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Genetics of human brain oscillations

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Abstract

In the last three decades, much emphasis has been placed on neural oscillations in vitro, in vivo, as well as in the human brain. These brain oscillations have been studied extensively in the resting electroencephalogram (EEG), as well as in the underlying evoked oscillations that make up the event-related potentials (ERPs). There are several approaches to elucidate the possible mechanisms of these brain oscillations. One approach is to look at the neurophysiology and neurochemistry involved in generating and modulating these oscillations. Another more recent approach is to examine the genetic underpinnings of these neural oscillations. It is proposed that the genetic underpinnings of these oscillations are likely to stem from regulatory genes which control the neurochemical processes of the brain, and therefore influence neural function. Genetic analyses of human brain oscillations may identify genetic loci underlying the functional organization of human neuroelectric activity. Brain oscillations represent important correlates of human information processing and cognition. They represent highly heritable traits that are less complex and more proximal to gene function than either diagnostic labels or traditional cognitive measures. Therefore these oscillations may be utilized as phenotypes of cognition and as valuable tools for the understanding of some complex genetic disorders. Genetic loci that have been recently identified regarding both resting and evoked brain oscillations involving the GABAergic and cholinergic neurotransmitter systems of the brain are discussed. It is concluded that 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.

Keywords: Brain oscillations; Endophenotypes; Psychiatric genetics; EEG; Event-related oscillations

1. Introduction

In recent years it has been amply demonstrated that brain oscillations represent important correlates of human information processing and fundamental aspects of cognition (Başar et al., 1999; Karakaş et al., 2000a,b). These oscillations have been studied in relation to normal cognition, but more recently have been used to characterize a variety of psychiatric and neurological-clinical disorders (Gallinat et al., 2004; Kamarajan et al., 2004; Spencer et al., 2004; Porjesz et al., 2005). However, for most psychiatric conditions, the clinical descriptors lack rigorous validity, or in some cases, significant reliability. Therefore, the use of phenomenological symptom descriptors for psychiatric disorders may be inadequate as rigorous phenotypic entities in genetic studies. Furthermore, psychiatric disorders are dichotomous; either an individual is affected or unaffected. Therefore it is difficult to use psychiatric diagnosis as the sole phenotype when studying the genetics of complex (non-Mendelian) disorders, which involve contributions from both genetic and environmental influences and their interactions. Thus, it is difficult to find the genes associated with common complex disorders (e.g. psychiatric disorders) that may result from small effects of many genes (polygenic), incomplete or low penetrance, clinical and genetic heterogeneity, the presence of phenocopies (non-genetic causes), and diagnosis uncertainty.

To the extent that most psychiatric disorders involve a variety of brain dysfunctions, the use of brain oscillations may provide the most informative phenotypes or endophenotypes (intermediate phenotypes). 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 biological markers (endophenotypes) serve as covariates that correlate with the main trait of interest (psychiatric diagnosis) and serve to better define that trait or its underlying genetic mechanism

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(Gottesman and Shields, 1972, 1973; Gottesman and Gould, 2003). These quantitative electrophysiological traits are less complex than clinical endpoints, are more proximal to gene function than either diagnostic labels or traditional cognitive measures (Tsuang and Faraone, 2000), and hence provide more power to localize and characterize disease susceptibility genes (Almasy, 2003).

In order to be considered as a good quantitative biological endophenotype, several criteria must be met (Begleiter and Porjesz, 1995). Firstly, the trait must be present in affected individuals and correlate with diagnosis and severity of disease or age of onset. Secondly, the trait must reflect susceptibility, and not be the consequence of transient states. Thirdly, the trait must be present in unaffected relatives of affected individuals with levels significantly higher than in random controls. Finally, the trait must be heritable. Thus 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, but rather are indices of underlying predispositions that can have different clinical endpoints. Thus, the endophenotype approach has many advantages in the genetic studies of complex disorders compared to using diagnosis as the sole phenotype. This approach can identify relatives of affected individuals who would be considered to be unaffected with dichotomous diagnostic systems, thus most importantly identifying individuals at risk before the development of the disease. In addition, there is a known neurobiology in endophenotypes, such as brain oscillations, that can be related to candidate gene effects. Candidate locations for the susceptibility loci can also be determined, as it is easier to identify genes influencing quantitative measures, such as brain oscillations, that also influence susceptibility to a disorder, than to find genes through direct analyses of disease status (Almasy, 2003).

As they meet the above criteria, brain oscillations may be utilized as phenotypes of cognitive processes, and as valuable endophenotypes for the understanding of some complex genetic disorders. Brain oscillations are highly correlated with a variety of cognitive processes as well as with brain dysfunction involved in the predisposition to some psychiatric disorders; most importantly, they are known to possess excellent heritability. Therefore, they provide a unique opportunity to go beyond a myriad of correlations between oscillations and cognition; that is, they offer the possibility to not only elucidate the basic neurophysiological mechanisms underlying these fundamental brain events, but also their underlying genetics. 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. Over the last several years, a major program of research in our laboratory has been to elucidate the genetic underpinnings of human brain oscillations during a resting condition and under specific cognitive operations. This chapter will discuss these genetic findings and their relevance to neurochemical processes that underlie neural function involved in cognition and their value in understanding complex genetic disorders.

2. Brain oscillations

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 designated 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. In addition, there are oscillations which are part of the ERPs but are not time-locked. 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. Hence, these brain oscillations offer unique opportunities for genetic analyses of neural function.

Brain oscillations characterize important correlates of human information processing and cognition. They represent traits less complex and more proximal to gene function than either diagnostic labels or traditional cognitive measures. Therefore these oscillations may be utilized as phenotypes of cognition, and as valuable tools for the understanding of some complex genetic disorders. It should be noted that the heritability of these oscillations obtained under resting conditions is estimated to be between 80% and 90% (van Beijsterveldt et al., 1996); heritability is the single most important characteristic of a quantitative trait to be used for genetic study.

2.1. Potential genes associated with brain oscillations

There are many possible approaches for finding genes for quantitative traits (e.g. brain oscillations) and complex diseases (e.g. psychiatric disease). These approaches fall into two main categories: genome-wide studies, which include linkage studies, and 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; yet each has both advantages and drawbacks (For a review of these approaches see Hirschhorn and Daly, 2005). To evaluate the potential role of individual genes in brain oscillations it is important to consider several methods of genetic analysis, and the pros and cons of each. Because of the rapidly evolving technology in the field of quantitative genetics, new methods are emerging that will facilitate the search for genes in the near future and will soon make these older methods obsolete. Nevertheless, as this chapter will indicate, we have used both approaches to successfully find some genes involved in brain oscillations that also are involved in risk for psychiatric disease. Therefore, in this chapter we plan to highlight both candidate genes and evidence of allelic associations as opposed to relying solely on traditional linkage findings.

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. 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; however, these methods have had only marginal success in locating genes associated with more common complex traits, which are likely the result of multiple small gene effects. Nevertheless, gene variants contributing to susceptibility for several complex common diseases (e.g. inflammatory bowel disease, schizophrenia and type 1 diabetes) have been found with this genome-wide linkage approach (Hirschhorn and Daly, 2005). As will be seen in this chapter, genes involved in the susceptibility for the development of alcohol dependence have also been found with this approach, using brain oscillations as endophenotypes.

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. 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 polymorphism. The selection of a candidate gene can be made in two ways: subsequent to a very 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, candidate genes could perhaps be regulatory genes that control neurochemical processes in the brain, and hence neural functions that are likely to influence brain oscillations. As will be seen in this chapter, both 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 noted that a positive association between an allele and an oscillation may also reflect various artifacts. Artifacts can arise from genotyping errors, as well as multiple testing. A 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 association studies, such as using family-based controls, or limiting analyses to ethnically homogeneous groups of individuals (e.g. only Caucasians). Because 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 single nucleotide polymorphism (SNPs), the possibility exists of identifying specific genes that affect human cognition and various neural oscillations that underlie them. While there are more than 6 million SNPs in the human genome, very few SNPs will be functional, i.e., result in changes in expression or proteins (Goldberg and Weinberger, 2004; Hirschhorn and Daly, 2005). The majority of these functional changes will affect the regulation of transcription via promoter polymorphisms. The organization of transcription may be affected through splice-site polymorphisms. 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). At this point in time, it is not possible to determine how many of these variations will affect brain oscillations and cognitive processes. 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.

2.2. 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 (8.0–11.5 Hz), beta (12.0–28.0 Hz), and gamma (28.5–50.0 Hz), with each frequency reflecting a different order of brain activity. Scalp recorded EEG is stable and reflects resonant loops in the cortex. In healthy adults, alpha (8–13 Hz) frequency predominates the awake resting EEG, followed by beta (14–30 Hz) and gamma (>30 Hz) with only sparse occurrence of low frequencies, such as delta and theta (0.3–7 Hz) (Nunez, 1995; Niedermeyer, 1999).

2.2.1. Genetic studies of resting 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 indicates that the resting EEG is highly heritable across all frequency bands: delta 76%, theta 89%, alpha 89%, and beta 86% (van Beijsterveldt and Boomsma, 1994; van Beijsterveldt et al., 1996). EEG coherence has also been reported to be heritable, with estimates between 50% and 70% (Stassen et al., 1988; van Beijsterveldt and Boomsma, 1994; van Baal et al., 1998; 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.

An alpha variant, namely low voltage alpha (LVA), has recently been reported to be associated with a genetic variant that leads to low activity in catechol-*o*-methyltransferase (COMT), the enzyme that metabolizes dopamine and norepinephrine (NE) in females (Enoch et al., 2003). In a previous study by the same authors, LVA had been reported to be associated with a subtype of alcoholism that is related to anxiety disorder (Enoch et al., 1999). Taken together, they hypothesize that altered NE levels on thalamic activity may partly explain the connection between LVA and anxiety disorders in alcoholic women. LVA has also been linked to the GABAergic system (Winterer et al., 2003c). These authors report an association between the exon 7 variant of the $GABA_B$ receptor gene and EEG alpha voltage (classified as LVA or normal).

In another study, Winterer et al. (2003b) also report that three 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. Susceptibility loci for epilepsy and schizophrenia have been mapped to this region of chromosome 6 (Liu et al., 1995; Straub et al., 1995; Izzi et al., 2003; Matthysse et al., 2004). In a series of studies, Winterer et al. report abnormal interhemispheric EEG coherence in the parietotemporal area of alcohol dependent, epileptic and schizophrenic patients as well as their relatives, suggesting that EEG coherence may serve as an endophenotype for these disorders. For example, increased interhemispheric EEG coherence has been reported in alpha and beta frequency bands in both long-term abstinent and non-abstinent alcoholics, particularly for the alpha 2 (10.5–12.0 Hz) frequency band, and was most pronounced at temporal, parietal and occipital regions, particularly when depression was included as a covariate; there was no effect of length of abstinence, indicating that these were "trait" rather than "state" related findings (Winterer et al., 2003a).

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). $GABA_A$ 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). Thus 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). Our genetic findings described below indicate the importance of $GABA_A$ receptor genes in the modulation of beta oscillations in the human brain.

In our laboratory, we have investigated the genetic underpinnings of the resting EEG rhythms (Porjesz et al., 2002). EEG recordings were obtained with 19 non-invasive scalp electrodes in the awake, eyes-closed condition. The filtered artifact-free data were transformed into horizontal bipolar derivations. EEG absolute power between 3 and 28 Hz were subdivided into theta (3.0–7.0 Hz), alpha 1 (7.5–9.0 Hz), alpha 2 (9.5–12.0 Hz), beta 1 (12.5–16.0 Hz), beta 2 (16.5–20.0 Hz), and beta 3 (20.5–28.0 Hz). A singular value decomposition procedure (Wang et al., 2000) was utilized to obtain phenotypic data for each of the six EEG power bands.

We performed a total genome scan using a variance component linkage analysis (SOLAR, Sequential Oligogenic Linkage Analysis Routines, Almasy and Blangero, 1998) to assess genetic linkage. This method yields a LOD score, indicating the likelihood that there is linkage between a genetic marker locus and the phenotype (EEG spectral band power). The linkage analysis of the EEG power was based on 1553 individuals in 250 families, with a total of 351 polymorphic microsatellite markers distributed across the genome. We found significant genetic linkage (Beta 1, LOD=3.39; Beta 2, LOD=5.01; Beta 3, LOD=2.17) between the beta frequency of the human EEG and a cluster of $GABA_A$ receptor genes on chromosome 4p (Porjesz et al., 2002). Combined linkage/linkage disequilibrium (Almasy et al., 1999) to test the association between the Beta 2 EEG phenotype and the $GABA_A$ receptor gene cluster on chromosome 4 was highly significant for association (LOD increased from 5.01 to 6.53; $p=0.004$) (Porjesz et al., 2002). The estimated disequilibrium parameter ($\rho_d=0.57$) indicated linkage disequilibrium between the GABA microsatellite marker and the functional QTL. In addition, a novel non-parametric multipoint linkage technique also gave strong evidence for linkage in this region ($p<1.0e^{-6}$) using the same EEG beta 2 phenotype (Ghosh et al., 2003).

With the use of multiple single nucleotide polymorphisms (SNPs) across this cluster of $GABA_A$ receptor genes on chromosome 4p, that includes *GABRA2*, *GABRA4*, *GABRB1* and *GABRG1*, we were able to specifically identify that it was variations in the *GABRA2* receptor gene that accounts for the linkage/linkage disequilibrium findings with the EEG beta frequency. 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). The rs279836 SNP in the *GABRA2* receptor gene showed the strongest association to the 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 power compared to individuals with all other genotypes. It is hypothesized that these individuals are more likely to manifest CNS disinhibition, and to be more at risk to develop impulsivity-related disorders, including alcoholism (see below).

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). Neuroimaging 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). Increased beta power in the resting EEG of alcoholics has been well documented (Propping et al., 1981; Costa and Bauer, 1997; Winterer et al., 1998; Bauer, 2001; Rangaswamy et al., 2002). Several studies also report increased beta power in the EEG of offspring of alcoholics (Gabrielli et al., 1982; Pollock et al., 1995; Finn and Justus, 1999; Rangaswamy et al., 2004); 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). 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 affect the level of neural excitability, which in turn affect the predisposition to develop alcohol dependence. Studies are underway to examine young individuals with the high risk *GABRA2* genotype (rarer rs279836 SNP) as they go through the age of risk.

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 regarding the nature of the genetic predisposition.

2.3. 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 (Başar 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.

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 (Başar-Eroğlu and Başar, 1991; Schurmann et al., 1995; Yordanova and Kolev, 1996; Karakaş et al., 2000a,b; Başar-Eroğlu et al., 2001; Demiralp et al., 2001; Schurmann et al., 2001). On sensory stimulation, random resting EEG oscillations become amplified and coupled, and this synchronization and enhancement of EEG activity give 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. Başar, 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 (Başar et al., 1999; Schurmann et al., 2001); theta: conscious awareness, recognition memory, and episodic retrieval (e.g. Klimesch et al., 1994, 2001; Doppelmayr et al., 1998; Gevins et al., 1998; Başar et al., 2001c); slow alpha: attribution of attentional resources (Başar 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. Başar-Eroğlu et al., 1996a,b; Schurmann et al., 1997; Başar et al., 2001a,b; Karakaş et al., 2001, 2003).

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 reflects 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).

2.3.1. Genetic studies of theta and delta EROs underlying P3

Several studies have demonstrated that P3 responses are primarily the outcome of theta and delta oscillations elicited during cognitive processing of stimuli (Başar-Eroğlu et al., 1992; Yordanova and Kolev, 1996; Başar et al., 1999; Karakaş

et al., 2000a,b; Anokhin et al., 2001), with delta oscillations more concentrated in the posterior region, while theta is more centered in the fronto-central region (Karakaş et al., 2000b); theta oscillations also contribute strongly to N2 components. Studies with implanted electrodes and more recently neuroimaging methods indicate that P3 has multiple sources, with contributions from frontal cortex (including anterior cingulate) and hippocampus (Halgren et al., 1980; Menon et al., 1997; Kiehl and Liddle, 2001; Ardekani et al., 2002). 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 addition to the study of genes involved in spontaneous oscillations recorded during rest, we have undertaken to examine the genetic underpinnings of oscillations recorded during event-related potentials (ERPs) under different task conditions. We have taken this approach of trying to identify genes underlying neural oscillations that underlie ERPs rather than to study the genetics of the ERP components themselves, as ERP components are not unitary phenomena, but complex traits. ERPs represent averaged electrical neural activity of superimposed oscillations of different spectral EEG frequencies emanating from multiple brain sources. Thus, it is more fruitful to examine the genes underlying the various oscillations that contribute to the ERP components, rather than the genetics of the complex components themselves; as the neural oscillations are closer to gene action, we are more likely to find genes with this approach.

Here, we will focus on oscillations underlying the P3 component obtained to an infrequent target stimulus in a visual oddball paradigm (see Fig. 1). 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 calculated with the S-transform (Stockwell et al., 1996) extracted for the P3 time window (300–700 ms), across the delta and theta frequency bands, the spectral bands that primarily account for P3. These energy estimates were averaged across three 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.

To test whether the observed theta band linkage findings were directly influenced by the *CHRM2* gene on chromosome

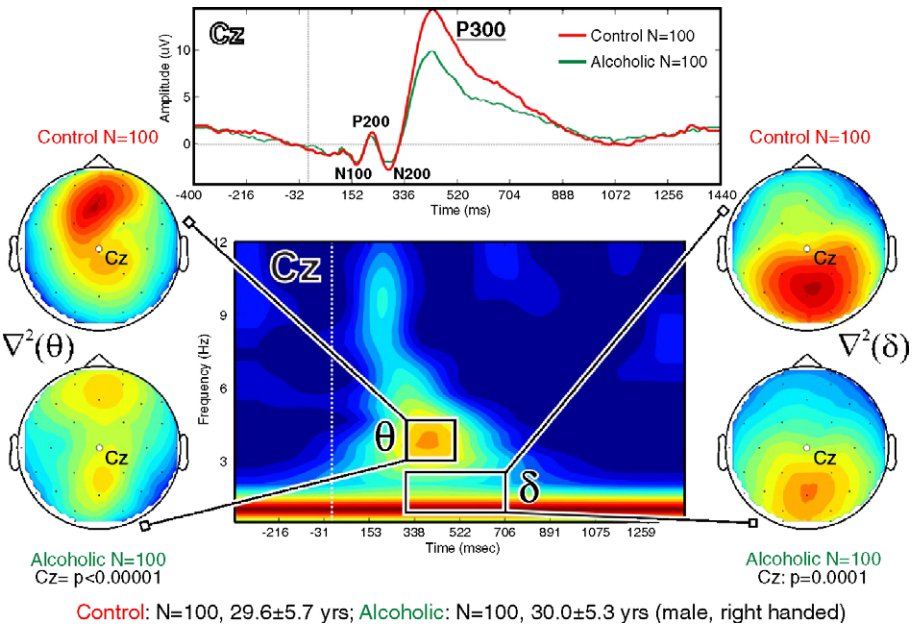

Fig. 1. Time-frequency and grand mean representation of visual oddball target case data for age matched control and alcoholic right-handed male subjects (100 controls and 100 alcoholics with mean age of 29.6 ± 5.7 years and 30.0 ± 5.3 years, respectively). The top plot depicts the traditional grand-mean event-related potential to the target stimulus (Cz electrode) for the control (red curve) and alcoholic subjects (green curve). The lower plot displays a time-frequency representation of the average instantaneous amplitude at Cz derived using the S-transform (Stockwell et al., 1996); for each subject the instantaneous amplitudes were averaged across individual trials so that non-phase-locked or imprecise phase-locked oscillatory energy is preserved. Within each subject mean-value ERO amplitude data are extracted using time-frequency regions of interest (TFROI), which is indicated with a rectangle on the plot; for the delta band (1–3 Hz) we use a 300–700 ms post-stimulus time window, and for the lower theta band (4–5 Hz) we use a 300–500 ms post-stimulus time window. The current source density (CSD) maps for each group separately are shown plotted in the head plots at the corresponding channel locations on the left for theta band and on the right for the delta band with controls above alcoholics. Note that the theta band has a frontal distribution, while the delta band has a posterior distribution and that these CSD plots show weaker sources for both frequency bands in the alcoholic group compared to the controls. 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: Cz channel, delta, $p < 0.00001$; Cz channel, lower theta, $p < 0.0001$.

7, SNPs were genotyped in and around the candidate gene. Estimates of measured genotype linkage disequilibrium with the *CHRM2* SNPs were obtained with the Caucasian sample only, in order to avoid stratification problems. Significant linkage disequilibrium (LD) was found between the theta phenotype at frontal and central regions and 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. It is interesting to note that the LD between the theta band and SNPs was most significant for more anterior leads, where theta is maximal during target processing, while the LD between the delta band and SNPs was most significant for more posterior leads, where delta is maximal during target processing. Significant linkage and LD were only obtained for the target and not the 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 involved in processing of the target stimulus (P3). 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). These results strongly support the role of acetylcholine in the generation of the N2 (theta oscillations), and P3 components (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 has yielded modified memory performance, and modified P3 amplitude in humans (Hammond et al., 1987; Dierks et al., 1994; 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 produce short episodes of theta oscillations; interestingly, carbachol-induced delta rhythms were not observed concurrent with carbachol-theta (Fellous and Sejnowski, 2000; Tiesinga et al., 2001). Thus, theta production may be evoked by increased high concentrations of muscarinic activity, whereas delta band oscillations may be the result of significant reductions in muscarinic activity.

It has long been reported that alcoholics and their offspring at high risk to develop alcoholism manifest reduced P3 amplitudes to target stimuli (Begleiter et al., 1984; Polich et al., 1994; Porjesz et al., 2005), particularly in visual paradigms. More recently we have found that both theta and delta band oscillations are reduced in alcoholics (Fig. 1) and offspring at high risk to target stimuli during a visual P3 task (Porjesz and Begleiter, 2003; Jones et al., in press; Rangaswamy, in preparation), as well as in a Go/No-Go paradigm (Kamarajan et al., 2004, in press). It should be noted that low visual P3 amplitude is not specific to alcoholism, but has been reported in various related disinhibitory conditions (externalizing disorders) such as substance abuse, antisocial personality, conduct disorder, attention deficit hyperactivity disorder (cf. Porjesz et al., 2005), as well as a number of other disorders (cf. Polich and Herbst, 2000). It has been proposed that these related behavioral traits should be viewed as variable expressions of a generalized disinhibitory complex (Gorenstein and Newman, 1980). Recent evidence suggests that studies of the genetics of externalizing disorders have indicated that a similar underlying genetic diathesis is passed on to the next generation, with each disorder representing a different endpoint or expression of the same underlying genetic vulnerability (Krueger et al., 2002; Hicks et al., 2004).

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.

3. Conclusion

Brain oscillations represent important correlates of human information processing and cognition. The advent of human genomic data, in combination with neurochemical and neuroanatomical information, has the unprecedented potential to unravel the complex interplay of the various subsystems relevant to the generation of brain oscillations elicited under different cognitive conditions. It is important to note that these brain oscillations represent traits less complex and more proximal to gene function than either traditional cognitive measures or conventional psychiatric diagnostic labels. Therefore, these neural oscillations may be utilized as phenotypes underlying cognition, and as valuable tools for the understanding of some complex psychiatric genetic disorders.

While the field of research linking gene variants to brain oscillations is in its infancy, we can see from the aforementioned findings that several interesting genetic correlates of different brain oscillations have already been noted. Because of the rapidly evolving technology in the fields of molecular and quantitative genetics, new methods are emerging that will facilitate the search for genes underlying complex traits in the near future. With the advent of SNP genotyping technology, genome-wide association studies using dense sets of SNPs across the genome will allow the identification of heritable quantitative traits that are risk factors for complex diseases. It will become increasingly important to use novel genetic approaches that can assess small gene effects, to determine the relationship between genetics, various brain oscillations and various aspects of cognition. Indeed, the value of the genetic approach should provide a better understanding of various subprocesses involved in cognition which are closely linked to neurobiology. We are actively pursuing a genetic approach

to elucidate our basic understanding of various human brain oscillations produced during the resting EEG as well as during different cognitive ERPs. Brain oscillations provide a very rich source of potentially useful phenotypes for psychiatric genetics as they represent important correlates of human information processing and cognition. In addition, the identification of suitable quantitative biologic markers that are genetically transmitted could elucidate the genetic factors involved in the etiology of various psychiatric disorders.

A better understanding of gene variants associated with specific brain oscillations which index cognitive processes will yield fundamental information about several clinical disorders that share common inherent causality and external manifestations of symptoms. It must be noted that the association between genes and oscillations is quite likely to involve epistatic as well as pleiotropic genetic effects, and the complex interaction of various cognitive systems. Moreover caution must be heeded as this endeavor is likely to yield multiple genes resulting in small effects.

The identification of genes which regulate our mental processes will be of enormous benefit not only to our understanding of cognitive processes, but will eventually have major salutary effects on our ability to deal effectively with various types of brain dysfunction. 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. The advent of genomics and proteomics and a fuller understanding of gene regulation will open new horizons on the critical neuroelectric oscillations so essential for human brain function.

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