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Uncovering genes for cognitive (dys)function and predisposition for alcoholism spectrum disorders: A review of human brain oscillations as effective endophenotypes

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ABSTRACT

Brain oscillations provide a rich source of potentially useful endophenotypes (intermediate phenotypes) for psychiatric genetics, as they represent important correlates of human information processing and are associated with fundamental processes from perception to cognition. These oscillations are highly heritable, are modulated by genes controlling neurotransmitters in the brain, and provide links to associative and integrative brain functions. These endophenotypes represent traits that are less complex and more proximal to gene function than either diagnostic labels or traditional cognitive measures, providing a powerful strategy in searching for genes in psychiatric disorders. These intermediate phenotypes identify both affected and unaffected members of an affected family, including offspring at risk, providing a more direct connection with underlying biological vulnerability. Our group has utilized heritable neurophysiological features (i.e., brain oscillations) as endophenotypes, making it possible to identify susceptibility genes that may be difficult to detect with diagnosis alone. We have discussed our findings of significant linkage and association between brain oscillations and genes in GABAergic, cholinergic and glutamatergic systems (*GABRA2*, *CHRM2*, and *GRM8*). We have also shown that some oscillatory indices from both resting and active cognitive states have revealed a common subset of genetic foci that are shared with the diagnosis of alcoholism and related disorders. Implications of our findings have been discussed in the context of physiological and pharmacological studies on receptor function. These findings underscore the utility of quantitative neurophysiological endophenotypes in the study of the genetics of brain function and the genetic diathesis underlying complex psychiatric disorders.

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Abbreviations: ADHD, Attention Deficit Hyperactivity Disorder; AMPA, Alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate glutamate receptor; ASP, Antisocial Personality Disorder; CHRM2, cholinergic muscarinic receptor type 2; CNS, Central Nervous System; COGA, Collaborative study on the Genetics of Alcoholism; EEG, electroencephalogram; ERO, Event-related oscillation; ERP, Event-related potential; FBAT, Family-based Association Studies; FDR, False discovery rate; GABA, gamma-aminobutyric acid; *GABRA2*, gamma-aminobutyric acid (GABA) A receptor, alpha 2; *GABRA4*, gamma-aminobutyric acid (GABA) A receptor, alpha 4; *GABRB1*, gamma-aminobutyric acid (GABA) A receptor, beta 1; *GABRG1*, gamma-aminobutyric acid (GABA) A receptor, gamma 1; GRM8, glutamate receptor, metabotropic 8; GWAS, Genome-wide Association Studies; LD, Linkage disequilibrium; LOD, Logarithm of Odds; LVA, Low voltage alpha; mGluR, metabotropic glutamate receptors; ms, millisecond; NMDA, N-methyl-D-aspartate glutamate receptor; QPDT, Quantitative Pedigree Disequilibrium Test; SNP, Single-nucleotide polymorphisms

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1. Introduction

An important focus of electrophysiological studies is to understand how large neuronal assemblies organize and function in the brain and the possible mechanisms for cooperation that form the basis for all sensory, cognitive, and motor processes in health and disease. Not only do electrophysiological indices provide a means to delineate the millisecond-by-millisecond structure and progression of information processing in the brain, but they also provide vital clues to points of aberration that may underlie a predisposition or vulnerability, especially to psychiatric conditions, and the extent of damage caused by the disease progression. Brain regions generally display a combination of delta (1–3 Hz), theta (4–7 Hz), alpha (8–12 Hz), beta (13–30 Hz), and gamma (>30 Hz) rhythms, as has also been seen in corticothalamic network operations (Buzsaki and Draguhn, 2004; Steriade, 2001; Steriade, 2006). Furthermore, several rhythms can coexist in the same area or interact across different regions; thus, adjacent frequency bands within the same neuronal network may be associated with different brain states (Steriade, 2001; Varela et al., 2001). The challenge of refining the exact combination of time and frequency elements corresponding to specific brain states is aided by new methods of analyses, such as the Continuous Wavelet Transform (Grossman and Morlet, 1984), Matching Pursuits (Mallat and Zhang, 1993), and most recently the S-Transform (Stockwell et al., 1996), among others.

Traditional physiological models of brain function inherent in the event-related potential (ERP) methodologies often conceptualize electrophysiological spontaneous activity as internal noise (Tomberg and Desmedt, 1999). Functional neuroimaging studies have shown how the baseline of spontaneous neuronal activity is organized in multiple highly specific functional anatomical networks, known as resting state networks (Damoiseaux et al., 2006; De Luca et al., 2006). The hemodynamic changes in these resting state networks have been shown to fluctuate at frequencies between 0.01 and 0.1 Hz, and strongly overlap with sensory, motor and cognitive networks that are commonly modulated during active behavioral tasks (Corbetta et al., 2000; Fox et al., 2005; Fox et al., 2006; Mazoyer et al., 2001). Hence, recent models propose that spontaneous activity may play an important functional role by providing constraints or opportunity that could be important to communication in sensory, cognitive, or motor activity networks (Engel et al., 2001; Llinas, 1988; Mantini et al., 2007; Varela et al., 2001).

Until recently, ERPs have been the basic electrophysiological indices of cognition and have provided valuable insights into human brain processes. There is now a substantial literature which suggests that some ERP features arise from oscillatory changes due to sensory and/or cognitive processes which influence the dynamics of ongoing electroencephalographic (EEG) rhythms of different frequency bands (Basar-Eroglu and Basar, 1991; Basar-Eroglu et al., 2001; Demiralp et al., 2001; Karakas et al., 2000a; Schurmann et al., 1995; Schurmann et al., 2001; Yordanova and Kolev, 1996). Sensory, cognitive and motor activities are associated with synchronization and enhancement of EEG activity, where random resting EEG oscillations become organized, amplified and coupled, thus giving rise to an 'evoked' (phase-locked) or 'induced' (non-phase-locked) rhythmicity. Event-related oscillations (EROs) have been proposed to arise in part from superpositioning or from a process-related 'partial-phase resetting' occurring in different EEG frequency bands in response to sensory or cognitive stimulation (Basar, 1980; Basar, 1999; Makeig et al., 2002). These oscillations thus 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 (Basar et al., 2001b; Doppelmayr et al., 1998; Gevins et al., 1998; Klimesch et al., 2001; Klimesch et al., 1994); slow alpha – attribution of attentional resources (Basar et al., 1997; Klimesch, 1997; Klimesch et al., 1998); fast alpha – semantic memory and stimulus processing (Klimesch, 1997; Klimesch et al., 1997a; Klimesch et al., 1997b; Klimesch et al., 1994); beta and gamma – sensory integrative processes (Basar-Eroglu et al., 1996a; Basar-Eroglu et al., 1996b; Basar et al., 2001a; Schurmann et al., 1997). The more recent models that evaluate brain function using oscillations, stress the importance of phase reorganization of these task-relevant oscillations in the understanding of cognitive brain function (see review, Klimesch et al., 2007).

The two new trends in cognitive neuroscience discussed in this section make it possible to study neural network dynamics in the human brain in health and disease; they have therefore, strongly contributed to the study of predisposition and brain dysfunction in psychiatric populations (Banaschewski and Brandeis, 2007; Ford et al., 2007; Herrmann and Demiralp, 2005; Porjesz et al., 2005; van der Stelt and Belger, 2007). In the following sections, we will elaborate on the utility of studying human brain oscillations in the search for genes involved in alcoholism. Recent evidence suggests that alcoholism/alcohol dependence is an important domain in the spectrum of disinhibitory disorders, which include externalizing and substance use disorders (Kendler et al., 2003). We will highlight the key oscillatory indices that have emerged as significant discriminators in the context of alcoholism, and will then provide a brief overview of the current genetic analysis methods used to trace the path from EEG and EROs to genes (Fig. 1). Finally, we will discuss the genes in the context of their physiological significance and the underlying genetic diathesis for alcoholism and related disorders.

2. Exploring key brain oscillations in alcoholism

The concept of "intrinsic" rather than resting activity contributing a large proportion of the measured activity is gaining prominence (Raichle et al., 2001; Raichle and Snyder, 2007). Hence, functional connectivity in the brain during these "rest" periods is likely to reflect the maintenance of dynamic equilibrium of the "intrinsic" networks (Llinas et al., 1999). Power estimates of EEG activity in different frequency bands have been demonstrated to corresponding to arousal and activity levels of the cerebral cortex (Niedermayer and Lopes Da Silva, 1999). Measures of synchronicity, such as coherence, offer a means to study

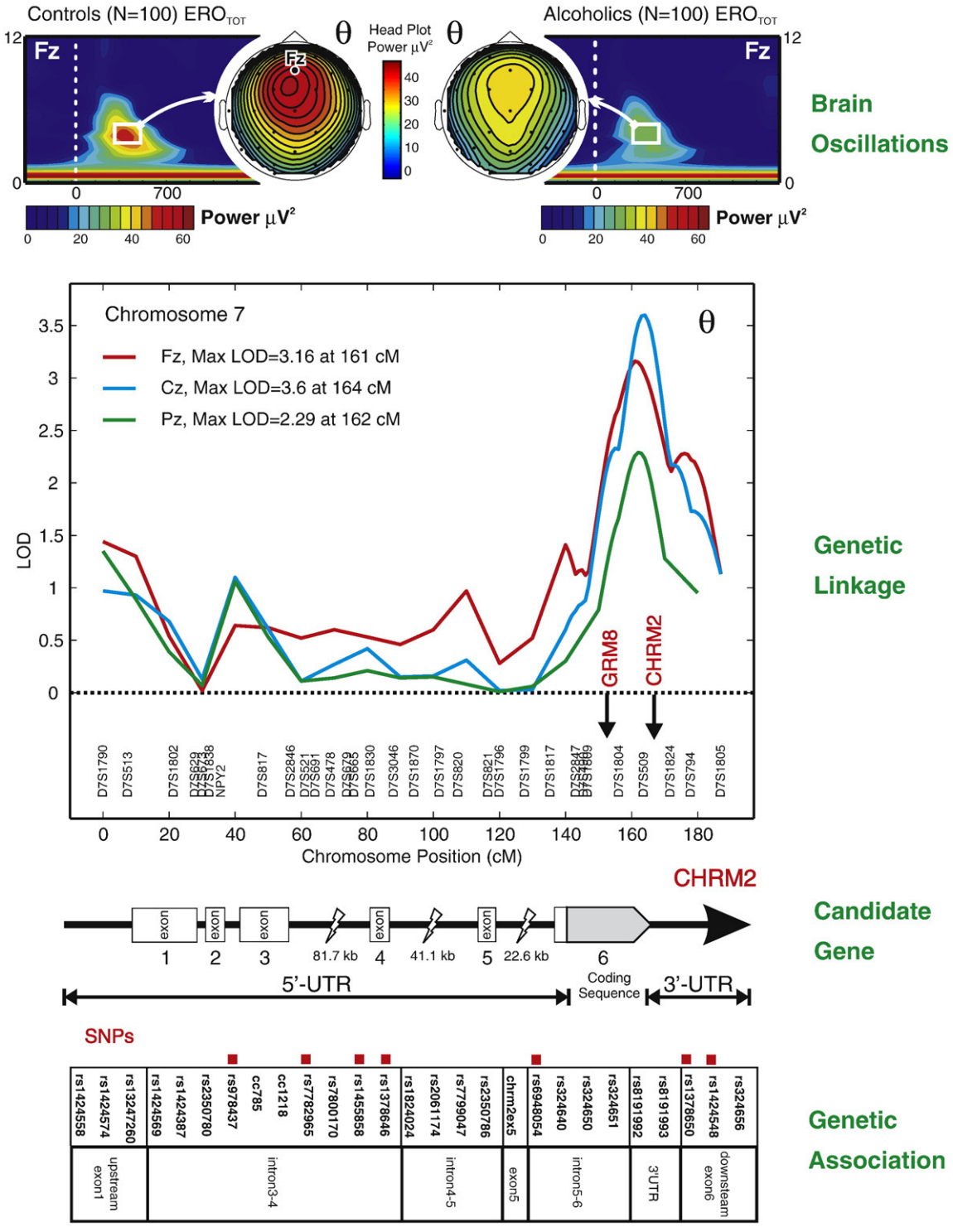

Fig. 1 – From indices of cognition to genes—Illustrating our strategy: *Brain oscillations*, such as theta (θ, 3–7 Hz) ERO underlying P3, are correlates of impaired cognitive processes in alcoholism and risk, as seen in this time-frequency representation of EEG response to target stimuli in a visual oddball task. Head plot displays differences in ERO power and topography. *Genetic Linkage* analysis scans the entire genome to assess if a polymorphic genetic marker from a chromosomal region can be linked to a quantitative trait (theta ERO power) within a family. The logarithm of odds (LOD) score plot for theta ERO power at Fz, Cz and Pz electrodes on chromosome 7 highlights 2 candidate genes under the linkage peak (*CHRM2*, *GRM8*). *Candidate gene* studies focus on genes underlying significant linkage peaks and/or with relevant biological significance. This is a schematic diagram of the *CHRM2* gene. *Genetic Association* tests are performed for each single-nucleotide polymorphism (SNP) identified within and flanking the candidate gene and the trait (theta ERO power). Significant associations (red dots) of the trait with the SNPs indicate loci of interest.

the functional relation between populations of neurons/regions. EEG coherence is a measure of phase correlation (Nunez and Srinivasan, 2006; Srinivasan et al., 1998) and reflects functional cortical connectivity, possibly arising from corticocortical or corticothalamic fiber networks. Functional connectivity impairments have been reported in other psychiatric and neurological conditions, such as attention deficit hyperactivity disorder (ADHD) (Barry et al., 2002; Clarke et al., 2007), autism (Murias et al., 2007) and schizophrenia (Higashima et al., 2007; Higashima et al., 2006). In our strategy to find genes, we have focused on brain oscillations that differentiate between alcoholics and controls as well as between high-risk offspring of alcoholics and low-risk offspring of non-alcoholics (Table 1). In the following sections we will discuss some key findings, both current and published, pertaining to two brain states – resting or intrinsic and cognitive challenge (visual oddball) that have been extensively studied in our laboratory and as part of the extended Collaborative study on the Genetics of Alcoholism (COGA), with respect to understanding risk and predisposition to alcoholism and the related spectrum disorders.

2.1. *EEG beta oscillations: power*

The signatures of the resting state of the brain as determined by electroencephalography (EEG) have revealed characteristic patterns in individuals with alcoholism and also those with high risk for developing alcoholism and related spectrum of externalizing conditions (Porjesz et al., 2005), review). Across most studies published in this field, increased beta power in the EEG has emerged as one such important feature; it is noted in affected (Bauer, 2001; Costa and Bauer, 1997; Propping et al., 1981; Rangaswamy et al., 2002; Winterer et al., 1998) and high-risk individuals (Finn and Justus, 1999; Gabrielli et al., 1982; Pollock et al., 1995; Rangaswamy et al., 2002; Rangaswamy et al., 2004b). The low voltage alpha (LVA) EEG variant has been shown to be associated with a subtype of alcoholism that is related to anxiety disorder (Enoch et al., 1999). It has been hypothesized that altered norepinephrine levels on thalamic activity may partly explain the connection between LVA and anxiety disorders in alcoholic women (Enoch et al., 2003).

Increased resting beta power has been reported at frontal leads in those who also have a diagnosis of antisocial personality disorder (ASP) (Bauer and Hesselbrock, 1993). Also, the beta power increase may be associated with increased vulnerability, as female high-risk subjects with a larger number of affected first-degree relatives displayed significantly elevated beta power compared to those with just one affected parent (Rangaswamy et al., 2002). Thus evidence of elevated beta power provides strong support to the excitation-inhibition imbalance model proposed to underlie the predisposition to alcohol dependence (Begleiter and Porjesz, 1999).

Table 1 – Brain oscillations as neurophysiological phenotypes: Comparing alcohol-dependent subjects with clean controls; and high-risk subjects with low-risk controls

Neurophysiological phenotype	Results	Citation
Resting EEG		
Theta power (3–7 Hz)	Increased theta power in alcohol-dependent subjects	Rangaswamy et al. (2003)
Beta power (12–20 Hz)	Increased beta power in alcohol-dependent subjects	Rangaswamy et al. (2002)
	Increased beta power in male high-risk subjects (12–16 Hz) and female high-risk subjects (16–20 Hz)	Rangaswamy et al. (2004b)
High Theta coherence (6–7 Hz)	Alcohol-dependent subjects have significantly increased interhemisperic theta band coherence	Rangaswamy, Chorlian, et al. (in preparation) (Fig. 2)
Visual oddball task (VP3)		
Theta 4–7 Hz ERO 300–500 ms	Decreased theta power during target processing in alcohol-dependent and high-risk subjects	Jones et al. (2006b); Rangaswamy et al. (2007)
Delta 1–3 Hz ERO 300–700 ms	Decreased delta power during target processing in alcohol-dependent and high-risk subjects	Jones et al. (2006a,b) Rangaswamy et al. (2007)
Gamma 29–45 Hz ERO 0–150 ms	Decreased gamma power during target processing in alcohol-dependent and high-risk subjects	Padmanabhapillai et al. (2006a,b)
Gambling Task		
Theta ERO	Decreased Theta power during outcome processing in alcohol-dependent individuals	Kamarajan et al. (in preparation)
Response inhibiton (Go/NoGo)		
Delta, Theta, Alpha ERO	Alcohol-dependent individuals had decreased delta and theta ERO power during NoGo trials. This reduction was prominent frontally	Kamarajan et al. (2004)
	High-risk subjects had significantly decreased delta, theta ERO power for Go and NoGo and an additionally decreased	Kamarajan et al. (2006)

2.2. EEG theta oscillations: synchrony

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 interhemispheric coherence (Kaplan et al., 1985; Michael et al., 1993). It has been reported that bilateral intrahemispheric coherences in alpha and beta frequency bands were increased in both long-term abstinent and non-abstinent alcoholics compared to controls (Winterer et al., 2003a). 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.

Most published studies on coherence have employed monopolar pairs in the analyses, a configuration that has a considerable amount of spatial smearing. Using bipolar electrode pairs effectively results in a low resolution spatial filter that controls this issue (Cook et al., 1998), and thus the coherence measure provides a better estimate of localized activity and possibly enhances the contributions of corti-cothalamic and interhemispheric fiber connections. In our laboratory we have observed significant increases in resting EEG interhemispheric high theta (6–7 Hz) coherence, using the bipolar montages, in alcohol-dependent subjects when compared to normal controls (Fig. 2). Peak theta band coherence was highest for posterior electrode pairs in alcohol-dependent subjects, displaying a shift from a more fronto-central prominence as seen in normal control subjects. Hence increased EEG coherence (cortical synchronization) may serve as an endophenotype (i.e. biological marker) for alcoholism.

2.3. Event-related theta and delta oscillations: power

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 (Begleiter et al., 1984; Porjesz et al., 2005). The low P3 amplitudes coupled with the weaker and less well-organized sources in alcoholics and offspring at risk suggest inefficient allocation of resources during neural processing. This undifferentiated neurophysiological pattern suggests a level of cortical disinhibition in alcoholics and individuals at risk.

The 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, ASP, conduct disorder and ADHD. Moreover, individuals with low P3 amplitudes manifest a significantly higher incidence of externalizing disorders and disinhibitory traits than those with high P3 amplitudes (Porjesz et al., 2005), review).

Several studies have demonstrated that P3 responses are primarily the outcome of theta and delta oscillations elicited during cognitive processing of stimuli (Basar-Eroglu et al., 1992; Basar et al., 1999; Karakas et al., 2000a; Karakas et al., 2000b; Yordanova and Kolev, 1996). Topographically, delta oscillation power peaks at the posterior region, while the theta power peak is located in the fronto-central region (Karakas et al., 2000b); theta oscillations also contribute strongly to N2 components.

In a visual oddball paradigm, alcoholics manifest significantly less evoked theta and delta ERO amplitudes while processing the target stimuli (Jones et al., 2006b); these findings are most significant anteriorly for theta, and posteriorly for delta (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., 2007). The two groups in the study compared children of alcoholics and normal children in the age range of 14–17 years. These results show that the adolescent offspring 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 ERO measures were superior to P3 amplitude in differentiating between high-risk and low-risk offspring. Hence, 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 (Fig. 3).

We have also reported theta and delta oscillatory deficits in alcoholics and high-risk subjects during the performance of tasks designed to assess response inhibition (a Go-NoGo task) and error/response evaluation (a gambling task), providing more evidence that these deficient oscillatory responses may antecede the development of alcoholism. A significant reduction in delta and theta band ERO amplitude was concentrated in the frontal region for alcoholics, particularly during NoGo processing in a Go/NoGo paradigm (Kamarajan et al., 2004); in the high-risk offspring the significant differences were more profound and showed a global decrease in theta and delta power (Kamarajan et al., 2006).

2.4. Event-related gamma oscillations: power

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 (Basar-Eroglu et al., 1996b; Fell et al., 2003). This phase-locked gamma is larger to attended stimuli 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). Some studies have found associations between stimulus induced amplitude modulations and reaction time and speed (Frund et al., 2007; Haig et al., 1999). Induced gamma oscillations have been associated with a wide range of cognitive processes and learning (Basar-Eroglu et al., 1996b; Gruber and Muller, 2006; Tallon-Baudry et al., 1999).

Our group (Padmanabhapillai et al., 2006a) has 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. Control subjects had significantly more gamma while processing the target when compared to their processing of the non-target stimulus. However, the alcoholics had

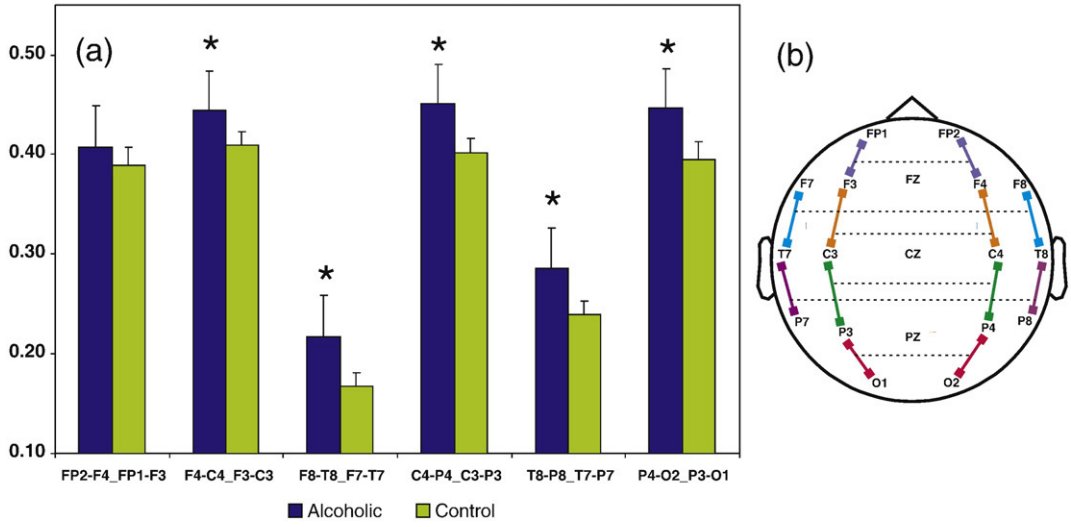

Fig. 2 – Interhemispheric high theta (6–7 Hz) coherence in resting EEG. (a) Bars display coherence mean and standard error at 6 interhemispheric pairs along anterior to posterior axis depicted in the head plot inset (b). Alcoholics (120 subjects, blue bars) manifest significant increases in resting EEG interhemispheric high theta coherence when compared to normal controls (120 subjects, green bars) {$F = 2.59$, $p = 0.019$; MANOVA [SPSS 12.0]} (Rangaswamy, Chorlian et al., in preparation).

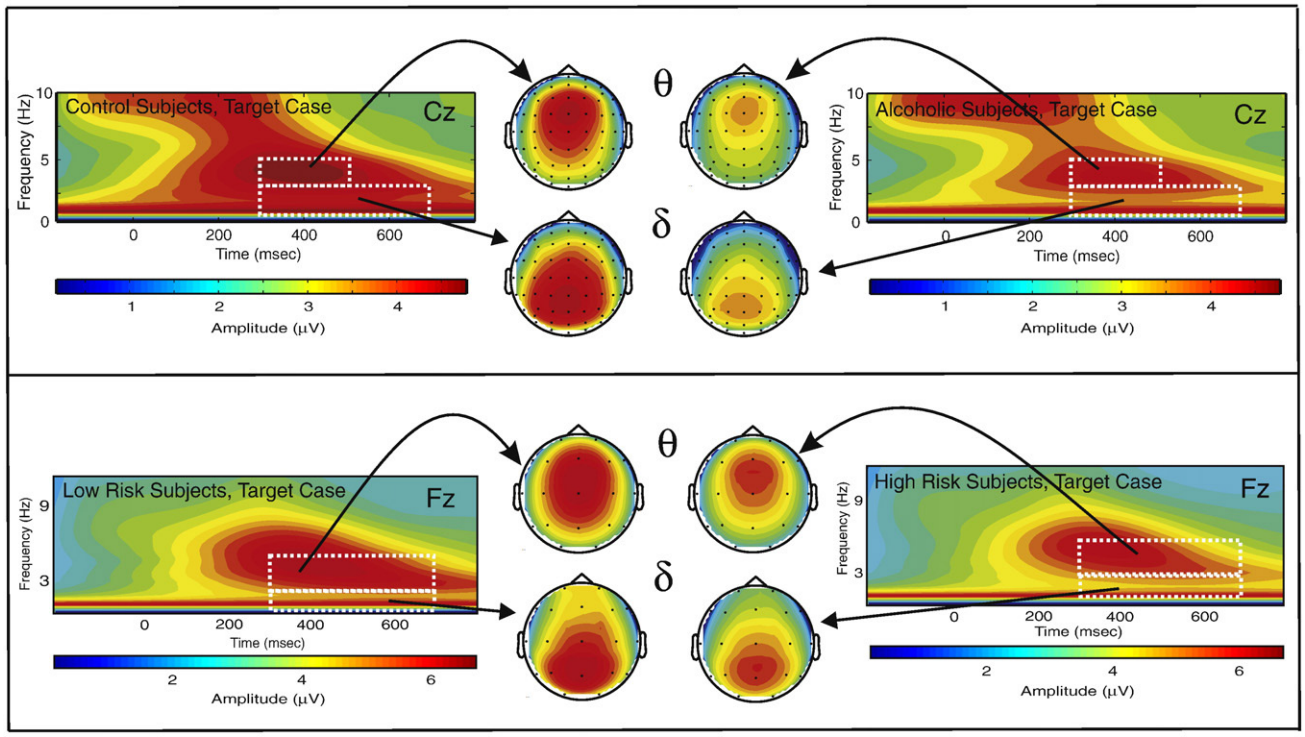

Fig. 3 – S-transform derived time-frequency representations of the average instantaneous amplitude that are z-scored for each frequency. Instantaneous amplitudes were averaged across individual trials of subjects so that non-phase locked oscillatory energy is preserved. Top panel: Plots for the target condition at Cz electrode in 120 alcoholic (right) and 120 control (left) subjects. Headplots of the time-frequency regions of interest (TFROIs) indicate that the theta band (4–5 Hz) power at 300–500 ms shows frontal maxima while the delta band (1–3 Hz) power at 350–700 ms has posterior maxima. Note that alcoholics have weaker responses in both theta and delta bands. Bottom panel: Plots for the target condition at Fz electrode in visual oddball task in 87 high-risk (right) and 57 matched low-risk (left) adolescent subjects. Head plots for the TFROI that extends from 300 to 700 ms for each band revealing frontal maxima for theta band power and parietal maxima for delta band power. Note that high-risk adolescents have weaker responses in both theta and delta bands to target stimuli, similar to the alcoholics.

an opposite profile, eliciting more gamma band response to non-target than to target stimuli. We have 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 and non-alcoholics was investigated using the same visual oddball task (Padmanabhapillai et al., 2006b). Subjects were in the age range of 14–17 and high-risk children came from families with at least one alcoholic parent. Topographically, peak gamma band response was observed in the frontal region for the target stimuli in both groups. High-risk children had significantly lower gamma activity than control children, especially in the parietal regions for the target condition. 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. It is likely that a dysfunctional fronto-parietal attentional network may underlie this deficit. There is clear evidence of deficient activations in inferior frontal and inferior parietal brain regions while high-risk subjects performed the visual oddball task in an fMRI study (Rangaswamy et al., 2004a).

3. Exploring genetics of key brain oscillations and their application to alcoholism and related disorders

Alcoholism is a common, complex (non-Mendelian) disorder with contributions from both genetic and environmental influences and their interactions. As psychiatric diagnosis is dichotomous (an individual is either affected or unaffected), it is difficult to use diagnosis as the sole phenotype when studying the genetics of complex disorders, such as alcoholism. It has been suggested that, ideally, molecular genetic studies should not be performed on psychiatric diagnoses alone, which reflect distal and variable effects of genes, but on quantitative neurobiological measures or markers that reflect more proximal effects of genes involved in the genetic predisposition for developing psychiatric disorders (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, 1973; Gottesman and Shields, 1972). The advantages of using quantitative neurobiological measures of risk as endophenotypes in the search for genes involved in complex disorders are that they are closer to gene action involved in the predisposition for the disorder, they are genetically simpler than clinical endpoints, and quantitative traits provide more power to localize and characterize disease susceptibility genes (Almasy, 2003; Dick et al., 2006c).

Recent evidence suggests that alcohol dependence is part of a spectrum of disinhibitory disorders, which include externalizing and substance use disorders. Many of the same genetic risk factors underlie these disinhibitory co-occurring disorders and can be explained by a small number of common underlying genetic factors (Kendler et al., 2003). This is also reflected in the similar electrophysiological findings from related disinhibitory disorders, as discussed in the previous section.

The identification of suitable quantitative biologic markers that are genetically transmitted could explicate the genetic factors involved in the etiology of alcoholism and related disorders, 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 excellent biological markers or endophenotypes. Understanding genetic control of brain electrical activity may provide clues about cerebral function, and may shed light on pathogenic mechanisms involved in neurological and psychiatric disorders, where impairment in brain electrical activity is apparent. Brain oscillations provide a rich source of potentially useful endophenotypes for psychiatric genetics, as they represent important correlates of human information processing and cognition.

In order to be considered as an endophenotype, there are certain criteria that must be met, the most important of which is that the trait must be heritable (Porjesz et al., 2005). The data on the heritability of EEG frequencies are quite compelling. High concordance rates in the spectral characteristics of resting eyes-closed EEG have been reported from monozygotic twin pairs compared to dizygotic twin pairs. A large twin study indicates that power in all frequency bands of the resting EEG is highly heritable: delta 76%, theta 89%, alpha 89%, and beta 86% (van Beijsterveldt and Boomsma, 1994; van Beijsterveldt et al., 1996) and EEG coherence has also been reported to be heritable, with estimates between 50% and 70% in twin populations (Stassen et al., 1988; van Baal et al., 1998; van Beijsterveldt and Boomsma, 1994; van Beijsterveldt et al., 1998) and estimates between 40% to 60% for coherences in theta and alpha band in posterior regions reported for a sib-pair population (Chorlian et al., 2007). In order for genetic studies to be successful, it is extremely important to select a well-characterized (endo)phenotype. Therefore, genetic studies of neuroelectric endophenotypes (brain oscillations, such as EEG and those EROs underlying ERPs, including the P3 component) provide a powerful strategy for identifying underlying susceptibility genes for developing alcoholism and related disinhibitory disorders.

3.1. *Exploring the gene targets: methods*

The possible approaches for finding genes associated with the variation in quantitative traits (e.g. brain oscillations) in complex diseases (e.g. psychiatric disease) fall into two main categories: (a) genome-wide studies, which include linkage studies and the more recent genome-wide association studies (GWAS), and (b) candidate gene studies, which are mostly association studies. Genome-wide studies do not require any hypotheses about gene function, while candidate gene studies are based on biological hypotheses. Both of these approaches have been successful in finding genes, and often, a successful strategy is to use both methods together; yet each has both advantages and drawbacks (For a review of these approaches see (Hirschhorn and Daly, 2005).

The most traditional method used to find genes is genome-wide linkage analysis. Linkage studies assess whether a polymorphic genetic marker from a chromosomal region can be linked to a specific trait (e.g. brain oscillation) within a family. Thus linkage analysis determines patterns of DNA sharing among family members that correlates with the phenotypic trait (Almasy and Blangero, 1998). This method serves to indicate chromosomal sharing within families, and precisely which alleles are shared can be different across families. The advantage of this approach is that the entire genome can be scanned without any prior hypotheses, and it is often successful in finding rare genes. Linkage is measured by the Logarithm of Odds (LOD) score, where a LOD score over 3 is taken as evidence of significant linkage (equivalent to *p*-value of 0.0001). Linkage analysis techniques have been successfully utilized to locate genes of rare Mendelian traits, where a single gene accounts for a disease. However, linkage may also be detected when multiple genes lie in the same chromosomal region, giving rise to a broad linkage peak with several candidate genes underlying the peak (see Figs. 1 and 5). While linkage methods have been less successful in locating genes associated with more common complex traits (e.g. psychiatric diagnosis), which are likely the result of multiple small gene effects, studies from our laboratory (COGA) have successfully used these methods to identify genes associated with quantitative traits (electrophysiological) that have often led to genes involved in psychiatric disease. As will be seen in this review, we have successfully used this approach with brain oscillations as endophenotypes, to target chromosomal regions using linkage that contain potential candidate genes that may be involved in both brain function and diagnosis of alcohol dependence and related disorders, which is then more closely investigated using association analyses (Fig. 1).

Rather than scan the entire genome, association studies test the strength of the relationship between the variants of a specific candidate gene and a trait, such as brain oscillations. Publicly available databases are used to identify single-nucleotide polymorphisms (SNPs) within and flanking candidate genes in the regions of the chromosome underlying very significant linkage peaks. The COGA strategy has sought to include SNPs in all regions, and not just restricted to coding regions or exons. Association studies need not be family based, and can be accomplished by comparing alleles of a particular variant between cases and controls. It is important to begin the search with a set of well-characterized heritable biological quantitative measures, such as brain oscillations, and some well-defined functional candidate gene. The selection of a candidate gene can be made in two ways: subsequent to a significant linkage finding, or determined on the basis of a priori biological facts associated with the trait under study. In the first approach, linkage analysis will identify a chromosomal region that will include a variety of potential candidate genes that may influence the trait; in the second approach, the candidates would be selected based on biological hypotheses. For example, in the case of brain oscillations, likely candidate genes could be regulatory genes that control neurochemical processes in the brain, and hence neural functions that are likely to influence brain oscillations. As will be illustrated, both linkage and association methods have successfully been used to find genes involved in brain oscillations as well as complex disorders for which they are endophenotypes. A positive association between an allele and a specific oscillation may indicate that the allele is a causative factor in the phenotype. In association studies, one allele is being tested, but it is quite possible that other nearby alleles are fully enriched in one of the tested genotype groups. This phenomenon is called linkage disequilibrium (LD). A given allele may serve as a proxy for other nearby alleles that have moved together across generations on the same chromosome.

It should be cautioned that a positive association between an allele and an oscillation may also reflect artifacts that arise from genotyping errors, as well as multiple testing. Another common source of artifact is the problem of population stratification. This refers to potential ethnic group difference in allelic frequency due primarily to effects of population of origin and geographical isolation which concentrate certain alleles in different populations. Therefore it is important to keep in mind the problem of population stratification in conducting association studies. Various methods have been implemented to deal with population stratification in conducting association studies, such as using family-based controls, or limiting analyses to ethnically homogeneous groups of individuals (e.g. only Caucasians). As will be seen in our studies, we have used all of these approaches to take these issues into account as much as possible (i.e. all association studies are performed only on Caucasians (which is the majority of our sample), and we use family-based association studies (FBAT), as well as controlling for multiple comparisons using statistical methods such as false discovery rate (FDR). Since the influence of any single gene on a given oscillation is likely to be small, we must also keep in mind other potential confounding factors such as gender, age, alcohol or drug abuse, psychopathology, etc.

With the completion of the human genome and the availability of SNPs and whole genome association studies (GWAS), the possibility exists of identifying specific genes that affect human cognition and various neural oscillations that underlie them, as well as the related biological mechanisms contributing to disease. While there are more than 6 million SNPs in the human genome, very few SNPs associated with these complex traits are likely to be in coding regions of the gene, and therefore may not involve changes in the encoded protein expression, and subsequently its function (Goldberg and Weinberger, 2004; Hirschhorn and Daly, 2005). Variations in the protein coding sequences can result in changes that range from synonymous (unchanged function of the protein) to non-synonymous or missense (changes in the function of the protein) mutations. It is more likely that the majority of these functional changes will involve the regulation of transcription via promoter variants or the organization of transcription through splice-site variants. At this point in time, it is not possible to determine how many of these variations will affect brain oscillations and cognitive processes. It is most likely that multiple genes with small effects may be involved. In addition to the aforementioned role of altered gene regulation impacting on brain oscillations and cognition, special consideration needs to be given to gene–gene interactions, gene–environment interactions and potential stochastic factors.

3.2. *Resting EEG beta power: GABRA2 gene*

As increased resting beta power is already observed in offspring before the onset of alcohol dependence, it antecedes the development of alcoholism and is considered to be a "trait" rather than a "state" measure. Significant linkage and linkage disequilibrium between the EEG beta frequency and a gamma-aminobutyric acid ($GABA_A$) receptor gene on chromosome 4 has been reported (Porjesz et al., 2002). With the use of multiple SNPs across this cluster of $GABA_A$ receptor genes on chromosome 4, that includes *GABRA2*, *GABRA4*, *GABRB1* and *GABRG1*, we were able to specifically identify that it was variations only in the *GABRA2* receptor gene that accounts for the linkage/linkage disequilibrium findings with the beta frequency (See Fig. 4; Table 2). Thus, variations in *GABRA2* (the gene encoding the alpha 2 subunit of the $GABA_A$ receptor) affect brain oscillations and are directly involved in the level of neural excitability (balance between excitation and inhibition). There is a strong relationship between the rs279836 SNP in the *GABRA2* receptor gene and Beta 2 EEG power. It is interesting to note that individuals who are homozygous for the rarer genotype (15%) of the rs279836 SNP have significantly increased EEG beta 2 compared to individuals with all other genotypes. These individuals are more likely to manifest CNS disinhibition.

Subsequent SNP (single-nucleotide polymorphism) analysis indicated that the same *GABRA2* gene associated with the EEG beta endophenotype is associated with DSM-IV diagnosis of alcohol dependence (Edenberg et al., 2004), substance dependence (Agrawal et al., 2006), ASP (Dick et al., 2006a), and childhood conduct disorder (Dick et al., 2006b). The association between *GABRA2* and alcohol dependence has been replicated by a number of groups throughout the world (Covault et al., 2004; Drgon et al., 2006; Enoch et al., 2006; Fehr et al., 2006; Lappalainen et al., 2005; Soyka et al., 2008).

It has been demonstrated that the beta rhythm is generated while maintaining the balance in networks of excitatory pyramidal cells and inhibitory interneurons, involving $GABA_A$ action as the pacemaker (Whittington et al., 2000). Fast synaptic inhibition in the mammalian central nervous system is mediated largely by activation of $GABA_A$ receptors (Tobler et al., 2001). $GABA_A$ actions are a fundamental requirement for both gamma (30–80 Hz) and beta oscillations to occur, and blockade of these receptors results in loss of synchronization (Haenschel et al., 2000). Beta rhythms can synchronize over long temporal delays between more spatially distant brain loci than gamma rhythms (Kopell et al., 2000). Although the recording of electrical oscillations from a neural population reflects the firing of multiple excitatory pyramidal cells, the mechanism underlying beta and gamma oscillations depends on the firing patterns of a network of inhibitory interneurons (Faulkner et al., 1999; Kopell et al., 2000), gated by their mutually induced $GABA_A$ action (Whittington et al., 2000).

Alcoholics and offspring at high risk manifest increased power in EEG beta oscillations, suggesting an imbalance between excitation-inhibition (CNS disinhibition). This provides a biological hypothesis relating the underlying CNS disinhibition to the genetic risk for alcohol dependence and related disorders (Begleiter and Porjesz, 1999). The involvement of the GABAergic system in alcoholism is supported by neuroimaging studies, which report specific deficits in GABA

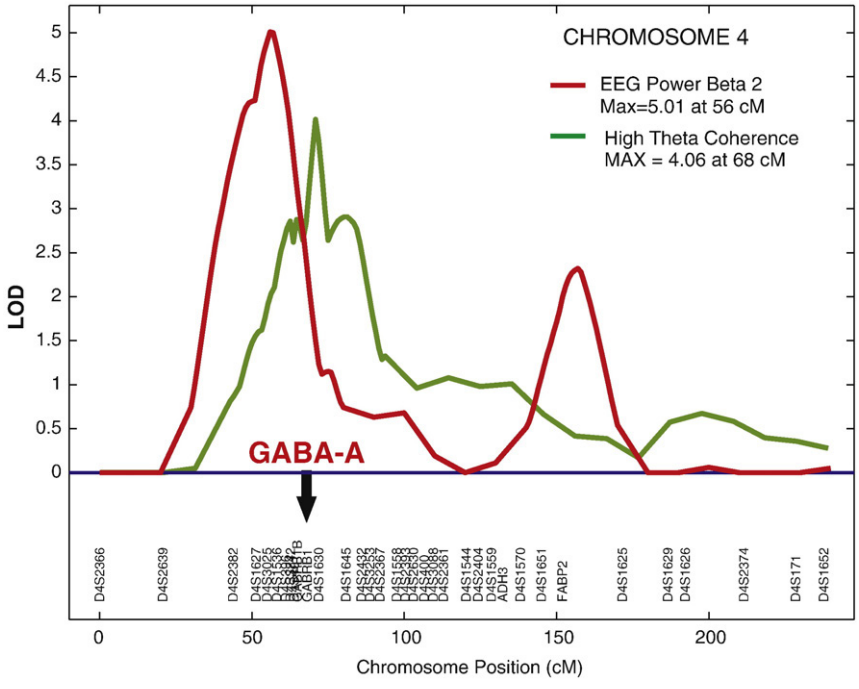

Fig. 4 – Linkage plot showing maximum LOD scores with significant linkage peaks over the $GABA_A$ receptor gene cluster on chromosome 4. (a) Red trace: Resting EEG beta band power – beta 2 (16–20 Hz). The dataset consists of 1553 individuals from 250 families. (b) Green trace: Resting EEG high theta band (6–7 Hz) interhemispheric coherence at parieto-occipital bipolar pairs of electrodes (P4_O2-P3_O1). The dataset consists of 1312 individuals from 251 families.

Table 2 – Summary of association results from the quantitative pedigree disequilibrium test (QPDT) for SNPs in the candidate gene *GABRA 2*

	GABRA2	
	Theta coherence	EEG beta power
3′	**rs490434**	rs490434
	rs576666	rs576666
	rs531460	**rs531460**
	rs561779	**rs561779**
	rs495818	**rs495818**
	rs497068	rs497068
	rs572227	**rs572227**
3′UTR	**rs573400**	rs573400
Intron 9	rs541418	rs541418
	rs481311	rs481311
	rs507788	**rs507788**
	rs532780	**rs532780**
	rs548583	**rs548583**
	rs10938435	rs10938435
Intron 8	**rs496650**	rs496650
	rs540363	rs540363
	rs526752	rs526752
	rs530329	**rs530329**
	rs483160	**rs483160**
Intron 7	**rs279871**	**rs279871**
Intron 6	**rs279869**	rs279869
	rs279867	**rs279867**
	rs279866	**rs279866**
	rs1808851	rs1808851
Intron 5	**rs279863**	**rs279863**
	rs279861	**rs279861**
Exon 5	**rs279858**	rs279858
Intron 4	**rs175931**	rs175931
	rs279843	rs279843
	rs279845	**rs279845**
	rs279846	**rs279846**
	rs183961	**rs183961**
	rs1440130	**rs1440130**
	rs279826	rs279826
	rs11503016	rs11503016
Intron 3	**rs279827**	**rs279827**
	rs279828	**rs279828**
	rs279834	**rs279834**
	rs279836	**rs279836**
	rs279837	rs279837
	rs279841	**rs279841**
	rs189957	rs189957
	rs1442059	**rs1442059**
	rs1442061	rs1442061
	rs1442062	rs1442062
	rs11503015	rs11503015
Intron 0	rs11503014	rs11503014
	rs3756007	rs3756007
5′	rs894269	rs894269
	rs1372472	rs1372472
	rs2165607	rs2165607
	rs1545234	rs1545234

SNPs showing significant associations for the two endophenotypes (theta coherence and EEG beta power) are indicated in bold red font.

benzodiazepine receptor function in the brains of alcoholics (Abi-Dargham et al., 1998; Krystal et al., 2006; 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.

3.3. *Interhemispheric theta coherence: GABRA2 and CHRM2 genes*

Recent studies have suggested a significant role for theta frequency coherence in normal and aberrant thalamocortical interactions (Sarnthein and Jeanmonod, 2007; Sarnthein et al., 2005). Impairments in neural synchrony have been reported in several psychiatric conditions, including alcohol dependence, as noted in an earlier section (EEG theta oscillations: Synchrony section). We conducted whole genome linkage analysis using the high theta coherence at parieto–occipital leads as the phenotype. Highly significant linkage was found in COGA on chromosome 4 in the same region spotlighted by the EEG beta power phenotype (Porjesz and Rangaswamy, 2007; Rangaswamy et al., in preparation). Family-based association analyses with the cluster of $GABA_A$ receptor genes under this linkage peak revealed strong association with a large number of SNPs (several at $p < 0.001$) genotyped in *GABRA2* for the Caucasian-only subset. There was no significant association with other genes in the $GABA_A$ cluster on chromosome 4 (Fig. 4; Table 2).

These results suggest that *GABRA2* may indeed influence susceptibility to alcohol and drug dependence, not just by modulating level of neural excitation, but also by influencing functional connectivity of interhemispheric networks. In their model of thalamocortical dysrhythmia, Llinas et al. have proposed that the enhanced low-frequency (theta) oscillations in the thalamocortical module can affect the lateral inhibitory drive in the cortex and eventually result in high frequency coherent activation of cortical modules (Llinas et al., 1999). This is particularly significant in light of our genetic findings where two resting state electrophysiological signatures—beta power (high frequency activity associated with arousal) and theta coherence (low-frequency synchrony) are both linked to $GABA_A$ receptor gene involvement.

In another study (Winterer et al., 2003c), the authors 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. Alpha rhythms in the scalp electrical activity are strongly influenced by the thalamus and this has been well supported by evidences from animal and human studies including noninvasive recordings. Some authors have suggested that similar mechanisms associated with thalamocortical cell populations may form the basis of theta (2–7 Hz) rhythms (Hughes and Crunelli, 2005). Interestingly, a study reported significant 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., 2003b). 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

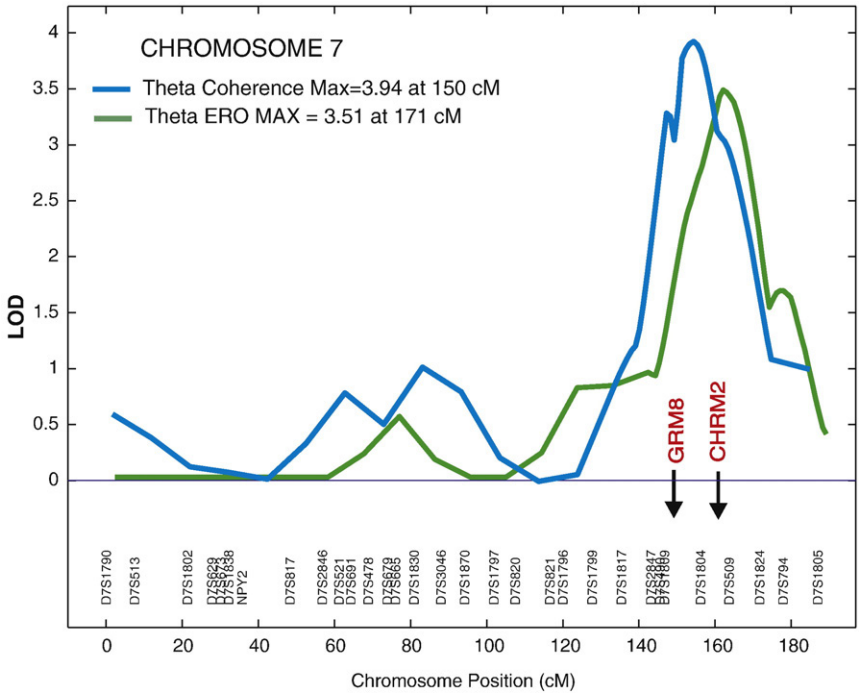

Fig. 5 – Linkage plot showing maximum LOD scores with significant linkage peaks on chromosome 7, over the region harboring two candidate genes: a cholinergic muscarinic receptor gene (*CHRM2*) and a glutamate receptor gene (*GRM8*). (a) Green trace: the central midline theta (4–5 Hz) ERO band power (between 300–700 ms, P3 latency window for visual target case) on chromosome 7. The dataset consists of 1337 individuals from 253 families; (b) Blue trace: Resting EEG theta band (6–7 Hz) interhemispheric coherence at centro-parietal bipolar pairs of electrodes (C4_P4-C3_P3) on chromosome 7. The dataset consists of 1312 individuals from 251 families.

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.

Significant linkage on chromosome 7 was observed for the interhemispheric high theta centro-parietal coherence phenotype in a whole genome linkage scan, and family-based association tests revealed very significant associations with a muscarinic acetylcholine receptor (M2) gene (*CHRM2*), underlying the linkage peak on chromosome 7 (Porjesz and Rangaswamy, 2007) (Fig. 5; Table 3). No significant association was observed for SNPs in another candidate gene underlying the linkage peak in this region — the *GRM8* gene.

Significant linkage and association for evoked theta band responses at the same *CHRM2* gene have been previously reported (Jones et al., 2006a; Jones et al., 2004) (see below). Both the GABAergic and cholinergic systems interact significantly in the functions of local inhibitory circuits, thus affecting network functions and influence cortical synchronization. Increased strength of GABAergic inhibition has been reported to be a likely mechanism underlying the impaired synaptic plasticity observed with M2 knockout mice. These mice demonstrate impaired behavioral flexibility and memory deficits (Seeger et al., 2004). In a recent study examining muscarinic control of long-range cortical GABAergic inhibition, the authors suggested that M2 receptor activation produces a presynaptic inhibition of GABA release by long-range inhibitory neurons of the perirhinal cortex projecting to the entorhinal cortex (Apergis-Schoute et al., 2007).

3.4. *Theta and delta event-related oscillations underlying P3: CHRM2 and GRM8 genes*

We have reported significant linkage and association between the *CHRM2* gene on chromosome 7 and frontal theta oscillations to target stimuli in a visual oddball task; association analyses using both population based tests (Measured Genotype) and pedigree based tests (Quantitative Pedigree Disequilibrium Test, QPDT) indicate significant association of the frontal theta band ERO phenotype with several SNPs surrounding exon 4 of *CHRM2* ($p<0.001$). Further, an examination of the slower frequency parietal delta band ERO revealed significant association with several SNPs surrounding the coding region of the *CHRM2* gene ($p<0.01$) (Jones et al., 2006a; Jones et al., 2004). (See Fig. 5; Table 3).

These findings implicate the possible role of *CHRM2* in the generation and/or modulation of evoked oscillations. Theta and delta EROs depend on the level of acetylcholine (muscarinic activation). M2 receptors inhibit presynaptic release of acetycholine, leading to inhibition of irrelevant networks. Muscarinic receptors are especially concentrated in the forebrain and possibly serve to maintain the effective balance of relevant/irrelevant networks, hence, having a direct influence on P3 generation (Frodl-Bauch et al., 1999). It is proposed

that the genetic underpinnings of evoked oscillations are likely to stem from regulatory genes that control the neurochemical processes of the brain and, therefore, influence neural function. The three major neurochemical substrates contributing to theta and delta rhythms and P3 involve strong GABAergic, cholinergic, and glutamatergic system interactions (Frodl-Bauch et al., 1999).

Moreover, the cholinergic muscarinic genes are shown to be involved in memory and cognition (Calabresi et al., 1998; Comings et al., 2003). Several studies, including the COGA study, have found evidence that this gene may be involved in intelligence (Comings et al., 2003; Dick et al., 2007b; Gosso et al., 2007). In the COGA study, evidence of association with multiple SNPs across *CHRM2* and Performance IQ, as measured by the Wechsler Adult Intelligence Scale — Revised (WAIS-R), was found. These results remain significant after taking into account alcohol dependence and depression diagnoses in the sample (Dick et al., 2007b).

Our results with the *CHRM2* gene and brain oscillations 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 the carbachol-induced delta rhythms were not observed concurrent with carbachol-theta (Fellous and Sejnowski, 2000; Tiesinga et al., 2001).

Recent evidence indicates that the *CHRM2* gene is not only associated with brain oscillations and cognition, but also clinical diagnosis. Significant linkage and association were reported for the *CHRM2* gene and a diagnosis of alcohol dependence and depression (Wang et al., 2004), comorbid alcohol and drug dependence (a more severe addiction profile) (Dick et al., 2007a), as well as a spectrum of externalizing disorders (Dick et al., 2008) in the COGA study. Other groups have also replicated these findings, reporting that the *CHRM2* gene predisposes to alcohol dependence, drug dependence and affective disorders (Luo et al., 2005), and major depression in women (Comings et al., 2002). 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 (Begleiter and Porjesz, 2006; Dick et al., 2006c).

Under the same theta ERO linkage peak on chromosome 7 is a glutamate receptor (*GRM8*) gene that is another very likely candidate gene for modulating electrophysiological networks, particularly as the glutamatergic system is also involved in theta oscillations and P3 (Frodl-Bauch et al., 1999). Family-based association analyses of theta EROs revealed significant associations with several SNPs in the *GRM8* gene and theta EROs to target stimuli at frontal, central, and parietal regions (Chen et al., in press). An interesting finding is that several *GRM8* SNPs were also significant for diagnosis of alcohol dependence using ICD-10 diagnostic criteria.

A 3-T proton magnetic resonance spectroscopy (1H-MRS) study has suggested the involvement of glutamatergic neurotransmission in integrative frontal-hippocampal processing (Gallinat et al., 2006) and the sensation seeking personality dimension (Gallinat et al., 2007). The study demonstrated a robust relationship between glutamate levels in the hippocampus and frontal theta activity during auditory stimulus processing. Glutamatergic neurotransmission and its neuroadaptive changes have been proposed as important molecular determinants of craving and relapse (Cornish and Kalivas, 2000; Tzschentke and Schmidt, 2000). In particular, it is suggested that a hyperglutamatergic state mediates, at least in part, alcohol relapse behavior and maintenance of alcoholism (Tsai and Coyle, 1998). Several studies have suggested the

Table 3 – Summary of association results from the quantitative pedigree disequilibrium test (QPDT) for SNPs in the candidate gene *CHRM 2*

	CHRM2		
	Theta ERO	Delta ERO	Theta coherence
Upstream of exon 1	rs1424558	rs1424558	rs1424558
	rs1424574	rs1424574	rs1424574
	rs13247260	rs13247260	rs13247260
Intron 3–4	rs1424569	rs1424569	rs1424569
	rs1424387	rs1424387	rs1424387
	rs2350780	rs2350780	rs2350780
	rs978437	rs978437	rs978437
	cc785	**cc785**	cc785
	cc1218	**cc1218**	**cc1218**
	rs7782965	rs7782965	rs7782965
	rs7800170	**rs7800170**	**rs7800170**
	rs1455858	rs1455858	rs1455858
	rs1378646	rs1378646	rs1378646
Intron 4–5	**rs1824024**	rs1824024	rs1824024
	rs2061174	rs2061174	**rs2061174**
	rs7799047	rs7799047	**rs7799047**
	rs2350786	rs2350786	rs2350786
Exon 5	chrm2ex5	chrm2ex5	chrm2ex5
Intron 5–6	**rs6948054**	rs6948054	**rs6948054**
	rs324640	**rs324640**	**rs324640**
	rs324650	**rs324650**	**rs324650**
	rs324651	**rs324651**	**rs324651**
3′UTR	rs8191992	**rs8191992**	**rs8191992**
	rs8191993	rs8191993	**rs8191993**
Downsteam of exon 6	**rs1378650**	rs1378650	**rs1378650**
	rs1424548	rs1424548	rs1424548
	rs324656	rs324656	**rs324656**

SNPs showing significant associations for the three endophenotypes (theta ERO, delta ERO and theta coherence) are indicated in bold red font.

involvement of glutamate receptors, NMDA and metabotropic, in alcohol relapse (Bachteler et al., 2005; Holter et al., 2000; Krystal et al., 2003). Acamprosate, a drug used to prevent relapse in alcoholic patients (Mann et al., 2004), has been suggested to act through a suppression of a hyperglutamatergic state created by alcohol addiction (Dahchour and De Witte, 2000; Spanagel and Heilig, 2005).

The glutamate receptors belong to two subfamilies: (a) glutamate-gated ion channels, including NMDA, AMPA/kainite type receptors, and (b) metabotropic glutamate receptors, consisting of mGluRs of which intracellular actions are mediated by G-proteins. Metabotropic glutamate receptors (mGluRs) belong to three groups, mGlu I, mGlu II and mGlu III, based on signal transduction pathways and sequence homology (Schoepp, 2001). The *GRM8* gene that encodes mGluR8 spans over 800 kb, and is composed of 10 exons and 9 introns (Shigemoto et al., 1997). Prominent mGlu8 expression has been observed in several areas of limbic system, especially the hippocampus, pontine nuclei, and lateral reticular nucleus of the medulla oblongata. Strong expression for mGlu8 has also been noted in scattered cells in the deeper layers of the cerebral cortex and pyramidal cells of the piriform cortex. The mGlu8 is detected in the presynaptic active zone in both glutamatergic and GABAergic terminals in various brain regions (Ferraguti and Shigemoto, 2006). Presynaptic inhibition of synaptic transmission via activation of mGluRs occurs very widely in the brain, with involvement of group II and group III mGluRs being especially prominent. The electrophysiological studies of these receptors have shown the regulation of synaptic sensitivity via suppression of presynaptic voltage-dependent calcium channels, the activation of presynaptic K+ channels and the direct inhibition of regulated exocytosis (Anwyl, 1999).

In light of the theta oscillations showing strong association to both *CHRM2* and *GRM8* genes, one could speculate a synergistic genetic mechanism underlying this electrophysiological phenotype, thus opening doors to future research in this direction. Interestingly, in studies on the rat hippocampus, authors have reported that a majority of interneurons strongly immunopositive for the muscarinic M2 or the mGlu1 receptors were the primary targets of mGluR8-containing terminals (Ferraguti et al., 2005). Rare neurons coexpressing calretinin and M2 were consistently targeted by mGluR8-positive boutons. The postsynaptic interneuron type-specific expression predicts a role in adjusting the activity of interneurons depending on the level of network activity.

4. Conclusion

This nascent field of investigation into the genetic underpinnings of the oscillatory dynamics is rapidly evolving, propelled by (a) technological advances in the field of genetic research, such as new SNP-chip technology, advanced functional studies, improved statistical genetic methods, and (b) new mathematical tools for signal analysis, improved imaging methods and the emerging idea of oscillatory interactions as units of dynamic functional brain states (Basar, 2006). Together, these advances provide a better means to understand brain function and make gene identification and understanding of gene expression imminently tenable. The recent identification of genetic loci regarding brain oscillations indicates that they are under genetic control and are modulated by genes controlling neurotransmitters in the brain. This approach has the unprecedented potential to unravel the complex interplay of various neural subsystems relevant to the generation of brain oscillations elicited under different cognitive conditions. The advent of genomics and proteomics and a fuller understanding of gene regulation will open new horizons on the critical electrical events so essential for human brain function. It is a hope that by combining these approaches we can eventually understand how much of the capacity to modulate these oscillations, in the context of a disease state, lies in control of genes and how environment influences this control.

Alcohol dependence and related disorders results 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. In our endeavor to study the genetic underpinnings of predisposition/risk, some key genes that have emerged from the quantitative phenotype studies are the $GABA_A$ receptor (*GABRA2*), the metabotropic glutamate receptor (*GRM8*), and the cholinergic muscarinic receptor (*CHRM2*) genes. These results do not imply that these genes are wholly responsible for the existence of the respective brain oscillations. It is however more likely that the individual variations in the oscillations are a product of genetic variation of the *GABRA2*, *GRM8* and *CHRM2* receptor genes, and the altered oscillatory activity is its cognitive correlate. Although no functional variant affecting the electrophysiological characteristics has yet been identified at the molecular level, there is a great deal of pharmacological evidence that attests to the relevance of these receptors to aspects of cognitive functions. Moreover, these genes are known to have very complex transcriptional patterns with different types of promoters and tissue specific expression patterns that add to the complexity.

Functional studies are underway to understand the effects of observed coding and/or non-coding variants of the key genes in gene expression and protein function in animal and *in vitro* models. Data from our COGA project indicate that in the case of *GABRA2*, the regulatory differences may affect alternative splicing and alternative promoter use (Tian et al., 2005). This eventually results in several isoforms in different brain regions, possibly with differing levels of functionality. Future molecular studies examining the functionality of isoforms will allow us to come full circle in determining the brain oscillation-to-gene connections.

Understanding genetic control of brain electrical activity may provide clues about cerebral function, and may shed light on pathogenic mechanisms involved in neurological and psychiatric disorders, where impairment in brain electrical activity is apparent. Once genes are identified and understood, risk genotypes and haplotypes can be used in prospective studies of young individuals, and can lead to an improved understanding of how cognitive changes contribute to susceptibility, which in turn can lead to the design of well-targeted prevention initiatives.

Acknowledgments

This manuscript is dedicated to the memory of Henri Begleiter (deceased April 6, 2006), Distinguished Professor of Psychiatry and Neuroscience, and founder and director of the Neurodynamics Laboratory, now renamed in his honor. His scientific vision brought together the fields of brain oscillations and genetics, culminating in the use of brain oscillations as endophenotypes, which is the subject of this manuscript. Our laboratory continues to follow the path that he envisioned, inspired by his innovative approaches to research.

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