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A *KCNJ6* gene polymorphism modulates theta oscillations during reward processing

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ABSTRACT

Event related oscillations (EROs) are heritable measures of neurocognitive function that have served as useful phenotype in genetic research. A recent family genome-wide association study (GWAS) by the Collaborative Study on the Genetics of Alcoholism (COGA) found that theta EROs during visual target detection were associated at genome-wide levels with several single nucleotide polymorphisms (SNPs), including a synonymous SNP, rs702859, in the *KCNJ6* gene that encodes GIRK2, a G-protein inward rectifying potassium channel that regulates excitability of neuronal networks. The present study examined the effect of the *KCNJ6* SNP (rs702859), previously associated with theta ERO to targets in a visual oddball task, on theta EROs during reward processing in a monetary gambling task. The participants were 1601 adolescent and young adult offspring within the age-range of 17–25 years (800 males and 801 females) from high-dense alcoholism families as well as control families of the COGA prospective study. Theta ERO power (3.5–7.5 Hz, 200–500 ms post-stimulus) was compared across genotype groups. ERO theta power at central and parietal regions increased as a function of the minor allele (A) dose in the genotype (AA > AG > GG) in both loss and gain conditions. These findings indicate that variations in the *KCNJ6* SNP influence magnitude of theta oscillations at posterior loci during the evaluation of loss and gain, reflecting a genetic influence on neuronal circuits involved in reward-processing. Increased theta power as a function of minor allele dose suggests more efficient cognitive processing in those carrying the minor allele of the *KCNJ6* SNPs. Future studies are needed to determine the implications of these genetic effects on posterior theta EROs as possible "protective" factors, or as indices of delays in brain maturation (i.e., lack of frontalization).

1. Introduction

Over several decades, electrophysiological brain signals recorded from the human scalp have provided a set of heritable quantitative measures of resting state (electroencephalogram, EEG) and of neurocognitive function during cognitive tasks (event-related potentials, ERPs) and their time-frequency constituents (event-related oscillations, EROs). Electrophysiological measures have proven to be highly useful in studying neurocognitive functions that unfold at the millisecond range of the time scale (compared to other neuroimaging methods, such as fMRI, PET). EROs represent the basic mechanisms of neural communication during cognitive tasks (Basar, 1999a), and they provide links to associative and integrative brain functions (Basar, 1999b) that can be used to investigate neurocognitive processes in normal as well as clinical conditions (Basar, 2013). Specific frequency bands within ERO responses are associated with particular cognitive processes (Basar, 1999b; Klimesch, 1999; Basar et al., 2001a; Kahana, 2006) based on the context and demand of the task.

Recent studies have indicated that ERO theta activity in particular is related to a variety of behavioral, cognitive, and motivational or emotional aspects of human information processing, including reward

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processing (Basar et al., 2001b; Kahana et al., 2001; Klimesch et al., 2005; Raghavachari et al., 2006; Cohen et al., 2007; Kamarajan et al., 2008). Specifically, ERO theta activity underlying feedback/outcome processing of monetary loss and gain (Luu et al., 2003; Gehring and Willoughby, 2004; Luu et al., 2004; Cohen et al., 2007; Kamarajan et al., 2008; Crowley et al., 2014) has been reported to be a highly useful measure to characterize reward circuitry dysfunction in psychiatric conditions (Oberg et al., 2011; Padrao et al., 2013; Andreou et al., 2015), including alcoholism (Kamarajan et al., 2012, 2015a).

ERO measures have been used as effective tools to understand brain mechanisms underlying alcoholism and its predisposition (for reviews, see Porjesz et al., 2005; Pandey et al., 2012; Rangaswamy and Porjesz, 2014; Kamarajan and Porjesz, 2015). Further, as reported in the combined analyses of ERP and ERO data, ERO measures yielded additional information than the traditional ERP measures to discriminate alcoholics from controls (e.g., Jones et al., 2006b) as well as high-risk from low-risk individuals (e.g., Rangaswamy et al., 2007).

In the Collaborative Study on the Genetics of Alcoholism (COGA), we have successfully used EROs as endophenotypes in the search for genes involved in alcoholism and related disorders (for reviews, see Porjesz et al., 2005; Pandey et al., 2012; Rangaswamy and Porjesz, 2014). Genetic studies of the theta ERO phenotype in a visual oddball task has been associated with several genes, including *CHRM2* (Jones et al., 2004, 2006a), *GRM8* (Chen et al., 2009), and *HTR7* (Zlojutro et al., 2011). Recently, in the first family-based GWAS of the frontal theta ERO phenotype, Kang et al. (2012) found genome-wide significant association between the frontal theta ERO power to targets in a visual oddball task and several SNPs (including a synonymous SNP, rs702859) in *KCNJ6* (KIR3.2/GIRK2, an inward rectifier potassium channel). GIRK2, the protein encoded by KCNJ6, is widely distributed in the brain and is an important functional element in dopaminergic, cholinergic, GABAergic and glutamatergic synapses, and hence the regulation of neuronal excitability (Saenz del Burgo et al., 2008). The advantage of a family-based study design is robustness against population substructure and the availability of the genotypes of both parents, which enables a more correct evaluation of genotype errors (cf. Kang et al., 2012). Following up this finding, a recent study from our group examined the effects of *KCNJ6* SNPs on developmental trajectories of the same theta ERO phenotypes in auditory and visual oddball tasks in adolescent and young adults (12–25) from the COGA prospective study; significant age- and gender-specific effects were found, with some effects of scalp locality and task modality (Chorlian et al., 2017).

ERO theta power during a monetary gambling task has been reported to be reduced while processing monetary loss and gain in both alcoholics and their high risk offspring (Kamarajan et al., 2012, 2015a), and the findings were interpreted as reward processing deficits in these groups. There is evidence to show that neural oscillations during reward processing underlie brain reward regions and/or circuits. For example, in a combined study of time-frequency ERO measure and fMRI data in human participants, (Mas-Herrero et al., 2015) reported that oscillatory activity elicited by monetary gains was associated with fronto-striatal-hippocampal reward network identified by the fMRI activity. Studies using implanted depth electrodes in rats have reported that neural oscillations were modulated by anticipation and delivery of reward (van der Meer and Redish, 2009; Kalenscher et al., 2010; Malhotra, 2014). Animal studies have also reported that genetic ablation of G-protein-regulated inward-rectifier potassium channel 2 (GIRK2, a protein encoded by KCNJ6 gene), promotes adaptations in the mesolimbic dopaminergic system (Cooper et al., 2012; Kotecki, 2015), a mechanism which is related to brain reward network and believed to promote chronic alcohol/drug intake leading to addiction (Arora et al., 2010). Based on these findings, it was conceptualized that studying the effect of a KCNJ6 SNP on brain oscillations during reward processing would help elucidate its role underlying the brain reward system.

There are studies implicating GIRK2/*KCNJ6* in regulating neuronal excitability. Studies have shown that GIRK2 contributes to the slow inhibitory postsynaptic potentials due to $GABA_B$ action (Luscher et al., 1997; Nicoll, 2004). Activity of GIRK receptors results in hyperpolarization that decreases neuronal excitability and this in turn directly influences neuronal activity (cf. Kang et al., 2012). There is also evidence that highlights the role of inhibition in pacing oscillations and establishing synchrony during cognitive processing in the brain (Isaacson and Scanziani, 2011). A simulation study examining decision time and theta rhythm suggests that a mixture of slow and fast inhibition can affect the power in the theta band and speed up the reaction times in a decision-making network (Smerieri et al., 2010).

The current study follows up the COGA genome-wide significant association of *KCNJ6* SNPs with theta EROs to targets during a visual oddball paradigm to determine its association with theta EROs during reward processing in a monetary gambling task, a phenotype similar to the one used in the original study, but tapping different neural processes, in order to determine if there is an association with theta EROs during a different task. The overall goal of the present study is to investigate the genotypic effects of a *KCNJ6* SNP (rs702859) on theta EROs during reward processing in subjects (17–25 years old) in the COGA Prospective study. This age range was selected as the study by Chorlian et al. (2017) indicated that the effects of this SNP on theta EROs were strongest in this age range of the prospective study. The rationale for selecting rs702859 was three-fold: (i) this SNP had a genome-wide significant association with theta ERO in the previous GWAS study; (ii) this SNP was in high LD with the top genome-wide significant genotyped SNPs, and (iii) this was the only exonic genomewide significant SNP in the *KCNJ6* gene. Given that there is empirical evidence showing relationships between (i) *KCNJ6* and the reward system, (ii) theta EROs and the reward system, and (iii) *KCNJ6* and brain oscillations, the primary hypothesis of the study is that variations in rs702859 genotypes will influence theta ERO power during loss and gain processing. In the current study, the term 'reward processing' is being used to mean neurocognitive processing related to both loss and gain, and any effect/context specific to either loss or gain will be properly mentioned. We expect that the findings from this study of variations in the *KCNJ6* gene on reward-related theta EROs may help to further our understanding of these genetic effects on reward processing and possible neurocognitive, behavioral and clinical implications.

2. Methods

2.1. Sample

The sample consisted of 1601 participants (800 males and 801 females) between 17 and 25 years of age from the prospective sample of the COGA study. The participants were offspring from families ascertained in previous phases of COGA (Begleiter et al., 1995; Edenberg et al., 2005): (1) multiplex alcohol dependent families (AD), many with multiple alcoholism-affected family members, and (2) community comparison families (CC) drawn from the general population. Participants enter the study when they are between the ages of 12–22 and are reassessed every two years with age-appropriate clinical, behavioral and neurophysiological assessments. For additional details of the sample characteristics, see Dick et al. (2013). For this study, participants within the age range of 17–25 years were selected; each individual was represented only once in the sample, at their earliest assessment within this age range. The number of subjects in each subgroup is shown in Table 1. The sample predominantly included participants with European ancestry (EA: 65.08%) and African ancestry (AA: 32.29), in addition to a small fraction with Hispanic ancestry (HA: 2.62%). Data from six collection centers have been included in this study: SUNY Downstate Medical Center at Brooklyn, New York; University of Connecticut Health Science Center; Washington University School of Medicine in St. Louis; University of California at San Diego; University of Iowa, and Indiana University School of Medicine. Recruitment and assessment procedures have been described elsewhere