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Invited review

The utility of neurophysiological markers in the study of alcoholism

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Abstract

Objective: This review attempts to differentiate neuroelectric measures (electroencephalogram (EEG), event-related potentials (ERPs) and event-related oscillations (EROs)) related to acute and chronic effects of alcohol on the brain from those that reflect underlying deficits related to the predisposition to develop alcoholism and related disorders. The utility of these neuroelectric measures as endophenotypes for psychiatric genetics is evaluated.

Methods: This article reviews the main findings of EEG and ERP abnormalities in alcoholics, offspring of alcoholics at high risk to develop alcoholism and the electrophysiological effects of alcohol on high risk compared to low-risk offspring. It highlights findings using EROs, a fast developing tool in examining brain function and cognition. It also reviews evidence of genetic findings related to these electrophysiological measures and their relationship to clinical diagnosis.

Results: Many of these abnormal neuroelectric measures are under genetic control, may precede the development of alcoholism, and may be markers of a predisposition toward the development of a spectrum of disinhibitory conditions including alcoholism. Genetic loci underlying some neuroelectic measures that involve neurotransmitter systems of the brain have been identified.

Conclusions: Quantitative neuroelectric measures (EEG, ERPs, EROs) provide valuable endophenotypes in the study of genetic risk to develop alcoholism and related disorders.

Significance: Genetic studies of neuroelectric endophenotypes offer a powerful strategy for identifying susceptibility genes for developing psychiatric disorders, and provide novel insights into etiological factors.

Keywords: EEG; P3; Alcoholism; Event-related oscillations (EROs); Endophenotype; Genetic predisposition; Psychiatric genetics

1. Introduction

It is widely recognized that alcoholics manifest brain damage/dysfunction, and electrophysiological methods have long been used to elucidate the nature of this brain dysfunction. Recording brain electrical activity using scalp electrodes provides a non-invasive, sensitive measure of brain function in humans. These neuroelectric phenomena may be recorded with the continuous electroencephalogram (EEG) when the subject is at rest and not involved in a task or with the time-specific event-related brain potentials (ERPs) during cognitive tasks. Newer methods of time–frequency domain analysis have uncovered the phenomenon of event-related oscillations (EROs) which are time-locked to the event in much the same way as ERPs. These new measures of dynamic brain processes have exquisite temporal resolution and allow the study of neural networks underlying sensory and cognitive events, thus providing a closer link to the physiology underlying them.

Electrophysiological measures are highly sensitive to the acute and chronic effects of alcohol on the brain, including intoxication, tolerance, withdrawal and long-term abstinence. For many years, it had been assumed that the aberrant electrophysiological characteristics observed in alcoholics were due to the neurotoxic effects of alcohol on the brain. More recently, data suggest that some electrophysiological characteristics in alcoholics are under genetic control and precede the development of alcoholism, and may be markers of a predisposition toward the development

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of alcoholism and related disorders. There is increasing evidence that offspring of alcoholics are at a 7-fold risk to develop alcoholism (Goldman, 1993). Studies of alcohol naïve offspring of alcoholics at high risk (HR) to develop alcoholism indicate that these anomalous electrophysiological characteristics observed in alcoholics are already apparent prior to prolonged alcohol exposure.

Alcoholism is a common familial disorder with increased risk among biological relatives of alcoholics. Studies of male adoptees in Scandinavia indicate that the biologic rather than the adoptive parent is predictive of later drinking problems, with increased risk in sons of alcoholics, even if adopted away and raised in non-alcoholic families (Bohman, 1978; Cadoret and Garth, 1978; Cadoret et al., 1980; Goodwin and Guze, 1974; Goodwin et al., 1973). A positive family history of alcoholism has been recognized as a robust and consistent predictor of alcoholism risk. Cotton (1979), reviewing several published family studies, concluded that alcoholics were 4–6 times more likely to have a parent who was also alcohol-dependent than were non-alcoholic controls. Furthermore, the concordance rate for alcohol abuse between identical twins is almost double the rate between fraternal twins (Kaij, 1960), and patterns of alcohol consumption have been reported to be highly concordant among identical twins (Jonsson and Nilsson, 1968; Loehlin, 1972; Partanen et al., 1966). A recent comprehensive review of the literature on the epidemiology of alcoholism concluded that genetic factors predispose sons of alcoholic fathers to alcoholism (Hesselbrock, 1995). More recently, female offspring were also determined to be at risk. Family, twin and adoption studies that highlight genetic contributions to alcoholism suggest that both genders are equally vulnerable (McGue and Slutske, 1996; Prescott et al., 1999). However, behavioral genetic studies estimating the heritability of alcoholism reveal more consistent estimates for males (0.50–0.60) and a highly variable estimate for females (0.0–0.56). A meta-analysis of family studies of alcoholism indicates that the rate of cross-gender transmission of alcoholism is comparable to the within-gender transmission, which in turn implies that the extent to which inherited factors are shared is roughly the same (McGue and Slutske, 1996).

Yet alcoholism is not a specific disease but part of a spectrum of co-occurring psychiatric and substance use disorders. The usual manifestation of alcoholism is as part of a class of disinhibitory disorders, which includes co-occurring substance abuse and psychiatric disorders. Many of the same risk factors underlie these common psychiatric disorders and can be explained by a small number of underlying factors (Kendler et al., 2003). Twin studies indicate substantial genetic overlap among disinhibitory syndromes including conduct disorder, child and adult antisocial behavior and drug and alcohol dependence (Jacobson et al., 2002; Kendler et al., 2003; Krueger et al., 2002; Slutske et al., 1998). A recent family twin study of externalizing disorders reported that a general vulnerability is what is passed on to the next generation, with each disorder representing a different expression of this general vulnerability (Hicks et al., 2004).

Several studies have demonstrated that alcohol dependence and substance abuse are often co-occurring with externalizing traits in children (Weinberg et al., 1998) as well as in adults (Wilens et al., 1994). The highest risk for developing alcoholism exists for individuals who used alcohol in the 11–14 years range (DeWit et al., 2000). Age at first drink has also been correlated with a broad range of indicators of disinhibited behavior (McGue et al., 2001). It has also been observed that an early onset of alcoholism is associated with increased likelihood of antisocial behavior (Babor et al., 1992; Cloninger, 1987) and disinhibitory behaviors (McGue et al., 1997, 1999; Tarter, 1988).

Longitudinal studies of childhood and adolescent precursors of adult alcoholism consistently identify a cluster of behavioral traits described as disinhibited, under-controlled, or impulsive, that significantly predict early onset alcohol abuse (Cloninger et al., 1988; Farrington, 1991). Gorenstein and Newman (1980) proposed that behavioral phenomena such as psychopathy, antisocial and impulsive traits, substance and alcohol abuse, should be viewed as variable expressions of a generalized disinhibitory complex. This perspective could prove advantageous because it places alcohol dependence within a theoretical framework (Fowles, 1987; Krueger et al., 2002; Newman, 1987) and suggests potential mechanisms that may mediate the disinhibited behavior-substance dependence (including alcohol dependence) relationship. Thus alcoholism is but one possible endpoint of a cluster of etiological factors with genetic and environmental causes. It should be noted that similar electrophysiological features have been reported in individuals with these underlying disinhibitory clinical conditions.

As this review will indicate, similar aberrant electrophysiological characteristics have been reported in individuals at risk to develop alcohol dependence as well as related disinhibitory disorders. Furthermore, these neuroelectric measures are under genetic control and involve neurotransmitter systems that control the balance between excitation and inhibition in the brain. Therefore, these electrophysiological measures have become useful biological markers of risk for vulnerability for a spectrum of disinhibitory disorders, including alcohol dependence. As these measures are less complex, more heritable and closer to gene action than clinical diagnoses, they offer a valuable tool in the search for genes involved in the predisposition to develop alcoholism and related disorders. Gottesman and Shields (1972) were the first to propose using biological markers that are related to diagnosis as intermediate phenotypes, or endophenotypes, as a valuable approach to find genes involved in complex, non-Mendelian disorders. The recent implementation of this approach using brain oscillations as endophenotypes has led to the identification of genes involved in both the neuroelectric measures and diagnosis.

This review attempts to tease apart electrophysiological indices related to the acute and chronic effects of alcohol on the brain and those that reflect underlying brain deficits related to a predisposition to develop alcoholism and related disorders. We review the salient neuroelectric findings using EEG, ERP, and ERO methods in chronic abstinent alcoholics and offspring of alcoholics at high risk. We offer some hypotheses regarding underlying neurophysiological predispositions involved in developing alcohol-related disorders. In addition, we review the evidence for genetic findings related to these electrophysiological measures and their relationship to genetic factors underlying clinical diagnosis of alcohol dependence and related disorders. Issues related to the complexity of the problems involved (e.g. co-occurring psychiatric disorders, gender, role of genetics, gene–environment interaction) as well as future perspectives are discussed.

2. Resting electroencephalogram (EEG)

The resting electroencephalogram (EEG) is the recording of ongoing spontaneous brain electrical activity with non-invasive scalp electrodes in an individual with eyes open or closed. The EEG consists of a mixture of sinusoidal-like oscillations representing the activity of an ensemble of generators producing rhythmic activity across several spectral frequency ranges. In the purely resting state, these oscillations are seemingly random. Typically, EEG is divided into the following frequency bands: delta (1.0–3.0 Hz), theta (3.5–7.5 Hz), alpha (8–11.5 Hz), beta (12–28 Hz), gamma (28.5–50 Hz), with each frequency reflecting a different order of brain activity. Scalp-recorded EEG reflects resonant loops in the cortex. In healthy adults, medium (8–13 Hz) and fast (14–30 Hz) frequencies predominate the awake resting EEG, with only sparse occurrence of low frequencies (0.3–7 Hz) and high frequencies (>30 Hz) (Neidermeyer, 1999; Nunez, 1995). The resting EEG is stable and highly heritable across all frequency bands: delta 76%, theta 89%, alpha 89%, beta 86% (van Beijsterveldt and Boomsma, 1994; van Beijsterveldt et al., 1996).

2.1. Theta band

Resting theta rhythm has its maximum power in the posterior scalp region. The normal adult waking EEG record contains very low theta power. Elevated tonic theta power in the EEG may reflect a deficiency in information processing capacity of the central nervous system (Klimesch et al., 2001). Increases of theta rhythm have been seen in altered neurophysiological states of the brain involving altered cholinergic functioning, such as Alzheimer's disease (Huang et al., 2000), aging (Neidermeyer, 1999), and the transition from wakefulness to sleep (Tanaka et al., 2000). Slow EEG activity (theta and delta) has been well correlated with cholinergic activity and central cholinergic pathways (Steriade et al., 1990). In vitro studies have revealed that the mode of action of acetylcholine may either inhibit or excite cortical pyramidal neurons (McCormick and Prince, 1986). The production of inhibition results from the excitation of the intrinsic inhibitory neurons in the cortex. The theta power increase may be an electrophysiological index of the imbalance in the excitation–inhibition homeostasis in the cortex.

Similar increased resting theta power in alcoholics has been reported in a number of studies in the literature (Pollock et al., 1992; Propping et al., 1981; Rangaswamy et al., 2003). Tonic absolute theta power in alcoholics has recently been examined in the large Collaborative Study on the Genetics of Alcoholism (COGA). The COGA study consists of families in which a proband and two additional first-degree relatives are affected with alcohol dependence (densely affected), and control families that are randomly ascertained from the population. Eyes-closed resting absolute theta (3.0–7.0 Hz) power in the EEG of 307 alcohol-dependent subjects was compared to 307 age and gender matched unaffected controls (Rangaswamy et al., 2003). Alcohol-dependent subjects manifested increased absolute resting theta power at all scalp locations. The theta power increase was higher in male alcoholics particularly at central and parietal regions and was prominent in female alcoholics at the parietal region when compared to the respective matched controls. Correlation of drinking variables with theta power exhibited no group-specific differences. A previous study in a heterogeneous sample of older recovered alcoholics also reported an elevation in theta power; no relationship between the length of abstinence and theta power was found (Pollock et al., 1992). Similar findings of increased theta in actively drinking alcoholics have been recently found by Fein and his colleagues (personal communication). However, an earlier study by Propping et al. (1981) reported a decrease in theta power in female alcoholics. In a study comparing heavy and light student drinkers (de Bruin et al., 2004) heavy drinkers had more synchronization in the theta (4–8 Hz) band than light drinkers during an eyes-closed condition.

Elevated resting theta activity observed in the EEG of alcohol-dependent individuals is indicative of a dysfunctional neurophysiological status in these individuals. One study examining different EEG bands after the administration of alcohol reported elevations in theta power in proportion to increasing blood alcohol level (Lukas et al., 1986). The authors suggest that this progression of increased theta activity may have been perceived as slowing of alpha in the earlier studies. Ehlers et al. (1989) also found a highly significant increase in both theta and low alpha band power 90 min after ethanol consumption. It is possible that the increases of theta produced by the acute administration of alcohol that is observed in healthy individuals, subsequently evolves into a more pervasive increase in theta power in the resting EEG of chronic alcoholics following prolonged

exposure. No strong evidence of increased resting theta has been reported in offspring of alcoholics, suggesting that this measure may index a state-dependent condition.

2.2. Alpha band

The alpha rhythm is the predominant EEG rhythm in the relaxed alert individual. It is obtained both with eyes open and eyes closed, and has its maximum power in the eyes-closed condition over the occipital regions. There is an extensive literature, dating back to the 1940s indicating unstable or poor alpha rhythm in alcoholics; alcoholics manifest less prevalent and lower alpha than do non-alcoholics (for review see Begleiter and Platz, 1972; Propping et al., 1981). However, some more recent studies did not find that alcoholics manifest low resting alpha power compared to non-alcoholics (Enoch et al., 1999; Pollock et al., 1992). A QEEG study (Saletu-Zyhlarz et al., 2004) reported a decrease in slow alpha activity in alcoholics and these findings were more pronounced in those who relapsed in a 6-month-period. After 6 months of treatment, abstaining patients showed an increase in slow activity, a decrease in fast alpha, and a deceleration of the alpha centroid.

Reduced EEG alpha power in the male and female offspring of alcoholics was reported by Finn and Justus (1999). The alpha band studied (8–13 Hz) was reduced in the frontal and occipital regions and did not significantly correlate with trait anxiety, a diagnosis of depression, or antisocial traits. On the other hand, some authors have shown that men with alcoholic fathers are more likely to have higher voltage alpha than men without a family history of alcoholism (Ehlers and Schuckit, 1991). This group has reported that women at high risk for developing alcoholism also have higher voltage alpha in their EEG (Ehlers et al., 1996).

An alpha variant, namely low-voltage alpha (LVA), has been reported to be associated with a subtype of alcoholism that is associated with anxiety disorder (Enoch et al., 1999). Recently, Enoch et al. (2003) found that among females, LVA is associated with a genetic variant that leads to low activity in catechol-*o*-methyltransferase (COMT), the enzyme that metabolizes dopamine and norepinephrine (NE). They hypothesize that altered NE levels on thalamic activity may partly explain the connection between LVA and anxiety/alcoholism.

Another recent study on subjects of African–American descent (Ehlers and Phillips, 2003) found that the presence of the LVA variant was not associated with drinking status, family history of alcoholism, or a personal history of anxiety disorders, but was associated with significantly higher extroversion scores. Participants who had a family history of alcoholism had significantly higher spectral power in the slow alpha frequencies (7.5–9 Hz). These findings suggest that considerable ethnic variation may exist in the prevalence of LVA EEG variants.

2.3. Beta band

Beta rhythm is more distributed over the scalp and has become an important neurophysiological index in the study of predisposition to alcoholism. Beta rhythm involves a balance in networks of excitatory pyramidal cells and inhibitory interneurons involving $GABA_A$ action as the pacemaker (Whittington et al., 2000). A genetic link between a $GABA_A$ receptor gene and the beta frequency band of the EEG has been recently reported by the COGA project (Porjesz et al., 2002a). Recent findings from the same project implicate the same *GABRA2* receptor gene and diagnosis of alcohol dependence (Edenberg et al., 2004). This finding has been replicated in several recent independent studies (Covault et al., 2004; Xu et al., 2004). This suggests that variations in the *GABRA2* gene affect level of neural excitability, which in turn affects the predisposition to develop alcohol dependence. The involvement of the GABAergic system in alcoholism is supported by neuroimaging studies, which report specific deficits in GABA benzodiazepine receptors in the brains of alcoholics (Abi-Dargham et al., 1998; Lingford-Hughes et al., 1998) and individuals at risk (Volkow et al., 1995). Taken together, these findings suggest GABA deficits in the brains of alcoholics and individuals at risk may account for their lack of CNS inhibition (hyperexcitability) and may be involved in the predisposition to develop alcoholism.

This hypothesis is reflected in studies of scalp-recorded EEG in alcoholics and individuals at risk. Increased beta power in the EEG of alcoholics, particularly in the resting condition, has been well documented (Bauer, 2001; Costa and Bauer, 1997; Propping et al., 1981; Rangaswamy et al., 2002; Winterer et al., 1998). Propping et al. (1981) reported differences in female but not male alcoholics. In the large COGA sample (Rangaswamy et al., 2002), increased beta power in alcoholics was prevalent at all scalp loci, but was most prominent in the central region for slow–medium frequency beta (12–20 Hz) and over the frontal regions for fast beta (20–28 Hz); age and clinical variables did not influence the increase. A QEEG study (Saletu-Zyhlarz et al., 2004) reported an increase in beta activity as well as an acceleration of the total centroid in alcoholics and these findings were more pronounced in relapsers than abstainers. Fast beta (19.5–39.8 Hz) power has been found to be superior to severity of illness, depression level and childhood conduct problems in predicting relapse in abstinent alcoholics (Bauer, 2001); anterior frontal brain regions were identified as the most likely source of this fast beta activity. Relapsing alcoholics have been reported to have more desynchronized beta activity over frontal areas than non-relapsers, which suggests a functional disturbance of prefrontal cortex (Winterer et al., 1998).

Several studies also report increased beta power in the EEG of relatives of alcoholics (Gabrielli et al., 1982; Finn and Justus, 1999; Pollock et al., 1995; Rangaswamy et al., 2004a). However, a few studies of the acute effects of

alcohol report an absence of pre-ethanol baseline differences in resting EEG between low- and high-risk subjects (Cohen et al., 1991; Kaplan et al., 1988; Pollock et al., 1983). Gabrielli et al. (1982) demonstrated elevation in beta band in male subjects with a family history of alcoholism. A positive family history for alcoholism along with a diagnosis of antisocial personality (ASP) has been shown to be associated with increased beta power in frontal leads (Bauer and Hesselbrock, 1993). Pollock et al. (1995) reported elevated beta power in family history positive (FHP) when compared to family history negative (FHN) subjects. A later study by Finn and Justus (1999) reported increased relative power in beta band at frontal and occipital locations. In a follow-up of the COGA study of beta power in alcoholics Rangaswamy et al. (2004a) demonstrated increased beta power in the resting EEG of a large sample of offspring of male alcoholics in COGA families. The sample was limited to offspring of male alcoholics to rule out the effects of possible maternal drinking on prenatal development. Male high-risk offspring of alcoholics had elevated slow beta power (12–16 Hz), and female high-risk offspring of alcoholics had increased faster beta power (16–28 Hz) when compared to low-risk offspring of non-alcoholics. Female high-risk offspring also showed significantly increased faster beta power (16–28 Hz) if they had two or more alcoholic first-degree relatives when compared with high-risk females having only an affected father.

Taken together, as the increase in beta power in alcoholics was not related to length of abstinence (Rangaswamy et al., 2002) and was also present in individuals at risk (Rangaswamy et al., 2004a), this suggests that it is not a direct effect of alcohol use, but also may antecede the development of alcoholism. The strong association of a $GABA_A$ receptor gene with the beta frequency band of the EEG coupled with GABAergic deficits observed in the brains of alcoholics and the elevated beta power in the EEG of alcoholics and subjects at risk supports the hypothesis that an imbalance in neural excitation–inhibition homeostasis is involved in a predisposition to develop alcohol dependence (Begleiter and Porjesz, 1999).

Most studies reporting beta band differences in alcoholics and high-risk offspring also underscore the issue of gender in electrophysiological research. In the study on a large sample of alcoholics from the COGA project (Rangaswamy et al., 2002), the male and female alcoholics were also examined separately. A significant elevation was observed in all 3 beta bands in the male subset of the sample. However, beta band power in the female alcoholics was not significantly higher than their respective controls. Gabrielli et al. (1982) attempted to characterize the differences in male and female high-risk subjects separately, and demonstrated elevation in beta band in male subjects only. The lack of differences between females was attributed to a possible ceiling effect in beta power in females. Finn and Justus (1999) reporting increased relative power in beta band at frontal and occipital locations noted no gender differences in the magnitude of increased relative beta power. Bauer and Hesselbrock (1993) reported EEG beta power differences in male high-risk subjects. The finding reported by Pollock et al. (1995) was more robust in male high-risk subjects. The male and female high-risk subjects displayed differential elevation of the 3 beta bands in a study of the offspring of male alcoholics (Rangaswamy et al., 2004a). Existing gender differences in the progression and pathology of alcoholism and spectral properties of EEG highlight the importance of studying risk indicators within the context of gender.

2.4. Alcohol challenge studies and resting EEG

The focus of alcohol challenge studies has been to assess whether naïve offspring of alcoholics who are at high-risk, respond differently to alcohol than offspring of non-alcoholics prior to alcohol exposure; this deviant response could indicate an underlying CNS liability that becomes apparent with exposure to alcohol. Several studies have looked at the EEG in offspring of alcoholics (Family History Positive, FHP) while alcohol was acutely administered to them and compared it to the profile of low-risk individuals who do not have a family history of alcoholism (Family History Negative, FHN). No differences have been reported between the high-risk and low-risk subjects in the uptake and clearance of alcohol in the blood as revealed by the blood alcohol curve (BAC) (for review see Newlin and Thomson, 1990). (For explanation of BAC see Fig. 1.)

The effects of alcohol on the EEG of average risk subjects as determined by spectral analysis methods are well known (Ehlers et al., 1989; Kaplan et al., 1988; Lukas and Mendelson, 1988; Lukas et al., 1986, 1989, 1990; Pollock et al., 1983; Stenberg et al., 1994). The prominent effects of low doses of alcohol are increases in slow alpha activity. Moderate doses of alcohol produce increases in slow alpha, but in addition have the effect of increasing theta activity as well as decreasing beta waves. Lukas et al. (1989) studied the topographic distribution of EEG alpha activity during ethanol-induced intoxication in women and reported pronounced increases in EEG alpha activity. Topographic analysis revealed a high-amplitude, fast alpha activity that extended temporally and further frontally to the central sulcus during ethanol intoxication than during control sessions or after placebo administration. In another study, Lukas et al. (1990) reported marked increases in EEG alpha activity during the ascending limb of the blood ethanol curve following the administration of 0.7 g/kg ethanol.

Pollock et al. (1983) compared EEG results between 31 male offspring of alcoholics and 17 controls, with similar weekly alcohol consumption and mean BAC. Blood alcohol concentration measurements failed to distinguish HR from control subjects, but quantitative measurements of EEG alpha activity differentiated them. The male offspring showed significantly greater increases than controls in slow alpha energy at 30 and 120 min after drinking.

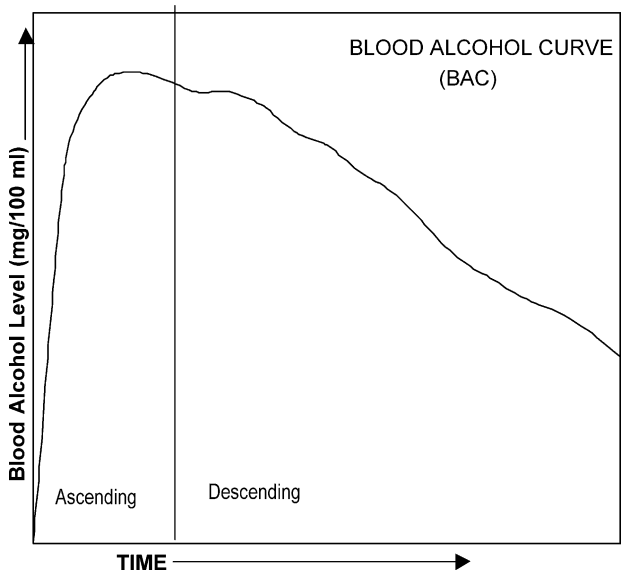

Fig. 1. Schematic illustration of blood alcohol curve (BAC). Increasing blood alcohol level peaks within the first 60 min. Despite no difference in the BAC between high-risk and low-risk individuals, the differentiator model proposes that the high-risk individuals display acute sensitization (enhanced response to alcohol) during the ascending phase of the BAC and demonstrate acute tolerance during the descending phase of the curve. The recovery of electrophysiological measures to baseline levels is also more rapid for the high-risk group during the descending phase. These patterns of responses are seen for several measures, e.g. serum biochemistry, autonomic function, motor responses, electrophysiological measures and subjective responses to ethanol ingestion (Newlin and Thomson, 1990).

The male offspring also exhibited greater decreases of fast alpha energy after alcohol administration than controls; the male offspring also showed greater decreases in mean alpha frequency after alcohol administration and this was localized to right and posterior scalp regions.

Kaplan et al. (1988) studied EEG responses to alcohol in 25 high-risk sons of alcoholics and 25 low-risk subjects. Both groups showed increases in EEG alpha activity (9–12 Hz) following alcohol consumption. This alpha activity was positively associated with desire to drink in the high-risk group before and after consumption, and was positively associated with perceived intoxication in the low-risk group only after consumption.

The EEGs of young adult sons of alcoholics and their matched controls were analyzed to assess activity in the 12–20 Hz (beta) range, after being exposed to ethanol and placebo (Ehlers and Schuckit, 1990). Males with alcoholic fathers displayed significantly more beta activity at 90 min post-ethanol consumption than the males who had no alcoholic relatives. In addition, when subjects were sorted into 'low' and 'moderate' drinkers depending on their drinking practices, within the family history negative subjects, moderate drinkers were found to have significantly more power in the beta frequencies at both baseline and at 90 min post-alcohol than low drinkers. No significant differences were found between moderate and low drinkers within the family history positive population. This study suggests that drinking practices and a familial history for alcoholism can modify the beta content of the EEG in the 12–20 Hz range in young men.

In another study by the same group, Ehlers and Schuckit (1991) analyzed EEG data from 24 sons of alcoholics (FHP) and their matched controls (FHN) before and 90 min following alcohol and placebo challenge. Blind analysis of the data revealed that FHP men had more energy in the fast-frequency alpha range (9–12 Hz) than did FHN subjects at baseline. EEG response to ethanol was also found to differ between the two groups. FHN but not FHP subjects evidenced a decrease in fast-frequency alpha power following ethanol challenge.

Cohen et al. (1993) examined the effects of placebo, low-dose and high-dose ethanol on EEG activity in a group of young adult male offspring of alcoholics and a group of age-matched low-risk males. Ethanol elicited significant power increases in slow alpha (7.5–10 Hz) activity, and this increase was higher for high-risk subjects on the ascending limb of the BAC. Risk group differences in slow alpha activity were observed only at electrodes F3, F4 and P4. These differences were the consequence of differential ethanol effects rather than differences in baseline slow alpha levels.

Ehlers et al. (2004) studied Hispanic and non-Hispanic American young adults with a family history of alcoholism, in order to investigate EEG alpha and response to alcohol. In this study, alcohol was found to produce significant effects on EEG power in the slow alpha frequency range. EEG power in the fast alpha frequency range (9–12 Hz) at baseline was also found to be negatively associated with level of response to alcohol. Although no overall effects of alcohol were found in the fast alpha frequency range, Hispanic participants had decreases in EEG fast alpha activity following alcohol administration, whereas non-Hispanics had alcohol-induced increases in power in this frequency range. These results confirm that increased EEG alpha power at baseline is predictive of a less intense response to alcohol.

One preliminary prospective study (Volavka et al., 1996) examined the EEG of high-risk men after alcohol administration and the development of alcohol use disorders in the same individuals 10 years later. This study showed that in high-risk men, a diminished alpha frequency EEG response to alcohol was related to the development of alcohol dependence 10 years later.

2.5. Summary: EEG in alcoholics and offspring at high risk

In summary, studies that have reported on the resting EEG composition indicate beta band increases as a primary characteristic feature in alcoholics and high-risk subjects, and less significantly theta band increases in the alcoholics. The alpha band differences are, however, not conclusive and remain equivocal. Alcohol challenge studies in high-risk and low-risk subjects uncover a reactive alpha system that

shows strong signs of slowing in terms of the frequency composition. These findings provide a strong lead for examining the neurophysiological and neurochemical bases of these differences. The findings also contribute in defining stronger phenotypes, thus aiding genetic analyses.

2.6. Genetics of EEG

Higher concordance rates in the spectral characteristics of resting eyes-closed EEG have been reported from monozygotic twin pairs compared to dizygotic twin pairs; the largest twin study to date estimates the heritability of spectral theta and alpha to be 0.89 and beta power to be 0.86 (van Beijsterveldt and Boomsma, 1994; van Beijsterveldt et al., 1996). It should be noted that these heritabilities are much higher than the heritabilities of alcohol dependence and other psychiatric diagnoses. EEG coherence has also been reported to be heritable, with estimates between 0.5 and 0.7 (Stassen et al., 1988; van Baal et al., 1998; van Beijsterveldt and Boomsma, 1994; van Beijsterveldt et al., 1998). Although the data on the heritability of EEG frequencies are quite compelling, it is only recently that some genes influencing EEGs have been identified.

There is evidence in the literature that not only do alcoholics manifest differences in EEG power in specific frequency bands, but they also manifest increased inter-hemispheric coherence (Kaplan et al., 1985; Michael et al., 1993). Recently Winterer et al. (2003a) reported increased bilateral intrahemispheric coherences in alpha and beta frequency bands in both long-term abstinent and non-abstinent alcoholics compared to controls. These findings were strongest for the alpha2 (10.5–12 Hz) frequency band, and were most pronounced at temporal, parietal and occipital regions, particularly when depressiveness was included as a covariate; there was no effect of length of abstinence on these findings. The authors conclude that increased EEG coherence (cortical synchronization) may serve as an endophenotype (i.e. biological marker) for alcoholism in conjunction with increased depressiveness, and suggest a possible involvement of GABAergic and/or glutamatergic neurotransmission. In another study, Winterer et al. (2003b) report that 3 exonic variants of the gene encoding the human GABA-B receptor on chromosome 6 modify cortical synchronization measured as scalp-recorded EEG coherence. Parietotemporal coherence showed statistical significance associated with exon 7 and the authors concluded that this exon may be functionally meaningful and impact on cortical EEG oscillations. These authors also report an association between the exon 7 variant of the $GABA_B$ receptor gene and EEG alpha voltage (classified as LVA or normal), for control but not alcoholic subjects (Winterer et al., 2003c). As discussed in Section 2.2, LVA in females has been associated with a genetic variant resulting in low COMT activity, which is involved in the dopaminergic system yielding low levels of norepinephrine (Enoch et al., 2003). The authors hypothesize that this finding may partly explain their observation of low LVA associated with anxiety disorders in alcoholic women.

Fast synaptic inhibition in the mammalian central nervous system is mediated largely by activation of $GABA_A$ receptors (Tobler et al., 2001), while $GABA_B$ receptors mediate slower inhibition (Hayar et al., 1996; Tamas et al., 2003) Beta rhythm involves a balance in networks of excitatory pyramidal cells and inhibitory interneurons involving $GABA_A$ action as the pacemaker (Whittington et al., 2000).

As reported in Section 2.3 of this review, findings from the COGA project have reported genetic linkage and linkage disequilibrium between the beta frequency of the EEG and a $GABA_A$ receptor gene on chromosome 4 (Porjesz et al., 2002a). These findings with brain oscillations led to finding that the same $GABA_A$ receptor gene (*GABRA2*) associated with the beta frequency of the EEG is also associated with a DSM-IV diagnosis of alcohol dependence (Edenberg et al., 2004), a finding that has been replicated in several recent independent studies (Covault et al., 2004; Xu et al., 2004). Neuro-imaging studies indicate deficient GABA benzodiazepine receptors in the brains of alcoholics (Abi-Dargham et al., 1998; Lingford-Hughes et al., 1998) and individuals at risk (Volkow et al., 1995). Dysfunction in $GABA_A$ receptor genes may underlie the imbalance between excitation–inhibition (hyperexcitability) reflected in anomalous brain oscillations, which may be involved in the predisposition to develop alcoholism and other disinhibition disorders. This suggests that variations in the *GABRA2* gene (the gene encoding the $\alpha 2$ subunit of the GABA-A receptor), affects the level of neural excitability, which in turn affects the predisposition to develop alcohol dependence.

Electrophysiological measures (such as EEG beta power) are more heritable and closer to gene action than clinical diagnosis (e.g. alcohol dependence). Genes involved in the expression of the electrophysiological measure may also be involved in the predisposition for the clinical outcome. As indicated in this section, this strategy of using EEG measures as endophenotypes in the search for genes involved in alcoholism has already been successfully implemented. These genetic findings indicate that they provide very promising endophenotypes for future studies that can help in the identification of genes that increase vulnerability for risk in developing alcohol dependence and related disorders. This approach also has the advantage of providing a biological hypothesis of what is involved in the genetic predisposition. This is discussed more fully in Section 6 of this review.

3. Event-related potentials (ERPs)

Event-related potentials (ERPs) are a series of positive and negative voltage deflections in the ongoing EEG that are time-locked to specific sensory, motor or cognitive events.

These electrical potentials are obtained by averaging several EEG epochs and represent the summation of electrical activity of large numbers of neuronal elements acting in synchrony during information processing. Early components, with a latency of less than 100 ms reflect sensory processes, while later components reflect higher cognitive computations. There are numerous reports in the literature that have employed several evoked and event-related potentials (Brain-stem Auditory-evoked potentials [BAEP], sensory gating (P50), Somatosensory-evoked potentials [SSEP], Visual-evoked potentials [VEP], Middle latency response [MLR], Mismatched Negativity [MMN], P300 (P3), N400, etc.) in order to assess chronic and/or acute effects of alcohol. This review is restricted to the examination of those ERP components that have proved most significant in the study of alcoholism.

The ERP task most commonly used to elicit the P3 is the 'oddball' task, in which rare 'oddball' stimuli (targets) are embedded in a series of frequent non-target stimuli (standards). If the subject is asked to attend or respond to the rare target stimulus, the P3s recorded to these task-relevant targets are maximum posteriorly on the scalp (over parietal regions) and are designated as P3b components. If the subject is not asked to attend to the rare stimuli, P3s recorded to these unattended rare stimuli in a repetitive background have a more frontal distribution and are designated as P3a. As most studies have dealt with the P3b component to target stimuli, in this review when unspecified, P3 refers to the P3b component.

3.1. P300 (P3a, P3b)

Most studies investigating electrophysiological deficits in alcoholics and individuals at risk have focused on the large positive P300 or P3 component that occurs between 300 and 700 ms after a 'significant' stimulus and is not related to its physical features. The P3 has been proposed to reflect attentional allocation and context updating processes of working memory (Polich and Herbst, 2000), cognitive closure (Desmedt, 1980; Verleger, 1988) and to involve the activation of inhibitory processes over widespread cortical areas (Birbaumer et al., 1990; Desmedt, 1980; Rockstroh et al., 1992; Tomberg and Desmedt, 1998; Verleger, 1988). The amplitude of P3 is taken to reflect CNS inhibition (the larger the P3, the more the inhibition) (Birbaumer et al., 1990; Desmedt, 1980), while its time of occurrence (latency) reflects mental processing speed (Polich and Herbst, 2000); the earlier and larger the P3, the easier the processing.

3.1.1. P3 deficits in alcoholics

Studies over the last few decades have found that the amplitude of P3 to task-relevant target stimuli (P3b) are of significantly lower voltage in abstinent alcoholics than in non-alcoholics, particularly over parietal regions where they are maximum (for reviews, see Porjesz and Begleiter, 1996, 1998). While this deficit in alcoholics occurs in both auditory and visual tasks, it is more consistent for visual tasks. More recent studies have indicated that low P3 amplitudes are not only present in male alcoholics, but are also apparent in female alcoholics, though not to the same extent as in males (Hill and Steinhauer, 1993a; Porjesz et al., 1996; Prabhu et al., 2001; Suresh et al., 2003). Not only do alcoholics manifest low amplitude P3b components to target (Go) stimuli, they also manifest low frontally distributed P3a components to rare non-target (No-Go) stimuli in both visual and auditory modalities; recent reports have indicated that alcoholics manifest reduced P3 amplitudes to No–Go as well as Go stimuli (Cohen et al., 1997a; Fallgatter et al., 1998; Hada et al., 2000; Kamarajan et al., in press-a; Pfefferbaum et al., 1991; Rodriguez Holguin et al., 1999a). Furthermore, alcoholics manifest less differentiation between their responses to task-relevant target stimuli and task-irrelevant non-target stimuli. In keeping with various neurophysiological explanations of the P3 component (Birbaumer et al., 1990; Desmedt, 1980; Klimesch et al., 2000; Rockstroh et al., 1992; Verleger 1988), low amplitude P3 in alcoholics is suggestive of reduced CNS inhibition. It has been hypothesized that this underlying CNS disinhibition (i.e. hyperexcitablity) is involved in a predisposition to alcoholism (Begleiter and Porjesz, 1999).

3.1.2. P3 in high-risk individuals

The P3 amplitude decrements in alcoholics do not recover with prolonged abstinence (Porjesz and Begleiter, 1985). Hence, examining P3 amplitude in high-risk offspring of alcoholics has helped to determine if the low P3 amplitudes are due to the prolonged effects of alcohol on the brain or antecedent to its development, perhaps indicating an underlying predisposition.

Begleiter et al. (1984) reported that young boys at high risk (HR) of developing alcoholism manifested significantly lower P3 voltages compared with matched low-risk (LR) boys coming from control families without first- or second-degree alcoholic relatives. The results of this study were rather striking because they were obtained without the use of an alcohol challenge or a placebo. These findings have been replicated in most but not all studies under many different experimental conditions, with and without alcohol administration, in both older and younger subjects at risk and has more recently been found in female as well as male offspring (Begleiter et al., 1987; Benegal et al., 1995; Berman et al., 1993; Cohen et al., 1997b; Ehlers et al., 2001, 2003; Hesselbrock et al., 1993; Hill and Steinhauer, 1993b; Hill et al., 1995; O'Connor et al., 1986, 1987; Porjesz and Begleiter, 1990; Ramachandran et al., 1996; Ratsma et al., 2001; Rodriguez Holguin et al., 1999b; Van der Stelt et al., 1998; Whipple et al., 1991). In addition to these findings with P3b, offspring of alcoholics have been reported to manifest low amplitude P3a components in both visual and auditory paradigms (Hada et al., 2001; Rodriguez Holguin et al., 1999b).

Most P3 studies in subjects at risk for alcoholism have focused on males. The results of studies of female offspring of alcoholics have been less consistent. Hill and Steinhauer (1993b) studied P3 responses to visual stimuli in both male and female pre- and post-pubertal offspring of male alcoholics and found that lower P3s were obtained only in prepubescent males, not in females or post-pubescent males. However, in an auditory study, the same group of investigators found that female offspring of female alcoholics manifested lower P3 amplitudes (Hill et al., 1995). Recently, data from the large national COGA study showed lower P3 amplitudes in female offspring of male alcoholics from dense alcoholic families, although not to the same degree as in males (Porjesz et al., 1996, 1998). Offspring of female alcoholics were excluded from the analysis to avoid the possible effects of prenatal alcohol exposure.

A study by Ehlers et al. (2003) of P3 responses to alcohol-related stimuli demonstrated that family history is significantly and selectively associated with lower P3 amplitudes in a group of young adult men and women of African–American heritage. Additionally, current usage of marijuana and alcohol did not modify P3 amplitudes.

In a comprehensive meta-analysis of all published high-risk versus low-risk studies at the time, Polich et al. (1994) found that the strongest P3 group differences were obtained in young male offspring with relatively difficult visual tasks and concluded that low-voltage P3 may have predictive value as an index of vulnerability for alcoholism. Thus, the low-voltage P3 component is a robust finding that characterizes individuals at risk for alcoholism, and perhaps provides a phenotypic 'trait' marker.

In addition, there is evidence that the P3 amplitude recorded during a visual oddball paradigm is directly related to the number of first-degree alcoholic relatives and not the drinking history of an alcoholic (Cohen et al., 1995; Pfefferbaum et al., 1991) or high-risk (HR) individual (Benegal et al., 1995). Furthermore, low P3 amplitude in prepubescence has been found to predict later substance abuse, including alcohol abuse in adolescence (Berman et al., 1993; Hill et al., 1995; Iacono et al., 2002, 2003). P3 amplitude distributions have been examined from the large Collaborative Study on the Genetics of Alcoholism (COGA), which consists of densely affected families with 3 or more first-degree alcoholic relatives and random control families representing population prevalence rates. Comparisons of visual P3 amplitude distributions between COGA family members and members of randomly ascertained control families indicate that low P3 amplitudes are prevalent in affected members of COGA families and their unaffected relatives, and not in control family members, even if they are alcohol-dependent. While affected members of COGA families are more likely to manifest low P3 amplitudes than unaffected members of these densely affected families, unaffected members of COGA families manifest low P3s compared to unaffected members of randomly ascertained control families from the general population. Importantly, P3 amplitudes are more likely to be of low amplitude in male and female offspring of alcohol-dependent males from COGA but not control families (Porjesz et al., 1996, 1998). It is these offspring with low P3 amplitudes from densely affected alcoholic families that are hypothesized to be at greater risk for a predisposition to develop alcohol dependence and related phenotypes.

3.1.3. P3 topography in alcoholics and individuals at high risk

While control subjects manifest maximum P3b amplitudes over parietal (posterior) regions of the scalp, and anterior maximum P3as to rare non-targets, alcoholics manifest similar amplitudes across all areas (Hada et al., 2000; Jones et al., in preparation; Kamarajan et al., in press-a; Rodriguez Holguin, et al., 1999a). In a recent paper by Kamarajan et al. (in press-a), it was found that the difference between Go and No-Go processing was more evident in controls than in alcoholics. The topography of current source density in alcoholics during the P3 response was found to be very different from that of controls, suggesting that alcoholics perhaps activated atypical brain circuitry during cognitive processing. The significantly reduced No-Go P3 along with the relatively less anteriorized current source density topography during No-Go condition suggests poor inhibitory control in alcoholics. Topographic map comparisons of P3 between alcoholics and controls and high-risk individuals and controls indicate weaker sources and less topographic specificity in alcoholics and high risk for both the visual and auditory modality (Hada et al., 2000, 2001; Kamarajan et al., in press-b; Rodriguez Holguin et al., 1999a,b).

Despite its maximal amplitude over parietal areas at the scalp, studies with depth electrodes in humans indicate the neural origins of P3 involve frontal cortex as well as the amygdala and hippocampus (Baudena et al., 1995; Brazdil et al., 1999; Halgren et al., 1995a,b; McCarthy et al., 1989). More recent functional magnetic resonance (fMRI) studies support these findings and implicate the anterior cingulate area of the frontal cortex as critical for P3 generation (Ardekani et al., 2002; Kiehl and Liddle, 2001; Menon et al., 1997). The lower amplitude P3 components coupled with the weaker and less well-organized sources in alcoholics suggest inefficient allocation of resources during neural processing. This global neurophysiological pattern suggests cortical disinhibition, providing further support for underlying CNS hyperexcitability in alcoholics and individuals at risk.

In order to determine whether there were underlying neuroanatomical deficits underlying the reduced P3 components observed in high-risk offspring of alcoholics, a functional MRI study was undertaken during the performance of a visual oddball task (Rangaswamy et al., 2004b). The high-risk subjects were male offspring of male alcoholics who had low P3 components, and the low-risk

subjects were male offspring of non-alcoholics who had high P3 components. Target counts showed that all subjects performed the task comparably. Analysis revealed two areas with significantly greater activation in the low-risk group when compared to the high-risk group: the bilateral inferior parietal lobule, and the bilateral inferior frontal gyrus. The inferior parietal lobule showed significantly lower activation in the high-risk group in contrast to the low-risk group and the inferior frontal gyrus was only activated in the low-risk group but not in the high-risk group. This finding indicates that a dysfunctional frontoparietal circuit underlies the low P3 responses in high-risk subjects. It also implies less than optimal functioning of the working memory system in the high-risk individuals.

3.1.4. Effects of alcohol challenge on P3 characteristics

Over the last 30 years, the effects of alcohol on normal brain function have been investigated in a number of studies (for review see Porjesz and Begleiter, 1985) These studies indicate that alcohol has a greater reducing effect on P3a amplitudes to unattended rare stimuli than to P3b amplitudes to attended stimuli. More recently, similar decreases in P3a following a low dose of alcohol have been reported by Marinkovic et al. (2001). Alcohol has a major effect on P3 latencies, particularly during the descending limb of the blood alcohol curve in normal individuals.

Differences in P3b characteristics have been observed between subjects at high and low risk (LR) for alcoholism after administration of alcohol. Significant P3 amplitude decreases in HR subjects as compared with LR subjects were reported after both alcohol and placebo ingestion by Elmasian et al. (1982) in San Diego; they explained their results in terms of differential expectancies for alcohol characterized by different brain events. This group of investigators did not replicate the initial placebo effect in a later study. Schuckit et al. (1988) reported that P3 latency delays returned to baseline values more rapidly in FHP men than in FHN men after a high dose of ethanol (1.1 ml/kg). In a study in our laboratory, sons of alcoholic fathers manifested reduced P3 component amplitudes and normal N1 amplitudes and P3 latencies before alcohol ingestion (Porjesz and Begleiter, 1990, 1996). The significantly lower P3 amplitude in high-risk subjects at baseline was larger than any alcohol effect on P3 amplitude. The high dose of alcohol significantly increased the latency of P3 to a difficult target in both groups of subjects, maximally between 60 and 90 min post-ethanol; namely, at peak and early descending blood alcohol levels. Although the HR and LR groups did not differ significantly in terms of initial alcohol-induced P3 latency delays, the HR group tended to recover more quickly to pre-alcohol ranges. However, they remained delayed in the LR group throughout the study (130 min post-alcohol). This replicates the findings of Schuckit et al. (1988), who reported that family history positive males recover more quickly from P3 latency delays induced by alcohol. While alcohol significantly reduced N1 amplitude in both groups, HR subjects exhibited a quicker recovery of N1 amplitudes after alcohol intake than LR subjects. Similar findings have been reported by Cohen et al. (1998) for auditory N1 and P2; these authors also report greater sensitization of P2 on the ascending limb of the BAC and faster recovery to baseline on the descending limb for both N1 and P2, in keeping with the differentiator model of Newlin and Thomson (1990). Taken together, these findings suggest that some electrophysiologic differences between HR and LR individuals are apparent only in response to ethanol challenges, possibly representing sensitization and tolerance in the HR subjects that may be innate.

One of the fundamental questions related to the presence of low-voltage P3 in high-risk individuals concerns the potential effect of alcohol in subjects with low P3 at baseline; these are the subjects who are presumably at risk. In a study on the determinants of P3 amplitude and response to alcohol in Native American Mission Indians, Ehlers et al. (1998) noted that a low P3 during a placebo condition was predictive of less reduction or an actual increase in P3 amplitude after alcohol challenge.

3.1.5. Summary: P3 in alcoholics and offspring at high risk

In summary, one of the most consistent robust findings in the literature is the reduced P3 amplitude in alcoholics and in offspring at risk prior to alcohol exposure The lower amplitude P3 components coupled with the weaker and less well-organized sources in alcoholics and offspring at risk suggest inefficient allocation of resources during neural processing. This global neurophysiological pattern suggests cortical disinhibition, suggesting underlying CNS hyperexcitability in alcoholics and individuals at risk; this underlying CNS disinhibiton may be involved in the genetic predisposition toward the development of alcohol dependence and related disorders. Thus, the P3 amplitude can be taken as a marker of risk and provides excellent endophenotype for genetic studies.

3.1.6. Genetic studies of P3

Twin studies indicate that the P3 component of the ERP is heritable: heritabilities range between 0.49 and 0.60 at posterior leads (Katsanis et al., 1997; O'Connor et al., 1994; Van Beijsterveldt, 1996). Data from COGA report comparable heritabilities for visual P3 using a family study approach in control families (Daw et al., 1995) and in COGA families (Almasy et al., 1999); higher heritabilities are reported for P3 amplitudes to target compared to nontarget stimuli, and for visual compared to auditory stimuli. Heritability estimates ranged between 0.43 and 0.54 for visual posterior leads and between 0.27 and 0.40 for auditory leads where the highest heritabilities were at central/frontal scalp locations. In COGA, significant linkage on several chromosomes to visual target stimuli in a visual oddball paradigm have been reported (chromosomes 2, 5, 6, 13, 17) (Begleiter et al., 1998; Porjesz et al., 2002b). Significant linkage to P3 has also been obtained in

a semantic priming task (chromosomes 4 and 5) (Almasy et al., 2001).

In order to determine whether the same genetic loci that influence P3 also influence alcohol dependence, COGA applied a bivariate analysis that jointly considers both the disease status (alcohol dependence, using a threshold model) and the quantitative trait (P3 amplitude) (Williams et al., 1999). This method can determine whether genetic correlations between P3 amplitude and alcoholism diagnosis stem from shared genetic influences. Indeed, P3 amplitude at all leads (strongest at central and temporal leads and weakest at occipital leads) showed negative genetic correlations with alcohol dependence, indicating pleiotropic loci that reduce P3 amplitude and increase heritability of the disease. A chromosome 4 region near the aldehyde dehydrogenase gene (ADH) strongly influenced liability to alcoholism with evidence for pleiotropic effects on P3. This ADH region of chromosome 4 has been found to be related to protective factors in alcoholism in Asian populations (Crabb et al., 1995; Edenberg and Bosron, 1997). Alleles at ADH2 and ADH3 on chromosome 4 encode isozymes that metabolize alcohol to acetaldehyde at a high rate, resulting in acetaldehyde accumulations that cause an aversive flushing reaction, thus reducing the risk of alcohol intake and hence alcohol dependence. Evidence from the COGA project found that linkage to the ADH region on chromosome 4 was related to the unaffected status (Reich et al., 1998) and also to maximum number of drinks an individual consumes in 24 h (Saccone et al., 2000). Taken together, these findings suggest that individuals with high P3 amplitudes in these alcoholic families are 'protected' against developing alcohol dependence; these findings underscore the importance of protective genes as well as susceptibility genes in determining psychiatric disease outcomes. As will be seen in Section 5, one approach that has successfully been used to study the genetics of P3 is to study the genetics of the EROs that underlie P3 (Jones et al., 2004). Thus, as will be discussed in Section 6, while the P3 may be of limited clinical use, its utility as an endophenotype for the study of the genetic risk of disinhibitory disorders, including alcoholism, is very promising.

3.2. Other ERP components

There are a few other ERP measures that differentiate the alcoholic population from non-alcoholic controls. However, they are not indicative of the vulnerability to alcoholism but tend to define the neural substrates that are vulnerable to alcohol. These measures address issues of chronicity. Only measures with a substantial literature are discussed.

3.2.1. Brain-stem auditory-evoked potential (BAEP)

BAEPs are a set of 7 positive waves recorded from the scalp in the first 10–12 ms as time-locked responses to rapid auditory click stimuli. They represent far field potentials that originate from the auditory pathway relay centers in the brain-stem (Jewett et al., 1970). The latencies of these peaks as well as their inter-peak conduction velocities are informative in localizing pathology from the eighth nerve to the brain-stem.

Studies have shown data for alcoholics were significantly more variable than that of controls (Spitzer and Newman, 1987). Studies have demonstrated significantly delayed latencies of peaks II–V in non-neurologically impaired alcoholic patients compared to control subjects (Begleiter et al., 1981; Cassvan et al., 1984), as well as in neurologically impaired alcoholics (for review see Porjesz and Begleiter, 1993). Alcoholics have been reported to manifest a delayed SAEP peak V and an increase in the III–V and I–V interval (Cadaveira et al., 1991; Diaz et al., 1990); a significant prolongation in the latencies of BAEP peaks III–VI and inter-peaks I–III, III–V, and I–V, in alcoholics (Chu and Yang, 1987). In the same study, the peak latency prolongation was associated with a reduction in all peak amplitudes, indicating that chronic alcoholics have subclinical dysfunction in the brain-stem auditory pathways irrespective of the complications of alcoholic liver disease. Brain-stem auditory-evoked responses (BAERs) were studied in alcoholic patients, including those with Wernicke–Korsakoff syndrome (Chan et al., 1985). The mean value of the I–V interval was prolonged in all patient groups. There were more patients with prolonged I–V and I–III intervals in the Wernicke–Korsakoff syndrome group than in the group without the syndrome. These abnormalities improved following thiamine treatment and abstinence from alcohol. Other authors have also shown the recovery of BAEP deficits on prolonged abstinence (Cadaveira et al., 1994; Fichtel et al., 1989). In a study that examined both BAEP and P3 amplitude in alcoholics in a long-term treatment program, delayed BAEPs recovered following 3–4 months of abstinence while P3 amplitudes remained significantly decreased (Porjesz and Begleiter, 1985). In another study, sons of alcoholics (7–13) were compared to a matched group of sons of non-alcoholics with no first- or second-degree alcoholic relatives; no differences in BAEPs were found between groups (Porjesz and Begleiter, 1996). Taken together, the findings with BAEP seem to reflect effects of the consequences of alcohol intake on the brain that do recover with prolonged abstinence.

3.2.2. Mismatch negativity (MMN)

An event-related brain potential (ERP) response called the mismatch negativity (MMN) is elicited by infrequent ('deviant') sounds occurring in a sequence of repetitive ('standard') sounds, particularly in the absence of attention to these sounds. MMN appears to be caused by a neuronal mismatch between the deviant auditory input and a sensory memory trace representing the standard stimuli. This automatic mismatch process is a preattentive process and is an objective measure of auditory discrimination and sensory memory (Näätänen, 1990).

Larger MMN amplitudes have been reported in recently detoxified alcoholics (Kathmann et al., 1995). The automatic stimulus-change detector mechanism associated with MMN generation is impaired in chronic alcoholics over the age of 40, suggesting that the neurotoxic effects of chronic consumption of alcohol are more prone to appear after a critical age (Polo et al., 1999). Pekkonen et al. (1998) observed that increasing durations of abstinence reduced the MMN amplitude. Ahveninen et al. (2000) found significantly enhanced mismatch negativity (MMN) amplitude to deviant sounds that correlated with reaction time lag caused by deviants, indicating pronounced distractibility and impaired reorienting to the relevant task in the alcoholics. The MMN enhancement also predicted poorer hit rates in the alcoholics. Both the MMN enhancement and reaction time lag correlated with an early onset of alcoholism. The study suggested that impaired neural inhibition of involuntary attention shifting is more pronounced in early-onset alcoholics. Grau et al. (2001) found that while the MMN component was not different between chronic alcoholics and controls for short memory probe intervals the MMN was absent in alcoholics, unlike the controls, when the interval was long.

MMN was investigated in the young adult HR offspring (19–30-year-olds) of alcohol-dependent fathers and a low-risk (LR) control group (Zhang et al., 2001). MMN responses in the HR group were significantly larger than those in the LR group. However, studies in younger high-risk subjects found no group differences in the MMN amplitude, in 9–18-year-olds (van der Stelt et al., 1997), and in 8–15-year-olds (Rodriguez Holguin et al., 1998). Most recently, a study reported no MMN differences between controls and alcoholics who were abstinent for an average of 6 years (Fein et al., 2004). In summary, the MMN component appears to be particularly sensitive to the state-related conditions rather than a predisposition to developing alcoholism.

4. Event-related oscillations (ERO)

There is evidence in the literature to suggest that many ERPs are not unitary phenomena, but represent averaged electrical neural activity that emanate from multiple sources in the brain, and consist of superimposed event-related oscillations (EROs) of different spectral EEG bands that are temporally related to sensory and cognitive processing (Basar et al., 1999). While this approach is still in its infancy, it is more established and useful with regard to the P3 component, where it enables the teasing apart of theta and delta contributions, both in terms of spatio-temporal distributions and functions. However, it should be noted that possibly not all ERPs can be viewed as EROs. Nevertheless, there is a substantial literature which suggests that some ERP features arise from oscillatory changes due to sensory or cognitive processes which influence the dynamics of ongoing EEG rhythms of different frequency bands (Basar-Eroglu and Basar, 1991; Basar-Eroglu et al., 2001; Demilrap et al., 2001; Karakas et al., 2000a,b; Schurmann et al., 1995, 2001; Yordanova and Kolev, 1996). On sensory stimulation, random resting EEG oscillations become amplified and coupled, and this synchronization and enhancement of EEG activity gives rise to an 'evoked' (phase-locked) or 'induced' (non-phase-locked) rhythmicity. In contrast to the ongoing EEG rhythms, it is thought that the EROs arise in part from a process-related 'partial-phase resetting' occurring in different EEG frequency bands in response to sensory or cognitive stimulation (e.g. Basar, 1980; Makeig et al., 2002). This rhythmicity may also occur in the absence of defined physical stimulation, triggered internally by cognitive operations. Thus in addition to sensory processing, these oscillations provide links to associative and integrative brain functions. Specific frequency rhythms of oscillatory responses have been attributed to underlie various cognitive processes, as follows: delta, signal detection and decision-making (Basar et al., 1999; Schurmann et al., 2001); theta, conscious awareness, recognition memory, and episodic retrieval (e.g. Basar et al., 2001c; Doppelmayr et al., 1998; Gevins et al., 1998; Klimesch et al., 1994, 2001); slow alpha, attribution of attentional resources (Basar et al., 1997; Klimesch, 1997; Klimesch et al., 1998); fast alpha, semantic memory and stimulus processing (e.g. Klimesch et al., 1994, 1997a,b); beta and gamma, sensory integrative processes (e.g. Basar et al., 2001a,b; Basar-Eroglu et al., 1996a,b; Schurmann et al., 1997).

While the EROs may be partitioned into the same frequency bands as spontaneous resting EEG (e.g. delta, theta, alpha, beta, gamma) they are functionally different from spontaneous resting EEG rhythms. Local resonances reflect sensory synchronization (i.e. feature binding in the visual cortex) between macrocolumns and produce very high frequency oscillations, above 30 Hz (gamma). Regional resonances reflect multimodal synchronization (e.g. between adjacent temporal and parietal cortex) between macrocolumns, several centimeters apart (beta and alpha). Global resonance reflect synchronization between widely separated areas (theta and delta); for example, frontal and parietal interactions during working memory (top-down processing) (Lubar, 1997). Hence, as the synchronization of the neural activity becomes more global, the ERO frequency becomes slower (von Stein and Sarnthein, 2000). Different scales of cortical integration require different frequencies. Faster frequencies lose synchronization over longer distances (Kopell et al., 2000).

4.1. Gamma during visual oddball paradigm

The early phase-locked gamma has been considered to represent an important processing step related to the selection and identification of target stimuli, indicative of a top-down mechanism involved in selective attention

(Fell et al., 2003). This phase-locked gamma is larger to attended compared to unattended stimuli, particularly over frontal regions (Basar et al., 1999; Yordanova et al., 2001). Neuro-imaging studies using attentional tasks have implicated the role of fronto-parietal networks in this top-down control of selective attention (Corbetta et al., 2000; Giesbrecht et al., 2003).

Padmanabhapillai et al. (submitted) have recently found that abstinent alcoholics manifest significantly less early (1–150 ms) gamma band response (28–45 Hz) in the frontal region during target processing in a visual oddball task than controls (Fig. 2). Control subjects had significantly more gamma while processing the target when compared to the processing of the non-target stimulus. However, the alcoholics had an opposite profile, eliciting more gamma band response to the non-target than to the target stimuli. It is suggested that the reduction in early evoked frontal gamma band response to targets may be associated with frontal lobe dysfunction associated with a deficient top-down processing mechanism in alcoholics.

Early phase-locked gamma band activity in the children of alcoholics was investigated using the same visual oddball task (Padmanabhapillai et al., submitted). Subjects comprised 68 children of alcoholics from COGA families who had at least one alcoholic parent, and 27 children of non-alcoholics from control families, with an age range of 14–17. Higher gamma band response was observed in the frontal region for the target stimuli in both groups. The results indicated that the COGA offspring of alcoholics had significantly lower gamma activity than control offspring of non-alcoholics, mainly in the parietal regions for the target condition (Fig. 2). Additionally, the offspring of alcoholics showed less differentiation between target and non-target stimuli in the parietal region compared to controls, indicating difficulty in early stimulus processing, probably due to a dysfunctional frontoparietal attentional network. This similar gamma profile in alcoholics and offspring of alcoholics suggests that the gamma deficit possibly antecedes the development of alcoholism.

4.2. Theta and delta bands underlying P3

Several studies have demonstrated that P3 responses are primarily the outcome of theta and delta oscillations elicited during cognitive processing of stimuli (Anokhin et al., 2001; Basar et al., 1999; Basar-Eroglu et al., 1992; Karakas et al., 2000a,b; Yordanova and Kolev, 1996), with delta oscillations more concentrated in the posterior region, while theta is more centered in the fronto-central region (Karakas et al., 2000b); theta oscillations also contribute strongly to N2 components. As mentioned earlier in this review, P3 has multiple sources, with contributions from frontal cortex (including anterior cingulate) and hippocampus (Ardekani et al., 2002; Halgren et al., 1980; Kiehl and Liddle, 2001; Menon et al., 1997). Reciprocal synchronization has been observed in the theta range between hippocampus and frontal and parietal regions in the brain during attentional tasks (von Stein and Sarnthein, 2000).

In a visual oddball paradigm, alcoholics manifest significantly less evoked theta and delta ERO amplitudes while processing the target stimuli (Jones et al., in preparation; Porjesz and Begleiter, 2003); these findings are most significant anteriorly for theta, and posteriorly for delta (see Fig. 3).

In order to determine whether these deficits in theta and delta oscillations antecede the development of alcoholism we examined high-risk children of alcoholics using the same paradigm (Rangaswamy et al., in preparation). The two groups in the study comprised 103 children of alcoholics from COGA families (58 males and 45 females) and 50 normal children from control families (23 males and 27 females) in the age range of 14–17 years. These results show that the 14–17 year-old children of alcoholics have reduced delta and theta band ERO amplitude (underlying P3) while processing the target stimuli compared to controls. The differences were most prominent centro-parietally for theta, and parietally for delta. Interestingly, the EROs were superior to P3 amplitude in differentiating between high-risk and low-risk offspring. Similar to the observations from P3 studies, the results of these two studies indicate that decreased theta and delta EROs to target stimuli may antecede the development of alcoholism and represent a strong trait marker.

In another recent study, delta and theta EROs were investigated using a Go/No-Go paradigm in abstinent alcohol-dependent individuals (Kamarajan et al., 2004). A significant reduction in delta and theta band ERO amplitude was observed in the frontal region of alcoholics, particularly during No-Go processing. In order to verify whether the reduced delta and theta activity were due to the neurotoxic effects of the chronic use of alcohol, or due to an inherent predisposition, these measures were compared between 50 offspring of alcoholics and matched normal controls (Kamarajan et al., in preparation). It was found that the offspring of alcoholics showed a significant reduction in delta and theta bands, suggesting that these oscillatory responses may antecede the development of alcoholism.

4.3. Alcohol challenge and EROs

There is no study that examines the effect of alcohol on the event-related oscillations in high-risk individuals and very few studies that have examined EROs in normal subjects. Laukka et al. (1997) found that alcohol significantly increased theta activity in subjects who were engaged in performing an attentional motor task of simulated automobile driving. Jaaskelainen et al. (2000) investigated the dose-related impact of alcohol on auditory transient-evoked 40-Hz responses during a selective attention task. They found that higher doses of alcohol significantly suppressed the early evoked gamma responses in both attended and non-attended conditions. As gamma band

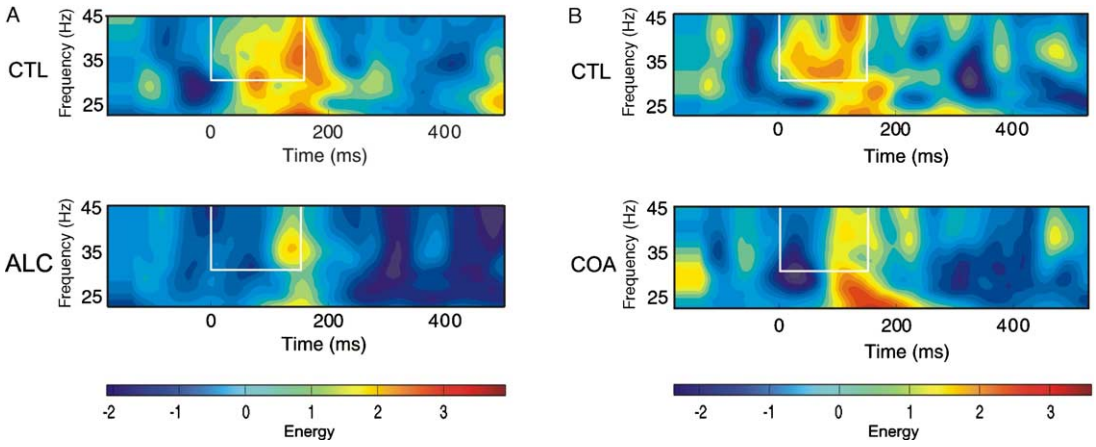

Fig. 2. Time–frequency distribution of evoked gamma band response (29–45 Hz) of visual oddball target case data using the S-Transform method, for (A) controls (CTL) and alcoholics (ALC) at F3 electrode, (B) controls (CTL) and children of alcoholics (COA) at Pz electrode. The time–frequency region of interest (TFROI) window used for analysis was 0–150 ms (white square). The figures shown above were obtained by calculating *Z*-scores within individual frequencies across the two groups of subjects in each section (A and B) separately. Significant reduction in early evoked gamma band response in alcoholics and high-risk subjects, for target stimuli during a visual oddball task are shown.

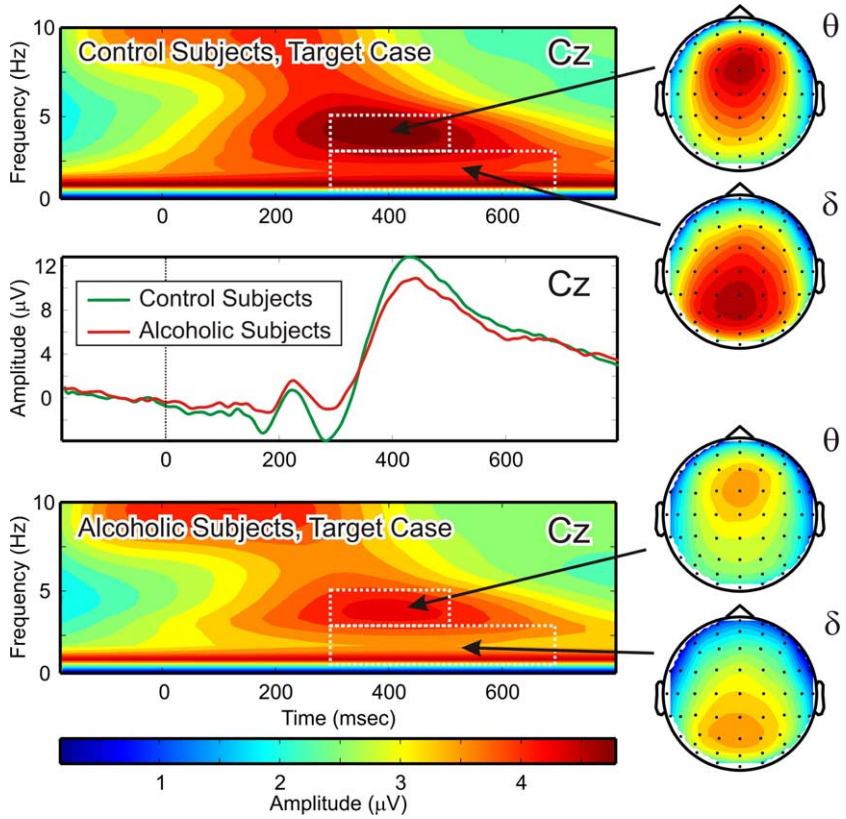

Fig. 3. Time–frequency representation of visual oddball target case data for age-matched control and alcoholic diagnosed male subjects (120 controls and 120 alcoholics with mean age of 29.7 ± 4.9 years) derived using the S-transform (Stockwell et al., 1996). The central plot depicts the traditional grand-mean evoked response to the target stimulus (Cz electrode) for the control (green curve) and alcoholic subjects (red curve). The upper plot displays a time–frequency representation of the average instantaneous amplitude for the control subject data; for each subject the instantaneous amplitudes were averaged across individual trials so that non-phase-locked or imprecise phase-locked oscillatory energy is preserved. The lower plot is a similar representation of the alcoholic subject data. Within each subject mean-value ERO amplitude data are extracted using time–frequency regions of interest (TFROI) and are shown plotted in the head plots at the corresponding channel locations. For the delta band (1–3 Hz) we use a 300–700 ms post-stimulus time window; for the lower theta band (4–5 Hz) we use a 300–500 ms post-stimulus time window. A statistical comparison of alcoholic and control subject mean-valued ERO amplitude data, using age as a covariate, indicates that control subjects having significantly higher instantaneous amplitude than alcoholic subjects: CPz channel, delta, $P < 0.00001$; FCz channel, lower theta, $P < 0.0001$ (for interpretation of the reference to colour in this legend, the reader is referred to the web version of this article).

responses have been associated with several cognitive functions, the authors concluded that this result indicates an alcohol-induced cognitive deficit. This study demonstrated that cognitive processing associated with gamma band activity is affected by alcohol administration. Krause et al. (2002) examined the effects of alcohol on EEG 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 in the 4–6, 6–8, and 8–10 Hz frequency bands. This indicates that alcohol has disorganizing effects on brain electric oscillatory systems in the theta and lower alpha frequency range during cognitive processing.

4.4. Summary: EROs

In summary, studies of event-related oscillations during visual oddball paradigms as well as Go No-Go paradigms indicate that gamma, theta and delta energy are 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. These markers of risk provide excellent endophenotypes that have been successfully implemented in genetic studies.

4.5. Genetic studies of theta and delta EROs

It is proposed that the genetic underpinnings of evoked oscillations are likely to stem from regulatory genes which control the neurochemical processes of the brain, and therefore influence neural function. Jones et al. (2004) examined the ERO mean energy for the P3 time window (300–700 ms), across the delta and theta frequency bands. These energy estimates were averaged across 3 scalp regions (frontal, central, and parietal) and were derived separately for targets and non-targets. A genome-wide linkage scan of the theta band data revealed significant linkage (LOD 3.5) on chromosome 7 at 171 cM with the frontal group of electrodes for the target stimulus; the central and parietal electrode groups showed weaker but suggestive linkage with the same feature. A cholinergic muscarinic receptor gene, *CHRM2*, is near this locus and is the most likely candidate to account for these linkage findings. Significant linkage disequilibrium (LD) was found between the theta phenotype at frontal and central regions and single nucleotide polymorphisms (SNPs) more upstream in the regulatory regions of the gene. The delta band power included in the P3 component showed weak linkage signals at the same *CHRM2* gene location. Highly significant LD was found between the target case delta from central and parietal regions and SNPs throughout the gene, strongest directly flanking the coding region. Significant linkage and LD were only obtained for the target and not non-target case, suggesting a functional significance associated with cognitive processing of the target case in the visual oddball paradigm for the *CHRM2* gene.

These findings implicate the possible role of *CHRM2* in the generation and modulation of evoked oscillations. Muscarinic receptors influence many effects of acetylcholine in the central and peripheral nervous system and hence are expected to have a direct influence on P3 generation (Frodl-Bauch et al., 1999). Moreover, the cholinergic muscarinic genes have a major role in memory and cognition (Calabresi et al., 1998; Comings et al., 2003). The results strongly support the role of acetylcholine in the generation of N2 (theta oscillations) and in the P3 component (delta and theta oscillations). The function of acetylcholine has been demonstrated with regard to stimulus significance (Perry et al., 1999), selective attention (Mitrofanis and Guillery, 1993) and P3 generation (Callaway, 1983). Administration of cholinergic agonists and antagonists have yielded modified memory performance, and modified P3 amplitude in humans (Dierks et al., 1994; Hammond et al., 1987; Potter et al., 2000). 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 that carbachol-induced delta rhythms were not observed concurrent with carbachol-theta (Fellous and Sejnowski, 2000; Tiesinga et al., 2001).

Recent evidence from the COGA project indicates that the *CHRM2* gene is not only related to the EROs associated with P3, but also clinical diagnosis. Significant linkage and association were reported for the *CHRM2* gene with a diagnosis of alcohol dependence and depression (Wang et al., 2004). Thus genes important for the expression of the endophenotype (brain oscillations) help in identification of genes that increase the susceptibility for risk of alcohol dependence and related disorders.

5. Important considerations

5.1. Methodological issues

It should be noted that there are numerous methodological differences across studies that must be considered when attempting to draw conclusions. There are technical differences in experimental paradigms, standards, data processing methods and criteria used across studies, e.g. the implementation of different experimental conditions, such as task difficulty, modality, type of stimulus used, etc. Similarly, differences in ascertainment and clinical assessment methods and criteria of diagnosis are used in various studies. Yet despite these differences, there are common

trends that emerge in the literature, and we have focused on these, rather than on differences between studies.

5.2. Frontal lobe dysfunction in predisposition to alcoholism

Frontal lobe pathology in alcoholism has been well documented at the neurophysiological, morphological and neuropsychological levels (for a review, see Moselhy et al., 2001). The children of alcoholics also exhibit a wide range of frontal lobe-related neuropsychological dysfunction which includes attentional and visuospatial tasks (Corral et al., 1999; Knop et al., 1993; Peterson et al., 1992; Tarter et al., 1989). Further, frontal executive deficits in high-risk individuals have been reported to be involved in the predisposition to alcohol/drug dependence and aggressive behavior (Giancola et al., 1996a,b). This pattern of functional deficits (executive function, visuospatial ability, gait and balance) implicates at least two neural systems involving frontal cortices: cerebellar-frontal system and cortico-cortical system between prefrontal and parietal cortices (Sullivan et al., 2000).

Moderate neuronal loss has been reported in the frontal cortex and in the cingulate gyrus of alcoholic subjects (Kril and Harper, 1989). A recent functional magnetic imaging (fMRI) study (Pfefferbaum et al., 2001) implicates a reorganization of frontal systems in alcoholics. Positron emission tomography (PET) studies report a decrease in glucose consumption selectively affecting the medial part of both frontal lobes, including the anterior cingulate gyrus, suggesting that a 'fronto-limbic' hypometabolism may contribute significantly to the perseverance of chronic alcohol intake (Adams et al., 1993; Dao-Castellana et al., 1998; Gilman et al., 1996). Single photon emission computerized tomography (SPECT) studies showed a decrease of regional cerebral blood flow in the right anterior cingulate (O'Carroll et al., 1991), left inferior frontal (Gansler et al., 2000) and anterior frontal lobes, often combined with global cortical hypometabolism (Volkow et al., 1992, 1994; Wang et al., 1993). The decreased frontal metabolism was associated with specific neuropsychological deficits (Adams et al., 1993; Gansler et al., 2000; Gilman et al., 1996; Wang et al., 1993).

In a recent PET study, Volkow et al. (2003) find that high-risk offspring of alcoholics have decreased activity in the orbitofrontal cortex compared to low-risk subjects; interestingly, some of the high-risk subjects had high levels of dopamine D2 receptors in the ventral striatum, perhaps indicating protective factors in these subjects. In an earlier pharmacological challenge study using PET, these authors also implicated cerebellar function in the sensitivity to alcohol and benzodiazepines in high-risk subjects (Volkow et al., 1995), suggesting that the cerbellar-frontal system may be impaired. As indicated above (Section 3.1.3), a recent fMRI study of a visual P3 paradigm comparing HR and LR subjects indicated that inferior parietal lobule showed significantly lower activation in the high-risk group and inferior frontal gyrus was only activated in the low risk but not high-risk group (Rangaswamy et al., 2004b). This finding suggests that a dysfunctional frontoparietal circuit may underlie the low P300 responses seen in high-risk subjects. These imaging studies strongly suggest that the frontal lobes and their connections with limbic and other cortical regions are compromised even in the subjects who are at risk for developing alcoholism and it is possible that these may be the structural bases of the electrophysiological indices of predisposition to alcoholism.

5.3. Imbalance in excitation–inhibition (CNS disinhibition) in predisposition to alcoholism and related disorders

Slow EEG oscillations (delta and theta) depend on level of muscarinic activation; the level of acetylcholine in the cortex and hippocampus is reduced during delta oscillations and elevated during theta activity. Experiments in vitro rat brain slices indicate that low acetylcholine concentration promotes slow rhythms, while higher concentration may allow faster rhythmic activity to develop by blocking after-hyperpolarizations (Fellous and Sejnowski, 2000). These authors report that production of theta and delta rhythms also involve strong GABAergic/cholinergic interaction. The frequency of theta is controlled by GABAergic inputs from the septum, while its power is controlled by septal cholinergic afferents (Tiesinga et al., 2001). Indeed, the frequency of neural oscillations is determined by $GABA_A$ receptor action (Whittington et al., 2000). Beta oscillations involve the balance between networks of excitatory pyramidal cells and inhibitory interneurons with $GABA_A$ action as the pacemaker.

Several neuro-imaging studies have shown specific deficits in $GABA_A$ receptors in the brains alcoholics, and this reduced GABA may underlie the deficient CNS inhibition in alcoholics. The recent finding that the same $GABA_A$ receptor gene (*GABRA2*) associated with the EEG beta frequency is also associated with diagnosis of alcohol dependence (Edenberg et al., 2004) suggests that variations in this gene affect the level of neural excitability, thus affecting the predisposition to develop alcohol dependence.

In contrast to the control subjects, who manifest differentially enhanced theta, delta and gamma oscillations as well as P3 components to the target compared to the non-target or novel stimuli in the visual oddball task, alcoholics and offspring at risk manifest less electrophysiological differentiation among the 3 stimulus categories. Furthermore, alcoholics and individuals at risk manifest increased resting oscillations (e.g. theta, beta) and decreased 'active' oscillations in the same frequency bands during cognitive tasks. Recent ERO findings indicate that alcoholics and offspring at risk manifest decreased theta and delta oscillations to both Go and No-Go stimuli in a Go/No-Go task. Topographic maps of P3 and corresponding EROs during target processing indicate that not only do alcoholics

and high-risk offspring manifest weaker sources, but they have less topographically distinct spatial–temporal patterns. This less differentiated mode of responding under various task conditions indicates that alcoholics and their offspring are less able to efficiently utilize available information (e.g. template in working memory) to respond differentially to incoming stimuli (targets, non-targets); hence each incoming stimulus must be evaluated anew. In healthy individuals, familiar stimuli are processed with less neuronal activity than unfamiliar stimuli. The undifferentiated and global mode of responding in alcoholics and individuals at risk regardless of stimulus and task requirements indicates a basic diminution of differential inhibition. Evidence from monkey studies indicates there is less neuronal firing to repeated stimuli, suggesting inhibition of masses of neurons (Miller et al., 1991), leading to increased synaptic efficiency. Differential inhibition facilitates the efficient processing of a given stimulus (e.g. target). Hence reduced differential neuronal inhibition to relevant and irrelevant stimuli in alcoholics may account for the electrophysiological aberrations observed in alcoholics.

Taken together, the findings strongly suggest an involvement of CNS disinhibition or hyperexcitability in the predisposition to develop alcoholism and related disinhibitory disorders (impulsivity). Recent evidence indicates that alcoholism is but one manifestation of a class of disinhibitory syndromes including conduct disorder, child and adult antisocial behavior, impulsive traits, and drug dependence, with the same underlying risk factors (Gorenstein and Newman, 1980; Jacobson et al., 2002; Kendler et al., 2003; Krueger et al., 2002; Slutske et al., 1998).

5.4. Specificity of electrophysiological measures for alcoholism

A low P3 amplitude is not only observed in abstinent alcoholics and offspring of alcoholics, but is also present in various disinhibitory conditions such as substance abuse (Anokhin et al., 2000; Biggins et al., 1997; Brigham et al., 1997; Herning, 1996; Iacono et al., 2003), antisocial personality (Costa et al., 2000; Hesselbrock et al., 1993; O'Connor et al., 1994), conduct disorder (Iacono et al., 2002), attention-deficit hyperactivity disorder (Klorman, 1991; van der Stelt et al., 2001). It has also been observed in schizophrenia for the auditory modality, as well as for a number of other disorders (cf. Polich and Herbst, 2000). An epidemiological P3 study in several hundred 17-years-old indicated that the group with low P3s contained significantly more individuals with alcohol dependence, nicotine dependence, and illicit drug abuse than the group with high-voltage P3 (Carlson et al., 1999; Iacono, 1998; Iacono et al., 2002, 2003). Moreover, the group with low P3 manifested a significantly higher incidence of externalizing disorders and disinhibitory traits than the high P3 group. In a longitudinal study by Hill and Shen (2002) that demonstrated differential developmental trajectories of P3 amplitude, the lowest amplitude was associated with a combination of both childhood psychopathology and a family history of alcoholism. Thus, the aforementioned studies strongly suggest that individuals with various disinhibitory clinical conditions such as alcoholism, as well as their relatives and individuals at risk, typically manifest a low-voltage P3.

Similarly, increased beta power is not limited to alcoholism and has been reported in those individuals with a family history of alcoholism and a diagnosis of antisocial personality in frontal leads (Bauer and Hesselbrock, 1993). In a study of female adolescents, these authors found again that the increased beta was associated with family history of alcoholism, with increases in broad-band alpha power accompanying those individuals with depression (Bauer and Hesselbrock, 2002). In a study of alcohol and substance-dependent individuals, Costa and Bauer (1997) found individuals with both alcohol-dependence and cocaine-dependence manifested increased beta power which did not correlate with quantity–frequency measures of use.

Taken together, both EEG and ERP measures that are sensitive to the presence of alcoholism or the family history of alcoholism, also occur in the presence of certain co-existing conditions. These co-existing conditions are an integral part of the clinical presentation of alcoholism in most populations and possibly reflect a common underlying vulnerability. Kendler et al. (2003) make a strong case for common genetic and environmental risk factors in certain groups of psychiatric disorders including alcoholism and drug abuse, and the lack of specificity of the electrophysiological measures reflects this feature.

6. Future directions: focus on genetics

Alcoholism is a common complex disorder with significant public health impact. Its development is influenced by underlying biological susceptibility factors, by environmental factors, and by complex interactions among genes and between genes and environment. Some of the genetically influenced underlying factors, such as impulsivity and neural disinhibition, involve frontal lobe function and influence a wider range of related outcomes, including externalizing and mood disorders and abuse of other substances. Thus rather than studying the clinical endpoints, such as a diagnosis of alcohol dependence, it is of more value to study the underlying predispositions.

6.1. Problems in studying the genetics of psychiatric disorders (alcoholism)

A psychiatric diagnosis (e g. alcohol dependence) is dichotomous; either an individual is affected or unaffected. Therefore, it is difficult to use diagnosis as the sole phenotype

in studying the genetics of complex (non-Mendelian) disorders, such as alcoholism, which involve contributions from both genetic and environmental influences and their interactions, for a number of reasons:

(1) These disorders are often polygenic, involving the influence of multiple genes, sometimes with small effects.
(2) There is often incomplete or low penetrance, where an individual may have the predisposing allele, but not manifest the disease.
(3) There is clinical heterogeneity, where there is a variable age of onset and a number of different symptoms that are classified with the same diagnosis
(4) There is often genetic heterogeneity, where different genes lead to clinically indistinguishable disease.
(5) There is often variable expressivity, where the same genes lead to different symptoms.
(6) There is the problem of phenocopies, where an individual can manifest the disease without the predisposing alleles (due to environmental, non-genetic causes).
(7) There is uncertainty of diagnosis, where there is instability of diagnosis over time, as individuals go into remission, denial, etc.
(8) Alcoholism is a common disorder in the population, with a high frequency of predisposing alleles, which may be difficult to detect.

6.2. Endophenotype approach

As psychiatric diagnoses are not unitary entities, but the consequence of several interacting traits, understanding the genetics of their development requires the correct identification of the inherited phenotype(s) The pros and cons of utilizing genetic variants of specific phenotypes in studying cognitive function has been reviewed quite extensively by Goldberg and Weinberger (2004). The review makes a strong case for this emerging field of neuroscience that offers novel ways of assessing complex psychiatric disorders. It has been suggested that diagnostic categories and their constituent symptoms, reflect distal and variable effects of genes that increase the vulnerability to psychiatric disorders. In contrast, neurobiological dysfunctions reflect more proximal effects of such genes (Tsuang and Faraone, 2000). Thus, ideally, molecular genetic studies should not be performed on psychiatric diagnoses alone, but on quantitative biological measures or markers of the genetic predisposition involved in developing psychiatric disorders (Tsuang and Faraone, 2000). 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 (Gottesman and Gould, 2003; Gottesman and Shields, 1972, 1973). In order to be considered as a good quantitative biological endophenotype, several criteria must be met:

(1) The trait must be present in affected individuals and correlate with diagnosis and severity of disease or age of onset.
(2) The trait must reflect susceptibility and not be the consequence of transient states, such as current intoxication, or due to the degenerative effects of chronic drinking. Newly diagnosed and abstinent alcoholics should also manifest the trait.
(3) The trait must be present in unaffected relatives of affected individuals with levels significantly higher than in random controls, and show meaningful variation in unaffected individuals. Alcohol naïve children of alcoholics, known to be at high risk would manifest significantly higher levels than children of non-alcoholics. The trait would have predictive power in prospective studies of alcohol-naïve children, correlating their quantitative trait values with eventual diagnostic status or age of onset.
(4) The trait must be heritable. Generally, the higher the heritability the better the chance of identifying specific genes influencing a trait. However, the heritability estimate reflects the strength of the overall genetic effects on a trait, and not the number of genes involved or the relative contributions of these genes.

These endophenotypes represent the genetic liability of the disorder among non-affected relatives of affected individuals. It should be noted that these biological endophenotypes need not be disease-specific. These biological quantitative endophenotypes are extremely useful in genetic studies of complex diseases, such as alcoholism, as they can alleviate many of the problems encountered when using diagnosis as the phenotype. Namely, they can:

(1) identify relatives of affected individuals who would be considered unaffected with typical dichotomous diagnostic systems,
(2) identify individuals at risk before the development of the disease, and
(3) identify a candidate location for illness-susceptibility loci.

6.3. Utility of brain oscillations (EEG, ERP, ERO) as endophenotypes

The identification of suitable quantitative biologic markers that are genetically transmitted could explicate the genetic factors involved in the etiology of alcoholism and also might elucidate the potential nature of the genetic factors Brain function is likely to be involved in a genetic predisposition to develop alcoholism and other psychiatric disorders, and neuroelectric events may serve as biologic markers. 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. These quantitative electrophysiological traits are less complex than clinical endpoints, are more proximal to gene function than either diagnostic labels or traditional cognitive measures, and hence provide more power to localize and characterize disease susceptibility genes (Almasy, 2003). Furthermore, they meet the criteria for endophenotypes: they are highly heritable, differentiate between cases and controls, are more prevalent in unaffected relatives of affected individuals, differentiate between high-risk offspring and controls and are predictive of future diagnosis.

Brain oscillations have successfully been used as endophenotypes in the search for genes involved in alcohol dependence in the COGA project. Genes that were identified to be important for the expression of brain oscillations (endophenotypes) were subsequently found to be related to the risk for alcohol dependence.

As indicated above (Section 2.3) genetic linkage and linkage disequilibrium between EEG beta frequency and a $GABA_A$ receptor gene on chromosome 4 has recently been reported by COGA (Porjesz et al., 2002a). Several neuroimaging studies have shown specific deficits in GABA benzodiazepine receptors in the brains of alcoholics (Abi-Dargham et al., 1998; Lingford-Hughes et al., 1998) and individuals at risk (Volkow et al., 1995). These studies implicate a potential GABAergic anomaly in alcoholism and suggest that a deficit in GABA in the brains of alcoholics may account for their lack of CNS inhibition (hyperexcitability) reflected in their EEG beta activity. Subsequent single nucleotide polymorphism (SNP) analyses in the COGA project indicated that the same $GABA_A$ receptor gene associated with the EEG beta frequency is also associated with a DSM-IV diagnosis of alcohol dependence (Edenberg et al., 2004). Thus with the use of the EEG endophenotype, a gene was found relating CNS disinhibition to genetic risk for alcohol dependence and perhaps related disorders. For the most significant SNP, individuals with a particular risk genotype had significantly elevated beta power compared to individuals with other genotypes. Prospective studies are underway in the COGA project, looking at the risk genotypes and risk haplotypes in young offspring of alcoholics, to determine whether they are more at risk to develop alcohol dependence and related disorders.

Similarly, as described above (Section 4.5), linkage and linkage disequilibrium has been recently reported in COGA between the theta and delta EROs underlying P3 to target stimuli and a cholinergic muscarinic receptor gene on chromosome 7, the *CHRM2* (Jones et al., 2004). Muscarinic receptors influence many effects of acetylcholine in the central and peripheral nervous system and hence are expected to have a direct influence on P3 generation (Frodl-Bauch et al., 1999). These findings near a *CHRM2* gene strongly support the role of acetylcholine in the generation and modulation of the delta and theta event-related oscillations underlying the P3 component. This indicates the importance of cholinergic receptor genes in human cognition via modulation of neuroelectric oscillations.

Recent evidence from the COGA project indicates that the *CHRM2* gene is not only related to brain oscillations but also clinical diagnosis; significant linkage and association were reported for the *CHRM2* gene and a diagnosis of alcohol dependence and depression (Wang et al., 2004). Thus genes important for the expression of the endophenotype (brain oscillations) help in identification of genes that increase the susceptibility for risk of alcohol dependence and related disorders.

Alcohol dependence and related disorders result from a complex interaction of changing genetic and environmental liabilities across development, with greater genetic loading for early onset disorders. The use of quantitative brain oscillations as endophenotypes provides the power to more easily localize and characterize disease susceptibility genes than diagnostic categories. The utility of electrophysiological measures as endophenotypes for the study of genetic risk of disinhibitory disorders, including alcoholism, is very promising. While the endophenotype approach is not a new idea, it is an approach whose time has come. Recent advances in SNP-chip technology in molecular genetics as well as novel statistical genetic techniques and computational power have made this approach very tenable in the near future. Once genes are identified, risk genotypes and haplotypes can be used in prospective studies of young individuals and can lead to prevention initiatives.

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