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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).

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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

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

Table 1
Number and percentage of participants categorized by genotypes across gender and family type (CC = community comparison family; AD = alcoholism dense family).

Groups (age range = 17–25 years)		Genotype			
		0 (AA) mean age = 19.29	1 (AG/GA) mean age = 19.25	2 (GG) mean age = 19.41	Total
Gender	Male	426 (50.84%)	298 (48.77%)	76 (50.00%)	800 (49.97%)
	Female	412 (49.16%)	313 (51.23%)	76 (50.00%)	801 (50.03%)
	Total	838 (100%)	611 (100%)	152 (100%)	1601 (100%)
Family type	CC	95 (11.34%)	98 (16.04%)	31 (20.39%)	224 (13.99%)
	AD	743 (88.66%)	513 (83.96%)	121 (79.61%)	1377 (86.01%)
	Total	838 (100%)	611 (100%)	152 (100%)	1601 (100%)

(Begleiter et al., 1995; Reich, 1996) and are also available at this website: https://zork5.wustl.edu/coganew/data/instruments.html.

Subjects were instructed to refrain from using alcohol and substances for at least 5 days prior to EEG recording. Subjects were excluded from neurophysiological assessment if they had any of the following: (1) recent substance or alcohol use (i.e., positive breath-analyzer test), (2) hepatic encephalopathy/cirrhosis of the liver, (3) history of head injury, seizures or neurosurgery, (4) uncorrected sensory deficits, (5) use of medication known to influence brain functioning, and (6) other acute/chronic medical illnesses that affects brain function.
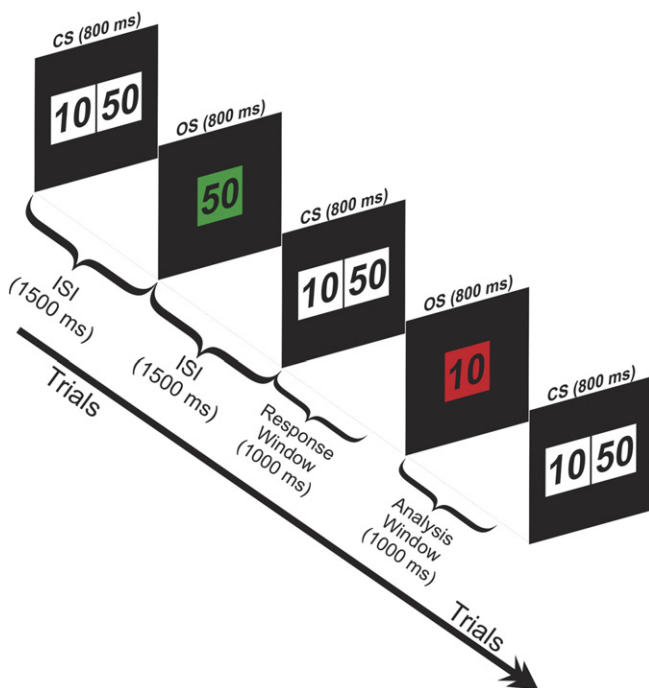
2.2. Monetary gambling task

The monetary gambling task (MGT) used in this study is illustrated in Fig. 1. Each trial begins with a choice stimulus (CS), with two numbers (representing monetary values in US cents) of 10 (left box) and 50 (right box), displayed for 800 ms. The participants select a bet of either 50¢ or 10¢, and receive feedback of either loss or gain for the selected amount (outcome stimulus, OS). The task details have been described in our previous publications (Kamarajan et al., 2008, 2012, 2015a, 2015b). The inter-stimulus interval between a CS and OS, and between an OS and the next CS is 1500 ms. The task involves a total of 172 trials, each with one of four possible outcomes: Loss 50, Loss 10, Gain 50, and Gain 10. The number of outcome events for loss/red and gain/green trials (OS) are equal (i.e., 50% loss and 50% gain trials regardless of the amount within each outcome), and the order of trial sequence is predetermined, pseudo-randomized, and identical for all participants. However, the participants are not aware of the probability or sequence of the trials. Although the loss and gain events are predetermined, the final outcome trials varied across the participants as they are free to choose either of the amounts in each trial.

2.3. EEG data acquisition and preprocessing

Identical experimental procedures and EEG acquisition systems were used at all neurophysiology collection sites with high inter-laboratory consistency in recordings (Alexander et al., 1994; Cohen et al., 1994; Kuperman et al., 1995; Rohrbaugh et al., 1997). Subjects were seated comfortably 1 m from a monitor in a dimly lit sound-attenuated RF-shielded booth (Industrial Acoustics, Inc., Bronx, NY, USA), and wore a 61-channel electrode cap (Electro-Cap International, Inc., Eaton, OH, USA) based on the Extended 10–20 System (Jasper, 1958; Chatrian et al., 1985, 1988; Oostenveld and Praamstra, 2001) (Fig. 2), with a

Fig. 1. Schematic illustration of the monetary gambling task. Each trial starts with a choice stimulus (CS) which lasts for 800 ms and displays two amounts (10¢ or 50¢) to bet with. The participant selects one of the amounts and receives an outcome of either gain (green box) or loss (red box) for the selected amount as shown by the outcome stimulus (OS). A trial with a gain of 50¢ and the next trial with a loss of 10¢ are illustrated. The ISI between the CS and the OS is 1500 ms. Participants were required to respond to the OS within 1000 ms (i.e., response window) by selecting one of the two amounts. ERO analysis was performed on trial epochs of 1000 ms post-stimulus period after the onset of the OS (i.e., analysis window).
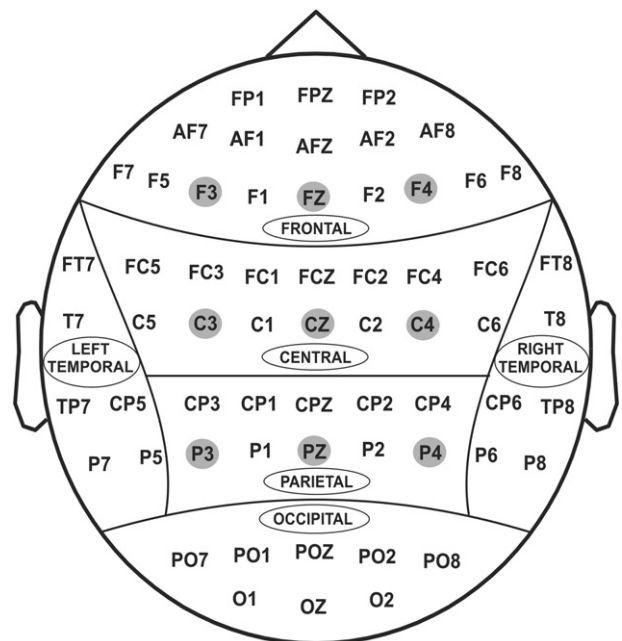
Fig. 2. Sixty-one electrodes were recorded in the current study from the surface of the scalp. Three regions, representing frontal (F3, FZ, F4), central (C3, CZ, C4), and parietal (P3, PZ, P4) electrodes were selected for statistical analyses (see shaded electrodes contributing to each of these regions).

reference electrode at the tip of the nose and with a ground electrode at the forehead. The electrooculogram (EOG) was recorded by a supraorbital vertical electrode and by a horizontal electrode on the external canthus of the left eye. Electrode impedances were maintained below 5 kΩ. Electrical activity was amplified 10,000 times using SynAmps2 amplifiers (Compumedics USA, Charlotte, NC) and was recorded continuously over a bandwidth between near-DC (0 Hz) and 100.0 Hz on a Neuroscan system (Versions 4.3–4.5; Compumedics USA, Charlotte, NC) at a sampling rate of 500 Hz. The EEG data were resampled offline to 256 Hz for the analyses. Then the waveforms were bandpass filtered offline with 0.05 Hz (low pass) and 55 Hz (high pass). EOG correction procedures were not applied. However, the trials with waveforms exceeding ± 100 μV (primarily due to eye movement artifacts) and other artifacts (e.g., low frequency (DC) drifts and shifts and high frequency noise above 50 Hz) were excluded from the analyses. EROs were extracted from the trial epochs of outcome stimuli (1000 ms post stimulus) which contained the feedback of either loss or gain condition (i.e., the epochs following colored frames in Fig. 1). The ERO data for the subjects whose ERP waveforms were morphologically aberrant were also further removed from the analyses. Only the trials containing loss and gain conditions for the bigger amount (50¢) were analyzed in the current study, as our previous work showed topographic similarity of theta power for both amounts within loss and gain conditions and more trials for the 50¢ conditions (Kamarajan et al., 2008). Each subject had a minimum of 15 artifact free trials for the ERO analyses.

2.4. ERO signal processing using S-transform

Time-frequency (TF) data were derived using the S-transform signal processing method, introduced by Stockwell et al. (1996). The S-transform has been explained in our previous papers (Kamarajan et al., 2008, 2012). The S-transform is derived from short-time Fourier transform and continuous wavelet transform, and has a greater flexibility, anti-noise performance, and utility in the processing of non-stationary and complex signals compared to other traditional methods, such as short-time Fourier transform and Wigner-Ville distribution (Yun et al., 2013). This method has been applied in several recent studies to analyze time-frequency signals of event-related oscillation (Jones et al., 2006b; Rangaswamy et al., 2007; Andrew and Fein, 2010; Kamarajan et al., 2012, 2015a; Pandey et al., 2016).

In the current study, total ERO theta power (which is a combination of both phase-locked and non-phase-locked activity) was computed from the outcome trials of the larger loss and gain conditions (50¢). Specifically, theta power (3.5–7.5 Hz) within the TFR corresponding to the 200–500 ms post-stimulus time window underlying both N2 and $P3$ components (Karakas et al., 2000; Harper et al., 2014) during 'loss 50' and 'gain 50' conditions was extracted at frontal (F3, FZ, F4), central (C3, CZ, C4), and parietal (P3, PZ, P4) regions. The average number of trials was 26.21 and 28.43 for the loss and gain condition, respectively.

2.5. Genotyping

Genotyping was performed at Washington University School of Medicine in St. Louis on an OpenArray platform, and at Indiana University School of Medicine in Indianapolis on the Sequenom MassArray system on a larger group of COGA subjects of which the sample described here is a subset. OpenArray genotyping is a multiplex TaqMan assay platform. The OpenArray Genotyping Plate Configurator was used to design assays. Arrays were scanned on the OpenArray NT imager and genotypes were called using the OpenArray SNP Genotyping analysis software. Sequenom Assays (iPLEX Gold) were designed using MassArray Assay Design Software (Sequenom, San Diego, CA). Hardy-Weinberg equilibrium (HWE) was computed separately in European Americans and African Americans, and cluster data were re-evaluated if HWE was significant at $p < 0.05$. All SNPs were cleaned for Mendelian inheritance using PEDCHECK (O'Connell and Weeks, 1998). SNP allele

frequencies and heterozygosities were computed in PLINK (Purcell et al., 2007) using data on founders only included in the larger group. Ethnic stratification was assessed with SNPrelate (Zheng et al., 2012) using 64 ancestry-informative SNPs, as part of a larger 96 SNP panel developed at the Rutgers University DNA and Cell Repository (RUID™). Further details on the genotyping data is available elsewhere (Olfson et al., 2014). The *KCNJ6* SNP assayed and used in this study, rs702859, is a synonymous SNP in exon 4 found to be associated with theta EROs to target stimuli in a visual oddball task in our previous GWAS at a genome-wide level of significance (Kang et al., 2012). This SNP had the nucleotides 'A' (adenine) as the major allele and 'G' (guanine) as the minor allele, and the participants were classified into one of three genotype groups based on the number of minor allele(s): 0 (AA), 1 (AG/GA), and 2 (GG).

2.6. Statistical analyses

Log-transformed ERO theta power, representing frontal (F3, FZ, F4), central (C3, CZ, C4), and parietal (P3, PZ, P4) electrodes, was compared across genotypes using repeated measures analysis of variance (RM-ANOVA) of the general linear model (GLM) by using (i) the genotype (0, 1, 2) as between subjects factor, (ii) task condition (loss, gain) and region (frontal, central, parietal) as within-subjects factors, and (iii) ethnic stratification (PC1, PC2), age, gender, and family type as covariates in the model (see Table 2). RM-ANOVA results were extracted from the multivariate test statistics (O'Brien and Kaiser, 1985; Field, 1988) as the ERO data for the within-subjects factors did not adhere to sphericity assumptions (i.e., the equality of the variances of the differences between levels of the repeated measures factor such as region). In other words, an appropriate alternative for the sphericity assumption while analyzing the EEG data is to use multivariate tests within a repeated-measures design (Bell and Cuevas, 2012), as used in the current study. F-values and p-values of Pillai's Trace (Pillai, 1955) were used. Further, on the figure illustrating the means of the EROs separated by genotype, region, and condition, the Bonferroni adjusted p-values of significant pairwise multiple comparisons have been provided [see Fig. 3].

3. Results

3.1. Theta EROs across genotypes

Mean age across genotype groups [AA = 19.29; AG = 19.25; GG = 19.41] was not significantly different. Significant main and interaction effects extracted from the ANOVA results have been presented in Table 2 and Fig. 3. There was a significant main effect of genotype showing an additive effect with increase in theta power corresponding to the number of minor alleles (GG > AG > AA ⟺ 2.82 > 2.74 > 2.70) [see Table 2]. The significant main effect of condition revealed that the gain condition (M = 2.79; SE = 0.02) displayed higher theta power than the loss condition (M = 2.71; SE = 0.02). The region main effect indicated that the parietal region had the highest theta power (M = 2.79; SE = 0.02)

Table 2
Significant main and interaction effects of theta power (Bonferroni corrected) as revealed by the RM-ANOVA analysis. Degrees of freedom (df) for hypothesis and error, F-value, p-value, level of significance (*$p < 0.05$, **$p < 0.01$), and effect size (partial eta square, η^2) are shown. The values for significant effects have been highlighted in bold font.

Factor(s)	df	F	p	η^2
Genotype	**2/1465**	**3.68**	**0.0255***	**0.0050**
Condition	**1/1465**	**4.07**	**0.0439***	**0.0028**
Region	**2/1465**	**3.77**	**0.0233***	**0.0051**
Genotype × condition	2/1465	0.91	0.3386	0.0012
Genotype × region	**4/2930**	**2.49**	**0.0411***	**0.0034**
Condition × region	**2/1465**	**3.08**	**0.0462***	**0.0042**
Genotype × condition × region	4/2930	0.46	0.7636	0.0006
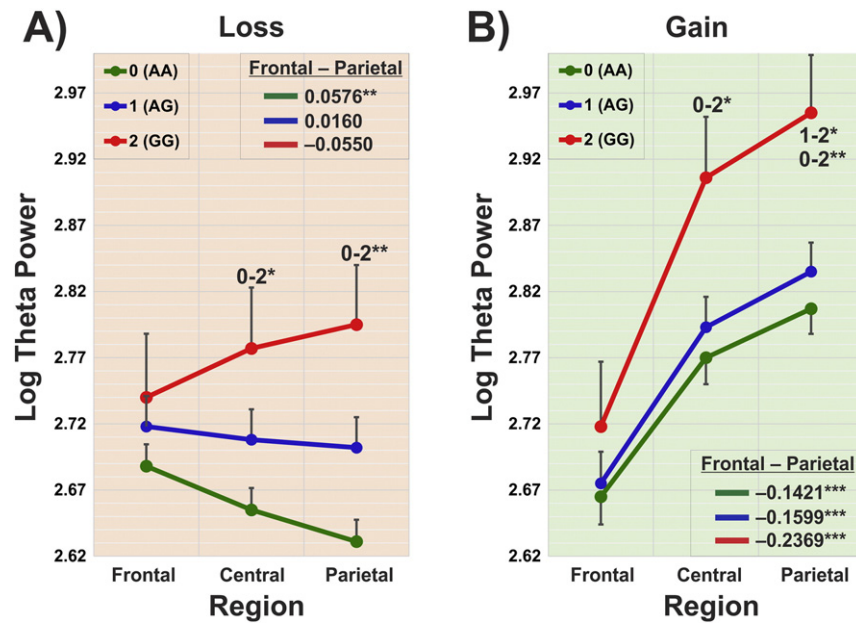
Fig. 3. Theta-band response elicited by loss (A) and gain (B) feedback in the gambling task. Log-transformed theta power (estimated marginal means) is plotted as a function of scalp region and rs702859 genotype. Bonferroni adjusted multiple comparisons of log-transformed theta power (estimated marginal means) across genotypes [AA/0 = green line; AG/1 = blue line; GG/2 = red line] at frontal, central, and parietal regions during loss (left panel) and gain condition (right panels) in all subjects. Significant differences in theta power between the genotypes (0, 1, and 2) have been marked with corresponding genotype numbers and asterisks ($^*p < 0.05$ and $^{**}p < 0.01$). Additive effect of genotype [GG > AG > AA] is seen with significant differences observed between AA and GG [GG > AA] at central ($^*p < 0.05$) and parietal ($^{**}p < 0.01$) regions during both loss and gain condition, while the gain condition additionally showed a significant difference between AG and GG [GG > AA] at the parietal region ($^*p < 0.05$). Step-wise increase in posterior theta power as a function of minor allele(s) is shown by the difference values between frontal and parietal regions (Frontal – Parietal) within each condition and genotype, positive values represent frontal maxima and negative values parietal maxima ($^{**}p < 0.01$ and $^{***}p < 0.001$). The vertical error-bars in the line graph represents 1 standard error, shown only for positive or negative direction in order to avoid any overlap with the data lines.

followed by central (M = 2.77; SE = 0.02) and frontal regions (M = 2.70; SE = 0.02). Genotype × region interaction effect indicated that theta differences between genotypes (GG > AA) were significant in central (2.84 > 2.71) and parietal (2.88 > 2.72) but not in frontal region (2.73 vs 2.68). Genotype × region interaction effect also revealed that theta power significantly varied between the regions (frontal vs. parietal) in each genotype group. Condition × region effect for theta power had a posterior maximum (parietal > central > frontal ⟺ 2.87 > 2.82 > 2.69) for gain ($p < 0.001$) and a topographic pattern that was not significant during loss (2.71 vs 2.71 vs 2.72). However, genotype × condition and genotype × condition × region interaction effects were not significant.

Bonferroni adjusted pairwise comparisons across genotypes, as derived from the estimated marginal means of the ANOVA model, have been illustrated in Fig. 3. Significant differences between AA and GG [GG > AA] at central ($p < 0.05$) and parietal ($p < 0.01$) regions during both loss and gain condition were found, while significant differences between AG and GG [GG > AG] were found only during gain condition at the parietal region ($p < 0.05$).

3.2. Topography of theta power across genotypes

Time-frequency (TF) plots and head maps of theta power across the genotypes during loss and gain conditions are shown in Fig. 4. There is an additive effect of genotypes [GG > AG > AA] with increasing theta power corresponding to the number of minor allele(s) during evaluation of loss as well as gain in central and parietal regions illustrating the effects shown in Fig. 3. Subtle topographic differences across genotypes manifested as gradual and relative increases of posterior theta power (i.e., minor allele(s) contributing to posteriorization of theta power). The ERP waveforms and P3 topography revealed a similar (but less robust) finding that the group with minor allele(s) displayed higher P3 amplitude compared to the group homozygous for the

major allele [GG/AG > AA], prominently at the posterior region, during the evaluation of loss as well as gain (see Fig. A1 in Appendix).

4. Discussion

The major findings of the current study are 1) an additive genotypic effect of the *KCNJ6* SNP on the ERO theta power phenotype during reward processing, increasing significantly across genotypes (GG > AG > AA) in central and parietal regions in both loss and gain conditions, and 2) genotypic effect on scalp topography of theta ERO phenotype during reward processing, with an anterior topography in those with the dominant AA genotype during loss evaluation not present in the AG and GG genotypes, while the 'anterior–posterior' effect was strongest in GG followed by AG and AA genotypes during gain processing. Our current study extends the previous findings showing an association between *KCNJ6* gene polymorphisms and theta ERO phenotypes to targets in an oddball task to an association with theta EROs during reward processing.

4.1. Genotypic effects on theta EROs

The major finding of the current study is that genotypic variations in the *KCNJ6* SNP (rs702859) influenced both magnitude and topography of ERO theta power with the minor allele (G) contributing to higher theta power (GG > AG > AA) at central and parietal regions (see Figs. 3 and 4). Previous studies have suggested that higher theta power during task conditions indicate efficient cognitive processing (Klimesch, 1999; Basar et al., 2001b). For example, individuals with and/or at risk for AUD have been shown to have lower theta power in several cognitive paradigms, reflecting deficient neurocognitive functioning in these individuals (Kamarajan et al., 2004; Jones et al., 2006b; Kamarajan et al., 2006; Rangaswamy et al., 2007; Kamarajan et al.,
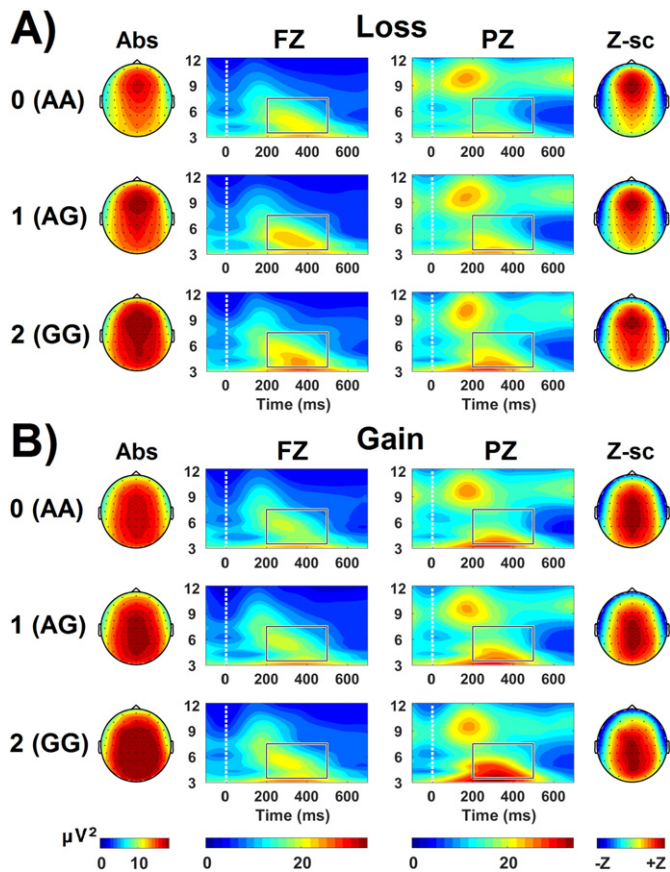
Fig. 4. Theta power (in μV^2) across genotypes (rs702859) during loss (panel-set A) and gain (panel-set B). Within these panel-sets, TF plots (middle panels showing x-axis with time in ms and y-axis with frequency in Hz for the loss and gain conditions at FZ and PZ electrodes) and head maps of absolute (left panels) and Z-scores (right panels) are illustrated. The dotted vertical line (at 0 ms) in the TF plots represents the onset of outcome stimulus. The smaller rectangles within the TF plots represent the TFROI of theta power (3.5–7.5 Hz within 200–500 ms) post outcome stimulus. During evaluation of loss as well as gain, there is an additive effect of genotypes [GG > AG > AA] with increasing power corresponding the number of minor allele(s) in central and parietal regions. Subtle topographic differences across genotypes (i.e., minor allele(s) contributing to posteriorization of theta power) are also shown.

2012, 2015a; Pandey et al., 2016). Therefore, the current findings of higher theta power during reward processing in the carriers of minor alleles may indicate that they have more efficient cognitive processing. Future studies will be needed to determine whether carrying the minor allele perhaps confers a 'protective' factor.

Our results also showed topographic differences of theta power across genotype during the loss condition (Fig. 4, panel A), with a gradual shift from a highly anteriorized topography of the AA genotype through a less anteriorized topography of the AG genotype to a weakly posteriorized topography of the GG phenotype. Similar results were seen in the ERP waveforms and topography across the genotype groups (see Fig. A1 in Appendix) but were less robust compared to the theta ERO findings, suggesting that time-frequency measures may be more useful to identify group differences. Previous studies have reported that ERO measures were better able to discriminate between alcoholics and controls and between high-risk offspring of alcoholics and low-risk offspring of controls (Jones et al., 2006b; Rangaswamy et al., 2007).

In a previous study of theta EROs during loss and gain in the same monetary gambling task, we reported topographic differences between the younger (12–15) and older (16–25) subsamples of the COGA prospective study in the same baseline condition (Kamarajan et al., 2015a). In that study, we found that the younger subsample (12–15)

showed more theta power and less frontalization, particularly for the loss condition, than the older subsample (16–25) (see Figs. 3 and 4 in Kamarajan et al., 2015a). Although the age range in the current study is not 'ideal' to examine these developmental changes in brain oscillations, when the topographic maps of late adolescents (17–18 years) and young adults (19–25 years) were compared (see Fig. A2 in Appendix), it was found that overall, the adolescent group showed more theta power and more diffuse posterior topography than the adult group, regardless of genotype. Furthermore, the subgroups with minor allele(s) (AG and GG) showed a more diffuse topography with less frontalization than those with the AA genotype, perhaps suggesting a delay in brain maturation. Electrophysiological (Matousek and Petersen, 1973; Gasser et al., 1988a, 1988b; Dustman et al., 1999; Segalowitz et al., 2010; Chorlian et al., 2015) and neuroimaging (Rubia et al., 2000; Gogtay et al., 2004; Sowell et al., 2004; Yurgelun-Todd and Killgore, 2006; Gogtay and Thompson, 2010; Rubia, 2013) studies of brain development indicate a reduction and focusing of activity, with a shift toward more frontal activity as pruning occurs in the brain (i.e., frontalization). Specifically, ERO theta power gradually decreases as children mature, becoming less in early adolescents, and even less in young adults (Yordanova and Kolev, 1998, 2009; Chorlian et al., 2015; Kamarajan et al., 2015a), as efficiency of cognitive functioning improves with increased phase locking of the theta system and hence neural communication in the course of development (Yordanova and Kolev, 1998, 2009). Therefore, given these suggested findings in the current study, it is possible that the minor alleles of *KCNJ6* could be associated with lack of frontalization and/or delayed brain maturation. It is also important to mention that the genotype × condition interaction was not significant, indicating that the main effect of genotype may be non-specific and pertain to the feedback evaluation process in general, rather than to loss or gain specifically. Since theta-band responses can be elicited by a variety of task-relevant stimuli, the effect observed could be non-specific. On the other hand, significant condition × region effect suggested outcome-specific theta activity, in which gain manifested posteriorly focused (parietal) theta power while the loss condition showed relatively anterior (fronto-central) focus. With regard to visual oddball paradigm, Kang et al. (2012) reported that theta power related to target processing was frontally focused, and the genome wide association was strongest for the frontal region, followed by central and parietal regions. Further studies are needed to ascertain the effects of task-specific theta activity on the genotypes of *KCNJ6* polymorphisms. Additional studies are also required to elucidate the exact role of variations in *KCNJ6* in modulating cognitive functioning and brain maturation.

4.2. Role of KCNJ6/GIRK2 in neurocognitive (dys)function and disorders

KCNJ6 gene encodes G-protein-coupled inwardly rectifying potassium channel 2 (GIRK2) which is one of four primary neuronal GIRK subunits, GIRK1-GIRK4 (Luscher and Slesinger, 2010). GIRK channels allow potassium ions to flow into the cell rather than out of the cell, a property referred to as "inward rectification" (Bodhinathan and Slesinger, 2014). GIRK channels have been shown to be critical for excitatory synaptic plasticity that underlies learning and memory, as GIRK2 null mutation or GIRK channel blockade has been found to abolish depotentiation of long-term potentiation in cultured hippocampal neurons (Chung et al., 2009). GIRK2 is also associated with opioid transmission in the brain and analgesic properties (Nishizawa et al., 2009). Further, GIRK2 is widely expressed in cerebellum, and an elevated expression of these channels may be involved in neuropathology, and contribute to a range of mental and functional disabilities in Down syndrome (Thiery et al., 2003; Harashima et al., 2006; Cramer et al., 2010). Alterations in GIRK channel function have been associated with pathophysiology of severe neurological disorders (cf. Bodhinathan and Slesinger, 2014), such as epilepsy (Signorini et al., 1997; Pei et al., 1999; Mazarati et al., 2006), Parkinson's disease and ataxia (Patil et al., 1995; Slesinger et al., 1996; Schein et al., 2005) and Down's syndrome (Siarey et al.,

1999; Cramer et al., 2010; Cooper et al., 2012). GIRK channels are implicated in motor activity, anxiety, reward and movement disorder (ataxia) (Pravetoni and Wickman, 2008). Recent studies have suggested possible role of KCNJ6/GIRK2 in bipolar disorder (Hamshere et al., 2009) and depression (Lazary et al., 2011). Further, there is also evidence to show that GIRK2/KCNJ6 function directly influences neuroelectric activity (EEG). For example, there are animal studies showing relationship between KCNJ6 and neuroelectric/seizure activity of the brain. A knockout mouse model found that animals deprived of functional KCNJ6 protein were susceptible to spontaneous and provoked seizures (cf. Hallmann et al., 2000). A recent study with a mouse model of seizure activity reported that GIRK2 channel (KCNJ6) may play a major role in the genesis of childhood epilepsy (infantile spasms) as measured by the changes in EEG activity and behavior (Blichowski et al., 2015). Importantly, animal studies have reported that GIRK2 channels influence reward network by promoting adaptations in the mesolimbic dopaminergic system, and thus could influence reward-related behaviors and actions including alcohol and drug addiction (Arora et al., 2010; Cooper et al., 2012; Kotecki, 2015). Taken together, these findings suggest that GIRK2 (or the KCNJ6 gene) may play a vital role in modulating neurocognitive function/dysfunction.

4.3. Role of KCNJ6/GIRK2 in modulating alcohol actions and addiction

Studies reporting alcohol modulation of GIRK channels have been well-documented (for a recent review, see Bodhinathan and Slesinger, 2014). KCNJ6/GIRK2 has also been found to be involved in addictions to several drugs, such as opioid/opiate (Lotsch et al., 2010), nicotine (Saccone et al., 2007; Nishizawa et al., 2014), morphine (Cruz et al., 2008), and cocaine (Morgan et al., 2003; Munoz and Slesinger, 2014). It is proposed that the regulator of G-protein signaling (RGS) proteins in the reward pathway might underlie adaptation to alcohol and other addictive drugs (Lomazzi et al., 2008). Neurochemical mechanisms underlying ethanol activation of GIRK channels have also been extensively studied (for reviews, see Luscher and Slesinger, 2010; Bodhinathan and Slesinger, 2014). It has been shown that mice lacking GIRK2 channels consumed more ethanol and failed to develop conditioned place preference for ethanol when compared to their controls (Blednov et al., 2001; Hill et al., 2003), suggesting that GIRK2 may be mediating the reinforcing and/or aversive motivational aspects of ethanol action. In a GWAS in the COGA sample with a neurophysiological phenotype (ERO theta power to targets in an oddball task) we have reported genome wide significant associations of KCNJ6 SNPs (Kang et al., 2012); however, the association of these SNPs with alcoholism (or other addictions phenotypes) in COGA were not examined. On the other hand, using a candidate gene approach, Clarke et al. (2011) reported a significant association of a KCNJ6 polymorphism (rs2836016) with alcohol dependence, hazardous drinking and early life stress, and suggested that individuals consumed more alcohol to experience its rewarding effects possibly mediated by the role of GIRK2 in dopaminergic signaling. However, this SNP is located in a different region of the KCNJ6 gene compared to the SNP explored in the current study. Since GIRK2/3 channels are exclusively expressed in VTA dopaminergic neurons (Cruz et al., 2004), these channel properties may have important implications for addiction in general and AUD in particular (Arora et al., 2010; Kotecki, 2015). Taken together, these findings may lead to uncovering new therapeutic targets as well as drug development for prevention and/or management of alcohol dependence (Kobayashi et al., 2004) by providing an opportunity to discover possible antagonists for ethanol-dependent activation (Bodhinathan and Slesinger, 2014).

4.4. Summary and implications

It is well-established that neuroelectrophysiological phenotypes, such as EEG, ERPs, and EROs are highly heritable (for reviews, see Begleiter and Porjesz, 2006; Anokhin, 2014). It is suggested that genetic

underpinnings of EROs likely stem from regulatory genes that control the neurochemical processes of the brain, thereby influencing neural function (cf. Pandey et al., 2012). Recent genetic studies and the current study have demonstrated associations of KCNJ6 with theta EROs (Kang et al., 2012; Chorlian et al., 2017). The current study has indicated that variations in the KCNJ6 SNP (rs702859) influence magnitude of theta ERO power at posterior leads during the evaluation of loss and gain, reflecting a genetic influence on neuronal circuits involved in reward processing. Higher theta power as a function of minor allele dose suggests more efficient cognitive processing in those carrying the minor allele of the KCNJ6 SNPs, as increased theta activity during cognitive tasks is indicative of efficient processing (Klimesch, 1999; Basar et al., 2001b). On the other hand, lack of frontalization in theta EROs observed in those carrying minor alleles may be suggestive of delayed brain maturation in these individuals. Future studies are needed to determine the specific effects of KCNJ6 on cognitive (dys)functions. Further, since KCNJ6/GIRK2 has been shown to be linked with the brain reward system though its modulation of dopaminergic signaling (Arora et al., 2010; Luscher and Slesinger, 2010; Cooper et al., 2012; Kotecki, 2015), these genetic findings with reward related brain oscillations may have behavioral and clinical implications.

Since KCNJ6/GIRK2 is related to alcohol action and addiction, it is possible that the finding has some relevance to alcoholism, although further studies linking KCNJ6 and human alcoholism are needed. As the KCNJ6/GIRK2 system modulates neuronal excitability and inhibition at a cellular and network level (Signorini et al., 1997; Luscher and Slesinger, 2010) and/or epilepsy (Pei et al., 1999; Mazarati et al., 2006), it may be involved in the neuronal hyperexcitabity (CNS disinhibition) indexed by high resting EEG beta and low P3 amplitude, theta and delta EROs that we have observed in our studies of alcoholics and those at risk, including during reward processing (for reviews, see Porjesz et al., 2005; Rangaswamy and Porjesz, 2014; Kamarajan and Porjesz, 2015). According to the 'CNS disinhibition' model of alcoholism proposed by Begleiter and Porjesz (1999), a heritable hyperexcitability of the CNS caused by homeostatic imbalance is involved in a genetic predisposition to develop alcoholism and related externalizing disorders. This model seems more relevant now than ever before, and the KCNJ6 system could very well be one of the factors involved in 'CNS hyperexcitability' that may be related to clinical manifestations of neurobehavioral disinhibition associated with risk for AUDs (Tessner and Hill, 2010) and other substance use disorders (e.g., Tarter et al., 2003). As KCNJ6/GIRK2 has been found to be related to neural excitability, reward processing, alcohol modulation and addiction, future studies are needed to investigate potential behavioral and clinical implications.

4.5. Limitations of the current study and suggestion for future studies

Although the current study has found that the KCNJ6 SNP (rs702859) is associated with reward related theta EROs, it has a few limitations. While the sample size of the current study appears large, it may not be sufficiently large for a genetic study to test multiple hypotheses involving several factors. Only a single KCNJ6 SNP has been explored in this study. Further studies exploring genetic effects on developmental trajectories of EROs from multiple task paradigms, including the monetary gambling task, are underway, and may offer important clues to better understand these factors. Future studies including the behavioral aspects associated with reward processing (e.g., risk-taking, decision making, reaction time, etc.) and clinical features (e.g., externalizing and internalizing) may offer valuable clues underlying connections between KCNJ6, risk propensity, brain oscillations, and potential clinical outcomes. Future studies are also needed to determine the implications of the genetic effects of variants in KCNJ6 on posterior theta EROs as possible "protective" or "risk" factors and the behavioral and clinical implications, and as indices of delays in brain maturation (i.e., lack of frontalization). Furthermore, functional studies are underway in COGA with KCNJ6 variants and 1) single cell

electrophysiology, as well as 2) induced pluripotent stem cells (iPSC) derived neurons generated from the human participants of COGA with several *KCNJ6* variants to examine acute and chronic effects of alcohol.

5. Conclusions

The present study has found that a *KCNJ6* polymorphism (rs702859) was associated with reward related theta EROs in a large sample of young adult subjects. The results of the present study suggest that *KCNJ6*, through its protein GIRK2, exerts strong moderating effects on theta EROs. Growing evidence from the literature suggests that *KCNJ6*/GIRK2 may be a promising therapeutic target for alcoholism and related disorders. Functional studies on the *KCNJ6* system, which are underway in COGA, may shed further light on neurogenetic mechanisms underlying cognitive processes and alcoholism.

Appendix A

Fig. A1. ERP waveforms (panels in columns 2, 3, and 4) flanked by P3 topography (panels in columns 1 and 5) across the genotypes (panels in rows) during loss and gain outcome. The group with minor allele(s) have displayed higher P3 amplitude than the group homozygous for the major allele [GG/AG > AA], prominently at the posterior region, during evaluation of loss as well as gain. Peak P3 amplitude values (in μV) for gain (green) and loss (red) are shown within the panels of ERP waveforms. The dotted vertical line (at 0 ms) in the waveform panels represents the onset of outcome stimulus. Uniform color scales have been used for all the head plots.
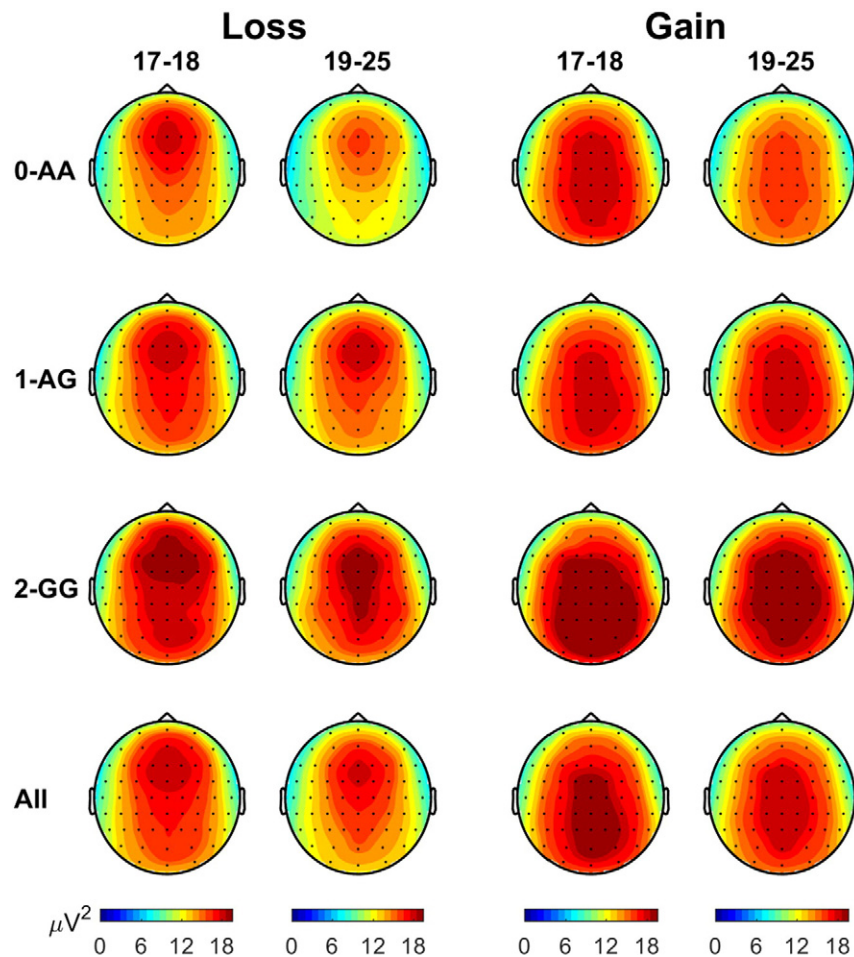
Fig. A2. Theta power (in μV^2) across genotypes (rs702859) and age groups during loss (left columns) and gain condition (right columns). Additive effect of genotypes [GG > AG > AA] with increasing power corresponding the number of minor allele(s) in adolescent (17–18 years) and adult (19–25 years) groups is shown during evaluation of loss as well as gain. The adolescents show more theta power and more diffused posterior topography than adults in each genotype group (top three rows) and in the combined sample (bottom row of head maps). Uniform color scales have been used for all the head plots.

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