in an age-matched sample of control (N=100) and alcoholic male subjects (N=100). The results indicated that the P3 waveform, commonly elicited using infrequent salient stimuli, was primarily composed of frontal theta and posterior delta band powers. Additionally, each ERO band activity contributed unique information to discriminate between the groups. In order to investigate whether these deficits in theta and delta oscillations antecede the development of alcoholism, Rangaswamy et al. [141] investigated adolescent offspring of alcoholics (14-17 years) with age-matched normal controls in the large Collaborative Study on the Genetics of Alcoholism (COGA), using the same paradigm. They found that similar to the alcoholics, the adolescent offspring of alcoholics had reduced delta and theta band ERO amplitude while processing the target stimuli compared to controls. The differences were most prominent centroparietally for theta, and parietally for delta. On the basis of the finding that stronger differences between groups were observed for the ERO oscillations than for the P3 amplitude, the authors suggested that the ERO measures appeared to be superior to P3 amplitude in differentiating between high-risk and low-risk offspring, and may serve as more stable and useful endophenotypes in the study of alcoholism and related disorders. Hence, the results of these two studies [78,141] indicate that decreased theta and delta EROs to target stimuli may prove to be a strong phenotypic marker in the development of alcoholism, which may be useful for genetic studies.

In a later study, Andrew and Fein [142] reported significantly lower evoked delta ERO power as well as total delta and theta ERO power in long-term abstinent alcoholics (LTAAs) compared to the nonalcoholic controls (NACs), replicating Jones et al. [78] results. However, on the basis of the similar magnitude of effect sizes for the ERO power and P3 amplitude in their study, in contrast to Jones et al. [78] and Rangaswamy et al. [141], these authors concluded that ERO power does not provide a more powerful group discriminator than P3 amplitude. In another study using the same sample, Andrew and Fein [143] reported significantly higher induced theta power in LTAAs as compared to NACs. Based on this finding, the authors concluded that induced (non-phase locked) theta oscillations are more powerful and independent group discriminators than the P3 amplitude.

Recently, using a principal component analysis (PCA) based time-frequency (TF) analysis, Gilmore et al. [144] examined the relationship between the P3, its associated ERO components in a spectrum of externalizing disorders, such as substance use disorders (including alcoholism), ADHD, and conduct disorder in a community-based sample of adolescent males. It was found that 1) P3 and each TF-PCA derived component could successfully discriminate diagnostic groups from controls, and 2) delta components in specific time ranges accounted for variance beyond that accounted for by P3. Further, one delta component was associated with all diagnostic groups, suggesting that ERO delta may represent a more parsimonious endophenotype for externalizing disorders than P3. In another similar study using data from a large twin sample (634 MZ and 335 DZ, male and female same-sex pairs), Gilmore et al. [145], analyzed several electrophysiological measures (the P3, delta and theta ERO components, and resting state beta frequency band) collectively

in externalizing disorders. They found these measures (1) were heritable, (2) showed significant phenotypic and genetic correlation with a general vulnerability to externalizing disorders, (3) showed modest phenotypic and genetic correlation with each other, and (4) were sensitive to genetic effects that differed as a function of gender. These relationships suggested that these endophenotypes were likely tapping into electrophysiological processes and genes that were both common across them and unique to each. All these electrophysiological endophenotypes were highly relevant to a biological vulnerability to externalizing psychopathology. These two studies further indicated that delta and theta EROs are useful endophenotypes not only specifically for alcoholism but also for the spectrum of related externalizing disorders that includes alcoholism.

Go/NoGo task—The Go/NoGo task has been most widely used to assess response inhibition, in which the subject withholds his/her response for one set of stimuli ("NoGo" trials) while responding to another set of stimuli ("Go" trials). The task can be either a type of 'reverse oddball', with more trials for the Go condition, or have equal trials in both Go and NoGo conditions [146]. Only a few studies have analyzed EROs using the Go/NoGo paradigm to investigate alcoholism. Using an equal probability visual Go/NoGo task, Kamarajan et al. [99] reported deficient delta and theta oscillatory activity in abstinent alcoholics. This reduction in delta and theta EROs in alcoholic subjects was found in the frontal region, particularly during NoGo trials [99]. To examine whether or not these deficits anteceded the development of alcoholism, the authors studied offspring of alcoholic parents and found that these high-risk subjects manifested significantly decreased ERO activity in delta (1-3 Hz), theta (4-7 Hz), and low alpha (8-9 Hz) bands during the NoGo condition, as well as reduced delta and theta activity during the Go condition. This study provided further evidence that these deficient oscillatory responses antecede the development of alcoholism [147] and perhaps could serve as effective endophenotypes in the study of alcoholism.

Gambling task—A typical gambling task involves 'choice' stimuli (for which the subjects have to choose one of two or more choices to bet with) and 'outcome' or 'feedback' stimuli which show the resultant outcome (e.g., loss or gain) for the choice made during a particular trial [148]. Alcoholics have been reported to have deficient ERP components obtained from gambling tasks [11,149]. However, to our knowledge, only one ERO study has used a gambling paradigm in alcoholics; Kamarajan et al. [150] examined the relationship among the factors of ERO measures, impulsivity, and alcoholism. In this study, ERO theta power in the time window of 200-500 ms (wherein the 'outcome-related' ERP negativity and positivity occur) was compared across alcoholic and control groups (Figure 1). The subjects in the study 1) were asked to select one of two amounts (10¢ or 50¢) to bet with, and 2) received feedback/outcome about the selected amount (i.e., Loss 10, Loss 50, Gain 10, and Gain 50). The alcoholic group showed significantly decreased theta power during reward/outcome processing compared to controls. A strong association between reduced anterior theta power and impulsive task performance was also observed. Furthermore, alcoholics exhibited increased impulsivity and risk-taking on the behavioral measures. Similar studies in high-risk offspring of alcoholics are underway to further evaluate this ERO measure (anterior theta power) and determine whether it antecedes the development of alcoholism, and can serve as a potential endophenotype.

In a simulated gambling task, Bernat et al. [151] examined the relationship between externalizing proneness and the feedback-related negativity (FRN), a brain response that indexes performance monitoring related to exogenous cues. They found delta-P300 amplitude was reduced among individuals high in externalizing proneness whereas theta-FRN response was unrelated to externalizing. The authors suggested that in contrast to previously reported deficits in endogenously based performance monitoring [152] as indexed by the error-related negativity (ERN), individuals prone to externalizing problems

show intact monitoring of exogenous cues. The results of Bernat et al. [151] appear to be in contrast with the findings of Kamarajan et al. [150], who reported deficient theta EROs in alcoholics compared to normal controls for the outcome related components. However, there are important differences in the methodologies of these studies in terms of the paradigms used, analysis methods, and subject samples under study. Kamarajan et al. [150] used an abstinent alcoholic sample (DSM-IV) whereas Bernat et al. [151] used a sample of undergraduate students who were classified into high and low proneness to externalizing. Secondly, Kamarajan et al. [150] used an S-Transform analysis to decompose TF signals where a broader time window of 200-500 ms was used that encompasses both outcome-related negativity and positivity (ORN/ORP). On the other hand, Bernat et al. [151] used a PCA based TF approach and included the components that accounted for most of the variance; i.e., they separated contributions of the delta (P3) and theta (FRN) time windows. It has been reported that P3 is primarily composed of delta and theta oscillations [72-78] and N2 is primarily composed of theta oscillations (e.g., [133,134,136,137,153]). Therefore, the differences in study samples and methodological approaches in these two studies may explain the contrasting results, but further studies will be required to resolve these issues.

Gamma ERO

The early phase-locked gamma has been considered to represent an important processing stage related to the selection and identification of target stimuli, indicative of top-down mechanisms involved in selective attention [105,106,154]. This phase-locked or evoked gamma is larger for attended stimuli compared to unattended stimuli, particularly over frontal regions [79,155], while the induced gamma oscillations have been associated with a wide range of cognitive processes, object representation, and learning [106,156,157]. Although many studies have examined the gamma band ERO activity in healthy individuals, such studies are very rare in clinical disorders including alcoholism.

Padmanabhapillai et al. [158] investigated early evoked gamma activity (during the first 150 ms poststimulus activity) using a visual oddball task. They found that alcoholic subjects showed significantly decreased evoked gamma activity at frontal regions during target processing compared to nonalcoholic controls. The authors suggested that this reduction in early evoked gamma response at frontal locations may be due to frontal lobe dysfunction associated with deficient top-down processing mechanisms in alcoholics. The authors further conducted a similar study in children of alcoholics (14-17 years) compared to an age-matched nonalcoholic control group [159]. They found that offspring of alcoholics, similar to alcoholics, showed significant reductions in early evoked gamma activity in frontal as well as parietal regions for the target condition, with the maximum difference in the parietal region. Additionally, high-risk offspring exhibited less differentiation between target and non-target conditions in terms of level of gamma activity, indicating a further deficiency in stimulus discrimination processes. It is likely that a dysfunctional frontoparietal attentional network may underlie this deficit as shown in an fMRI study during a visual oddball task in high-risk subjects, reported by Rangaswamy et al. [15].

Alcohol-Induced ERO alterations

There are a number of studies showing the changes in resting EEG and ERPs due to the direct effects of alcohol ingestion [160-162]. However, studies on alcohol-induced alterations in EROs are quite rare. Krause et al. [163] examined the effects of alcohol on event-related desynchronization (ERD) and event-related synchronization (ERS) during an auditory memory task. It was found that the administration of alcohol decreased the early-appearing ERS responses during auditory encoding and increased the later-appearing ERD responses during retrieval; these effects were significant in the slow theta (4-6 Hz), fast theta (6-8 Hz), and slow alpha (8-10 Hz) frequency bands. The authors concluded that alcohol

intake has a direct effect on the brain and cognitive functioning by disorganizing the brain oscillatory systems in the theta and lower alpha frequency range during stimulus/task processing. In another study during a selective attention task, Jaaskelainen et al. [164] investigated the dose-related impact of alcohol on auditory transient evoked 40-Hz responses and found that evoked 40-Hz response amplitude was suppressed by alcohol during both attended and non-attended conditions, starting at the blood alcohol concentration (BAC) level of about 0.05%. This study further demonstrated that cognitive processing associated with gamma band activity is affected by alcohol administration.

Recently, Boha et al. [165] studied the acute effects of alcohol on task-related EEG during the performance of a mental arithmetic task that involved working memory. While no detrimental alcohol effect was seen on behavioral indices of task performance, alcohol decreased the usually occurring task-related frontally dominant theta increase corresponding to the working memory demand. Further analysis using complexity measures by the same group of authors [166] suggested that task-related decrease of the omega complexity (OC, reflecting the lesser level of complexity or higher spatial correlation between different electrodes) and increase of the synchronization likelihood (SL, reflecting the higher strength of coupling between EEG-channels) was found in the theta frequency band, indicating increased synchrony in the event-related theta band. Further, high dose of alcohol intake increased the OC values and decreased the anterior SL values under working memory condition, indicating decreased synchrony in ERO theta band.

Apart from these studies on the direct effect of alcohol, there has been an attempt to examine EROs in the groups of social drinkers. For example, De Bruin et al. [167] conducted a task-related EEG study on heavy social drinkers with 24 hours abstinence before the recording session. Functional connectivity was assessed with the SL method. It was found that heavy drinking students had more synchronization in the theta (4-8 Hz) and gamma (30-45 Hz) band than light drinking students during a mental-rehearsal task, which the authors attributed to possible changes in hippocampal-neocortical connectivity.

Animal Studies of EROs related to Alcoholism

Animal models have been developed to simulate several relevant human phenotypic markers or traits associated with alcohol use and dependence. In the models relating to electrophysiological measures, differences in EEG (e.g., [168]), ERP (e.g., [168,169]), and ERO [170,171] responses have been identified to distinguish high alcohol preferring (HAP) from low alcohol preferring (LAP) mice. It was confirmed that these electrophysiological changes in high versus low alcohol preferring mammals closely resemble differences seen in human studies of individuals with high and low risk for alcohol dependence. Ehlers and Criado [172] first demonstrated that EROs can be generated in cortical sites in mice in the delta, theta, alpha/beta frequency ranges in response to auditory stimuli. They observed that oscillations in the 7.5-40 Hz frequencies were significantly affected in the 0-50 ms time window in response to differences in tone frequency, whereas, changes in tone loudness produced changes in oscillations in the 7.5-40 Hz frequencies in the 350-800 ms time window.

In their first ERO study of animal models of alcoholism, Criado and Ehlers [170] investigated the utility of EROs as effective risk markers by using genetic mouse models of high alcohol preference. The authors measured delta, theta and alpha/beta ERO energy and the degree of phase variation in groups of high and low alcohol preferring mice and found that the decreased P3 amplitudes previously shown in B6 mice (with a low level of withdrawal severity), compared to D2 mice (with extreme withdrawal severity) [169], was related to reductions in evoked delta ERO energy and delta and theta phase locking. In contrast, the increase in P1 amplitudes reported in HAP mice, compared to LAP mice, is

associated with increases in evoked theta ERO energy. Further, these differences in delta and theta ERO measures in mice mirrored the changes observed in human subjects between high and low risk for alcoholism where changes in EROs were found to be more significant than group differences in P3 amplitudes. Based on these findings, the authors suggested that ERO these measures are more stable endophenotypes in the study of alcohol dependence than P3.

In another recent study by Criado and Ehlers [171], EROs in selectively bred adult alcohol-preferring (P) and alcohol-non preferring (NP) rats were compared. While the previous electrophysiological studies have shown P rats exhibited more EEG fast frequency activity and reduced P3 amplitude in the parietal cortex than NP rats [173], findings that are more common in alcohol-dependent individuals, the authors tested the possibility that EROs could be excellent endophenotypes associated with ethanol dependence using similar animal. The findings confirmed that the decrease in P3 amplitudes previously shown in P rats were significantly associated with decreases in evoked delta and alpha/beta phase locking. These findings in animal models of alcoholism further confirmed the findings of human studies that that ERO measures provide good endophenotypes in the study of alcoholism.

In summary, studies of EROs during visual oddball, Go/NoGo, and gambling paradigms indicate that delta, theta, and gamma power is reduced in alcoholics. As these findings are also obtained in offspring at high risk, it suggests that these ERO differences antecede the development of alcoholism. Hence, not only is the traditional finding of P3 amplitude reduced in alcoholics and subjects at risk, but the underlying delta and theta oscillations are also reduced. Animal studies utilizing high and low alcohol preferring model appear to confirm these findings in alcoholic human subjects and their offspring. As will be seen in the next section, these ERO markers of risk provide excellent endophenotypes that have been successfully implemented in genetic studies.

EROs as Endophenotypes

Alcoholism is a common, complex (non-Mendelian) disorder with contributions from both genetic and environmental influences and their interactions [41]. As psychiatric diagnosis is dichotomous (either affected or unaffected), it is difficult to use diagnosis as the sole phenotype when studying the genetics of complex disorders, such as alcoholism. It has been suggested that, ideally, molecular genetic studies should not be performed on psychiatric diagnoses alone, which reflect distal and variable effects of genes, but on quantitative neurobiological measures or markers that reflect more proximal effects of genes involved in the genetic predisposition for developing psychiatric disorders [174]. These quantitative biological markers (endophenotypes or intermediate phenotypes) serve as covariates that correlate with the main trait of interest (diagnosis) and serve to better define that trait or its underlying genetic mechanism [43,175,176]. The advantages of using quantitative neurobiological measures of risk as endophenotypes in the search for genes involved in complex disorders are that they are closer to gene action involved in the predisposition for the disorder, they are genetically simpler than clinical endpoints, and quantitative traits provide more power to localize and characterize disease susceptibility genes [177].

In order to be considered as an endophenotype, several criteria must be met [43]: 1) the endophenotype must be associated with illness in the population, 2) the endophenotype must be heritable, 3) the endophenotype must be primarily state-independent (manifests in an individual whether or not illness is active), 4) within families, endophenotype and illness co-segregate, and 5) the endophenotype must be found in affected family members, and must also be found in non-affected family members at a higher rate than in the general population. Endophenotype-based strategies have successfully identified genes associated with many psychiatric disorders.

Brain function is likely to be involved in a genetic predisposition to develop alcoholism and other psychiatric disorders, and neuroelectric events may serve as excellent biological markers or endophenotypes. Understanding genetic control of brain electrical activity may provide clues about cerebral function, and may shed light on pathogenic mechanisms involved in neurological and psychiatric disorders, where impairment in brain electrical activity is apparent. Brain oscillations provide a rich source of potentially useful endophenotypes for psychiatric genetics, as they represent important correlates of human information processing and cognition.

In order for genetic studies using the endophenotype approach to be successful, it is extremely important to select well characterized (endo) phenotypes that meet the criteria of Gottesman and Gould [43]. Neuroelectric phenotypes (brain oscillations, such as EEG and those EROs underlying ERPs, including the P3 component) meet these criteria for endophenotypes for alcoholism, as they are heritable, and characterize not only those who are affected, but also offspring at risk [42]. The data on the heritability of EEG frequencies are quite compelling. High concordance rates in the spectral characteristics of resting eyes-closed EEG have been reported from monozygotic twin pairs compared to dizygotic twin pairs. A large twin study indicates that power in all frequency bands of the resting EEG is highly heritable: delta 76%, theta 89%, alpha 89%, and beta 86% [57,58]. The power estimates of frequency bands may be more heritable than ERP components giving them a slight edge as endophenotypes [178]. As reviewed in the previous sections, event-related oscillations (EROs) meet the criteria of endophenotypes for alcoholism, as reduced delta, theta and gamma oscillations not only characterize affected alcoholics, but also their relatives, particularly offspring at risk prior to the onset of the illness. Therefore, the use of quantitative ERO endophenotypes provides a powerful strategy for identifying underlying susceptibility genes for developing alcoholism and related disinhibitory disorders.

One ERO endophenotype for genetic studies, event-related theta power, has been examined in densely affected alcoholic families in the large Collaborative Study on the Genetics of Alcoholism (COGA). The densely affected families consisted of a proband and two additional first-degree relatives affected with alcohol dependence (DSM-IV), and control families that were randomly ascertained from the general population. These studies reported significant linkage and association between the *CHRM2* (cholinergic muscarinic receptor M2) gene on chromosome 7 and frontal theta oscillations to target stimuli in a visual oddball task. Association analyses using both population based tests (Measured Genotype) and pedigree based tests (Quantitative Pedigree Disequilibrium Test, QPDT) indicated significant association of the frontal theta band ERO phenotype with several single-nucleotide polymorphisms (SNPs) surrounding exon 4 of *CHRM2*. Further, an examination of the slower frequency parietal delta band ERO revealed significant association with several SNPs surrounding the coding region of the *CHRM2* gene [179,180].

These findings implicate the possible role of *CHRM2* in the generation and/or modulation of EROs. Theta and delta EROs depend on the level of acetylcholine. Muscarinic acetylcholine (M2) receptors inhibit presynaptic release of acetylcholine, leading to inhibition of irrelevant networks (cf. [181]). M2 are especially concentrated in the forebrain and possibly serve to maintain the effective balance of relevant/irrelevant networks, hence, having a direct influence on P3 generation [182]. Our results with the *CHRM2* gene and brain oscillations support the role of acetylcholine in the generation of N2 (theta oscillations) and in the P3 component (delta and theta oscillations). A role of acetylcholine has been reported with regard to stimulus significance [183], selective attention [184], and P3 generation [185]. Administration of cholinergic agonists and antagonists have resulted in modified memory performance, as well as modified P3 amplitudes in humans [186-188]. In vitro administration of moderate amounts of the muscarinic agonist carbachol in the rat

hippocampus induces synchronized delta oscillations, whereas higher concentrations produced short episodes of theta oscillations, and the carbachol-induced delta rhythms were not observed concurrent with carbachol-theta [189,190].

Recent evidence indicates that the *CHRM2* gene is not only associated with brain oscillations and cognition, but also clinical diagnosis. Significant linkage and association were reported for the *CHRM2* gene and a diagnosis of alcohol dependence and depression [191], comorbid alcohol and drug dependence [192], as well as a spectrum of externalizing disorders [193] in the COGA study. Other groups have also replicated these findings, reporting that the *CHRM2* gene predisposes to alcohol dependence, drug dependence and affective disorders [194], and major depression in women [195]. Thus, genes important for the expression of the endophenotypes help in identification of genes that increase the susceptibility for risk of alcohol dependence and related disorders [196,197].

Under the same theta ERO linkage peak on chromosome 7 is a glutamate receptor (*GRM8*) gene that is another very likely candidate gene for modulating electrophysiological networks, particularly as the glutamatergic system is also involved in theta oscillations and P3 [182]. Family-based association analyses of theta EROs revealed significant associations with several SNPs in the *GRM8* gene and theta EROs to target stimuli at frontal, central, and parietal regions [198]. An interesting finding is that several of the same *GRM8* SNPs were also significant for diagnosis of alcohol dependence using ICD-10 diagnostic criteria.

Using 3-T proton magnetic resonance spectroscopy (1H-MRS), Gallinat et al. [199] have suggested the involvement of glutamatergic neurotransmission in integrative frontal-hippocampal processing [199] and the sensation seeking personality dimension [200]. The study demonstrated a strong relationship between glutamate levels in the hippocampus and frontal theta activity during auditory stimulus processing [199]. Glutamatergic neurotransmission and its neuroadaptive changes have been proposed as important molecular determinants of craving and relapse [201,202]. In particular, it is suggested that a hyperglutamatergic state mediates, at least in part, alcohol relapse behavior and maintenance of alcoholism [203]. Several studies have suggested the involvement of glutamate receptors, NMDA and metabotropic, in alcohol relapse [204-206]. Acamprosate, a drug used to prevent relapse in alcoholic patients [207], has been suggested to act through a suppression of a hyperglutamatergic state created by alcohol addiction [208,209]. Although there have been as yet no ERO/ERPs studies done in alcoholics during/after the administration of anti-craving/anti-dependence medications, such as acamprosate, naltrexone, etc., a few resting EEG studies in animals [210-212] and in humans [213-215] found EEG alterations after administration of these drugs. While animal studies indicated a slowing or reduction of frequency, human studies were equivocal. Future electrophysiological research (especially ERP and ERO studies) should further investigate this important aspect.

In a first genome-wide case-control association study (GWAS) of an ERO endophenotype (frontal theta ERO from the target response in visual oddball task), Zlojutro et al. [216] reported some important genetic associations. This was a two-stage GWAS study that first identified four markers, ARID5A, GNAS1, ANXA13, and *HTR7* with nominally significant association with frontal theta ERO, with the most significance in ARID protein 5A gene (ARID5A) on chromosome 2q11. The most intriguing association was with a serotonin receptor gene (*HTR7*) on chromosome 10q23, implicating the serotonergic system in the neurophysiological underpinnings of theta EROs. They also found a significant association of alcohol dependence diagnosis (DSM-IV) with several *HTR7* SNPs among GWAS case-controls. Significant recessive genetic effects were also detected for alcohol dependence in both the COGA case-control and family-based samples, with the *HTR7* risk allele corresponding to theta ERO reductions among homozygotes. These results suggested a role

of the serotonergic system in the biological basis of alcohol dependence, and therefore demonstrated the utility of brain oscillations as a powerful approach to understanding complex genetic psychiatric disorders such as alcoholism.

In summary, it can be said that the genetic underpinnings of evoked oscillations are likely to stem from regulatory genes which control the neurochemical processes of the brain, thereby influencing neural function. The major neurochemical substrates contributing to theta and delta rhythms and P3 has been suggested to be strongly glutamatergic, with strong modulatory influences from both cholinergic and GABAergic sources that elicit excitatory and inhibitory post-synaptic potentials, and indirect system interactions and contributions from the serotonergic, dopaminergic and noradrenergic systems [182,216].

Summary and Conclusions

EROs are measures of cognitive processing in response to a stimulus or event, and are considered to be building blocks of various neurocognitive functions; each frequency activity of EROs represents several specific cognitive functions [79,217]. EROs facilitate neural communication across brain regions through synchrony, with low frquency oscillations (such as delta, theta and alpha) for long-range communication and high frequency oscillations (such as beta and gamma) for short-range communication [108].

Studies with alcoholics and their offspring have consistently reported ERO deficits in delta, theta, and gamma bands in visual oddball tasks. Furthermore, deficits in theta ERO power have been reported across several task paradigms (e.g., oddball, Go/NoGo, and gambling) in these groups. Since theta ERO contributions to the P3 as well as N2 components of the ERP are mainly from frontocentral regions of the brain, it can be hypothesized that the deficits in theta ERO power in these groups may be associated with the dysfunctional frontal processing. Further, these frontal theta ERO deficits in the offspring of alcoholics indicate that they antecede the development of alcoholism. Importantly, the frontal theta EROs have successfully served as endophenotypes in genetic studies of alcoholism, and have been found to be significantly associated with SNPs in *CHRM2* [179,180], *GRM8* [198], and *HTR7* [216] genes, SNPs that have also been found to be significantly associated with alcohol dependence. This suggests the involvement of glutamatergic, GABAergic and serotonergic systems in the modulation of theta oscillations especially in the context of alcoholism.

The use of quantitative brain oscillations as endophenotypes provides the power to more easily localize and characterize disease susceptibility genes than diagnostic categories. The recent identification of genetic loci associated with human brain oscillations indicates that they are under genetic control and are modulated by genes controlling neurotransmitters in the brain. Several receptor genes have emerged from the genetic studies of event-related oscillations as endophenotypes, that are involved in variation in brain oscillations and hence their cognitive correlates; specifically, theta EROs have been associated with the cholinergic muscarinic receptor (*CHRM2*), metabotropic glutamate receptor (*GRM8*), and serotonin receptor (*HTR7*) genes. Although no functional variant affecting the electrophysiological characteristics has yet been identified at the molecular level, a large body of pharmacological evidence attests to the relevance of these receptors to aspects of cognitive function. The advent of genomics and proteomics and a fuller understanding of gene regulation will open new horizons on the critical electrical events so essential for human brain function. This approach has the unprecedented potential to unravel the complex interplay of various neural subsystems relevant to the generation of brain oscillations elicited under different cognitive conditions and in the disease states.

It is interesting to note that in the genetic studies using brain oscillations as endophenotypes significantly associated SNPs lie in the same genes that are also associated with alcohol dependence and related disorders. Thus, genes underlying the variations in endophenotypes are also associated with the disease state. This highlights the utility and importance of using this endophenotype approach with quantitative brain oscillations in the identification and understanding of genes involved in alcoholism and related disorders. As alcohol dependence results from a complex interaction of changing genetic and environmental liabilities across development, it is hoped that by combining these approaches we can eventually understand how much of the capacity to modulate these oscillations, in the context of a disease state, lies in the control of genes and how environment influences this control; prospective studies of young individuals with “risk genotypes” can lead to an improved understanding of how neural and cognitive changes contribute to susceptibility across development, which in turn can lead to the design of well-targeted prevention initiatives. Understanding genetic control of brain electrical activity may provide clues about cerebral function, and may shed light on pathogenic mechanisms involved in neurological and psychiatric disorders, where impairment in brain electrical activity is apparent. Once genes are identified and understood, risk genotypes can be used in the development of both targeted treatment and prevention initiatives.

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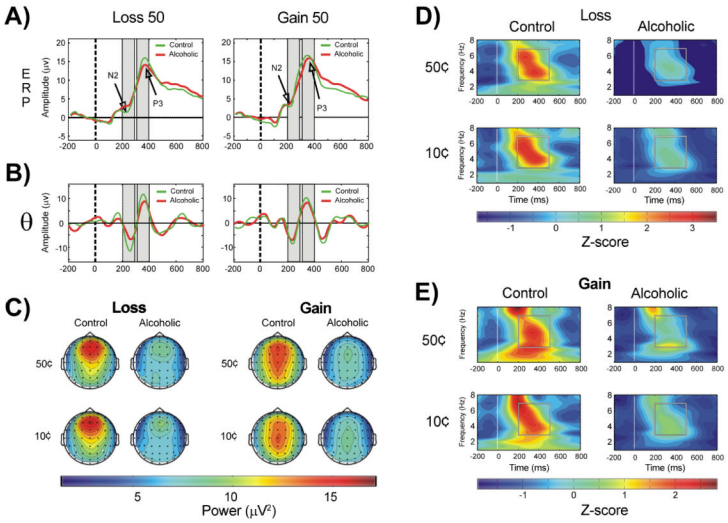

Figure 1.

A) The grand-averaged ERP waveforms for Loss 50 and Gain 50 conditions; B) Theta bands during Loss 50 at FZ electrode and Gain 50 at CZ electrode are shown. The region of ORN (N2) and ORP (P3) peaks and the corresponding theta activity during the time window are shaded in gray color. There is a partial phase-alignment of the theta activity corresponding to ORN (200-300 ms) and ORP (300-400 ms) components. Alcoholics showed decreased amplitude in theta (3–7 Hz) band more anteriorly (frontal) for the loss condition and more posteriorly (centro-parietal) for the gain condition. The dashed vertical line (at 0 ms) represents the onset of an outcome stimulus; C) Topographic maps of theta (3-7 Hz) power in control and alcoholic groups illustrating that the loss condition had an anterior topography and the gain condition had a posterior topography. Decreased theta band power in alcoholics in both conditions is illustrated; D) Time-frequency (TF) plots during the loss condition at the Fz electrode in the alcoholic and control groups; and E) TF plots during the gain condition at the Cz electrode. The square box inside TF plots marks the time-frequency region of interest, namely the time interval of 200–500 ms across the theta frequency range 3-7 Hz for analysis. The alcoholic group showed a significant reduction in theta power during each outcome condition. The color scale (in TF plots) represents the theta power in terms of Z-scores, which were computed from the overall data (representing all groups and conditions) and hence are comparable among the TF plots.