



Reward processing deficits and impulsivity in high-risk offspring of alcoholics: A study of event-related potentials during a monetary gambling task



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ARTICLE INFO

Article history:

Received 14 April 2015

Received in revised form 8 September 2015

Accepted 11 September 2015

Available online 18 September 2015

Keywords:

Alcohol use disorders

Family history of alcoholism

P3

Current source density

Reward processing

Impulsivity

Endophenotype

Brain maturation, hypofrontality

Frontalization

ABSTRACT

Background: Individuals at high risk to develop alcoholism often manifest neurocognitive deficits as well as increased impulsivity. The goal of the present study is to elucidate reward processing deficits, externalizing disorders, and impulsivity as elicited by electrophysiological, clinical and behavioral measures in subjects at high risk for alcoholism from families densely affected by alcoholism in the context of brain maturation across age groups and gender.

Methods: Event-related potentials (ERPs) and current source density (CSD) during a monetary gambling task (MGT) were measured in 12–25 year old offspring ($N = 1864$) of families in the Collaborative Study on the Genetics of Alcoholism (COGA) Prospective study; the high risk (HR, $N = 1569$) subjects were from families densely affected with alcoholism and the low risk (LR, $N = 295$) subjects were from community families. Externalizing disorders and impulsivity scores were also compared between LR and HR groups.

Results: HR offspring from older (16–25 years) male and younger (12–15 years) female subgroups showed lower P3 amplitude than LR subjects. The amplitude decrement was most prominent in HR males during the loss condition. Overall, P3 amplitude increase at anterior sites and decrease at posterior areas were seen in older compared to younger subjects, suggesting frontalization during brain maturation. The HR subgroups also exhibited hypofrontality manifested as weaker CSD activity during both loss and gain conditions at frontal regions. Further, the HR subjects had higher impulsivity scores and increased prevalence of externalizing disorders. P3 amplitudes during the gain condition were negatively correlated with impulsivity scores.

Conclusions: Older male and younger female HR offspring, compared to their LR counterparts, manifested reward processing deficits as indexed by lower P3 amplitude and weaker CSD activity, along with higher prevalence of externalizing disorders and higher impulsivity scores.

Significance: Reward related P3 is a valuable measure reflecting neurocognitive dysfunction in subjects at risk for alcoholism, as well as to characterize reward processing and brain maturation across gender and age group.

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1. Introduction

Alcoholism is a complex disorder with multiple etiological pathways involving a host of genetic and environmental factors along with their interactions in its onset, manifestations, course, and treatment outcome. Converging evidence supports the notion that there may be a wide range of genetic, biological, neurocognitive and environmental factors involved in the causal pathways to develop alcoholism. Electrophysiological

measures, such as electroencephalogram (EEG), event-related potentials (ERPs), and event-related oscillations (EROs) have played a vital role as biological markers or endophenotypes to understand neurocognitive mechanisms involved in alcohol use and related disorders (see Porjesz et al., 2005, for a review). These electrophysiological methods provide a direct measure of brain activity with high temporal sensitivity to understand neurocognitive processes, while being non-invasive and inexpensive for its applications. Specifically, ERPs can measure dynamically changing brain activity in real time during perceptual, motor, and cognitive processing while performing a task (Picton and Hillyard, 1988). ERPs have been widely and successfully used to examine neurocognitive processing during various experimental tasks in normal populations as

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well as in a range of clinical conditions including alcoholism (Porjesz and Begleiter, 1985; Begleiter and Porjesz, 1990a; Porjesz et al., 1996, 2005; Porjesz and Begleiter, 1997).

A landmark finding in the electrophysiology of human alcoholism is that individuals with alcohol dependence as well as their high risk offspring show low voltage P3(00) amplitude (for reviews, see Begleiter and Porjesz, 1990b; Porjesz and Begleiter, 1990, 1991, 1997; Polich et al., 1994; Porjesz et al., 2005). P3 is a robust, positive going ERP wave occurring around 300–700 ms following the onset of a stimulus, indicative of its context (Donchin and Coles, 1988) or importance (Sutton et al., 1978; Begleiter et al., 1983) during signal/cognitive processing. Since the first report by Begleiter et al. (1984) of low P3 amplitude in the sons of alcoholic fathers (in a study without any alcohol challenge), this finding has been replicated across many different experimental paradigms in male as well as female high risk subjects (i.e., offspring of alcoholics) in diverse samples (for reviews, see Porjesz et al., 2005; Rangaswamy and Porjesz, 2014).

It was a turning point in alcoholism research that lower P3 amplitude, observed in alcoholic individuals (Porjesz and Begleiter, 1981; Oscar-Berman, 1987; Pfefferbaum et al., 1987; Porjesz et al., 1987; Cohen et al., 1995, 1997b; Rodriguez Holguin et al., 1999a; Hada et al., 2000; Prabhu et al., 2001; Cohen et al., 2002; Suresh et al., 2003; Kamarajan et al., 2005a, 2010; Fein and Chang, 2006; Fein and Andrew, 2011), was also found in individuals with a family history of alcoholism who were considered to be genetically vulnerable but had not yet developed alcoholism (Elmasian et al., 1982; O'Connor et al., 1987; Porjesz and Begleiter, 1990; Benegal et al., 1995; Porjesz et al., 1996; Ramachandran et al., 1996; Kamarajan et al., 2005b) and had never or only rarely been exposed to alcohol (Begleiter et al., 1984, 1987; Whipple et al., 1988, 1991; Hill and Steinhauer, 1993; Steinhauer and Hill, 1993; Hill et al., 1995). However, it must be stated that P3 reduction in high risk subjects, as a phenomenon, is not consistent or ubiquitous in the literature, but often with equivocal as well as subgroup-specific findings, and has been found to be strongest in younger males (for a meta-analysis, see Polich et al., 1994). For example, some studies reported that P3 reductions were observed only in boys of alcoholic parents (e.g., Hill and Steinhauer, 1993), while other studies found the effect in both genders (e.g., Porjesz et al., 1996). Similarly, this effect has been found to be stronger in younger subjects (e.g., Begleiter et al., 1987; Polich et al., 1994) but still robust in adolescents/young adults (O'Connor et al., 1987; Porjesz and Begleiter, 1990; Porjesz et al., 1996; Ramachandran et al., 1996; Van der Stelt et al., 1998; Kamarajan et al., 2005b). Possible reasons for these inconsistent and/or subgroup specific findings may include the following: (i) the studies may differ methodologically (in terms of sample characteristics, task paradigms, ERP recording and signal processing, statistical techniques, etc.); (ii) definition of “risk” may differ across studies; and (iii) P3 reduction may in fact be a function of age, gender, and task paradigms and may be moderated by several confounding (or unmeasured) factors such as personality traits, situational/familial/sociocultural factors, and other variations due to genetic and epigenetic factors.

It is also important to note that low P3 is not unique to alcoholics and their high risk relatives, but is also found in individuals with one or more externalizing disorders or disinhibitory conditions (Carlson et al., 1999; Hill and Shen, 2002; Iacono et al., 2002, 2003; Iacono and McGue, 2006; Patrick et al., 2006; Carlson et al., 2007; Hicks et al., 2007; Iacono et al., 2008; Patrick, 2008; Gilmore et al., 2010a,b, 2012). As reported by several studies, an underlying feature among risk propensity, externalizing disorders and alcoholism is the concept of “impulsivity”, which is a conglomerate of personality traits that can result in premature, unduly risky and poorly conceived actions, and is known to be closely related to disinhibitory traits and clinical vulnerability (Gorenstein and Newman, 1980; Martin et al., 1994; Olson et al., 1999; Krueger and Piasecki, 2002; Hall et al., 2007; Kamarajan et al., 2007; Crews and Boettiger, 2009; Romer et al., 2009). Interestingly, P3 amplitude has been found to be either negatively correlated with impulsivity or

lower in high impulsive subjects regardless of having a diagnosis of alcoholism and/or related disorders (Justus et al., 2001; Moeller et al., 2004; Chen et al., 2007; Ruchisow et al., 2008; Kamarajan et al., 2010).

Alcoholism has often been characterized as a reward deficit disorder (Koob, 2013; Forbes et al., 2014), and several studies have successfully used ERPs to examine reward processing in healthy individuals (Homerberg et al., 1980, 1981; Begleiter et al., 1983; Ivanitsky et al., 1986; Gehring and Willoughby, 2002; Yeung and Sanfey, 2004; Hajcak et al., 2005; Nieuwenhuis et al., 2005; Toyomaki and Murohashi, 2005a,b; Hajcak et al., 2006, 2007; Holroyd et al., 2006; Yu and Zhou, 2006; Kamarajan et al., 2009, 2010), as well as in alcoholic and HR offspring (Porjesz et al., 1987; Ramsey and Finn, 1997; Fein and Chang, 2008). Major ERP components studied during outcome/feedback processing during monetary gambling tasks (MGT) are the outcome-related negativity (ORN) or N2 (between 200 ms and 300 ms) and the outcome-related positivity (ORP) or P3 (between 300 ms and 600 ms) (Gehring and Willoughby, 2002; Yeung and Sanfey, 2004; Hajcak et al., 2005, 2006; Yeung et al., 2005; Holroyd et al., 2006; Cohen and Ranganath, 2007; Kamarajan et al., 2009). In our previous ERP study of reward processing using a MGT in alcoholics, we found that alcoholics showed significantly lower amplitudes of N2/ORN and P3/ORP components and decreased current density in cingulate gyrus, along with higher levels of impulsivity and risk-taking features than controls (Kamarajan et al., 2010). While FRN/N2 is another important component of feedback processing, the current study focuses solely on the P3 component for the following reasons: 1) dealing with both components (P3 and N2) in a single study with multiple factors (risk group, gender, age group) may render the study too complex; 2) with regard to alcoholism and risk, P3 is considered to be the most robust ERP component and a sensitive biomarker, and therefore the analysis of P3 has assumed its precedence in the current study; 3) FRN/N2 is a relatively subtle component and more prone to artifact distortions, rendering it more difficult to measure (especially in such a large sample of adolescents and young adults) compared to the large P3 component; and 4) implementation of a more sophisticated source localization method (e.g., sLORETA) may be essential to examine the key brain sources (e.g., anterior cingulate region) attributed to the FRN (Crowley et al., 2013). For these reasons, only the P3 component has been dealt with in the current study. As current source density (CSD), a source derivation method of electrophysiological activity, has been successfully used in several neuropsychiatric disorders including alcoholism (for a review, see Kamarajan et al., 2015), we have also compared CSD topography across the groups (see Section 2.5 for more information on the CSD method).

The overarching aim of the present study is to examine reward processing (as indexed by P3 amplitude and CSD), and externalizing features in HR offspring recruited from high density alcoholism families in comparison with LR (comparison) subjects recruited from a community sample in the COGA Prospective Study, in the context of brain maturation across age groups and gender. This is the first ERP study using a monetary gambling paradigm to study HR offspring, and has been designed to examine the following hypotheses: (1) HR offspring will show lower P3 amplitude during reward processing than low-risk (LR) individuals from the comparison families; (2) HR group will show current density differences in both magnitude and topography as compared to the LR group; and (3) HR group will have higher impulsivity scores than the LR group. As the literature regarding P3 reduction in high risk subjects, as mentioned earlier, has often been equivocal with regard to gender- and age-based subgroups, the current study also investigates the effects of age and gender on P3 amplitudes in specific subgroups. It is expected that findings of the present study may shed further light on the complex relationship among reward processing deficits (indexed by P3 amplitude and CSD), impulsivity, and externalizing disorders involved in the development of alcoholism.

2. Materials and methods

2.1. Participants

The sample included 1864 adolescents and young adults (903 males and 961 females) between 12 and 25 years of age (see Table 1) and was derived from the prospective study of the Collaborative Study on the Genetics of Alcoholism (COGA) (Begleiter et al., 1995; Edenberg et al., 2005). The prospective study began in 2004, focusing on participants who were relatives (e.g., offspring) of the high-risk and comparison (comparison) families ascertained in previous phases of COGA. Participants are reassessed every two years with clinical, behavioral and neurophysiological assessments. Data from six collection sites 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 (Begleiter et al., 1995; Reich et al., 1998; Foroud et al., 2000; Nurnberger et al., 2004), and are also available at this website: <https://zork5.wustl.edu/coganew/data/instruments.html>. The experimental protocols were approved by each site's institutional review board, and informed consent was obtained from all participants.

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 and/or urine screen), (2) hepatic encephalopathy/cirrhosis of the liver, (3) history of head injury, seizures or neurosurgery, (4) uncorrected sensory deficits, (5) history/symptoms of psychoses, (6) self-reported positive test for human immunodeficiency virus, and (7) other acute/chronic medical illnesses that affects brain function. The HR group consisted of individuals from the COGA high density alcoholism families who had at least one parent with DSM-IV alcohol dependence, while the LR group consisted of individuals from the community families without any parental history of alcohol dependence. The groups were further subdivided based on gender and age group (12–15 and 16–25 years old) (see Table 1). As the age distribution was skewed in the overall sample (i.e., relatively more subjects were represented at younger ages), the sample was subdivided into these age groups, in order to provide adequate sample sizes for each age group and ensure good pubertal and post-pubertal representation. Table 2 shows lifetime prevalence rates of externalizing disorders for HR and LR groups. These externalizing scores were higher in HR offspring compared to LR individuals in each gender as well in the total sample (see Table 2).

2.2. Assessment tools

The clinical and impulsivity data of the sample were collected with three instruments: (1) SSAGA – The Semi Structured Assessment for the Genetics of Alcoholism (Bucholz et al., 1994) evaluated clinical diagnoses and symptoms; (2) FHAM – The Family History Assessment

Module (Rice et al., 1995) assessed major psychiatric disorders among relatives of the participants; and (3) BIS – The Barratt Impulsiveness Scale (BIS) (Patton et al., 1995) provided ratings of impulsivity in three categories viz., attentional, motor, and non-planning, yielding individual as well as total scores.

2.3. Monetary gambling task

The monetary gambling task (MGT) used in this study is illustrated in Fig. 1. Each trial began with a choice stimulus (CS), with two numbers 10 (left box) and 50 (right box), with a monetary value in US cents, 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, 2009, 2010, 2012). The inter-stimulus interval between a CS and OS, and between an OS and next CS is 1500 ms. The task involved a total of 172 trials, each with one of four possible outcomes: Loss 50, Loss 10, Gain 50, and Gain 10. P3 amplitudes were measured during the ERP epochs of outcome stimuli (1000 ms poststimulus) which contained the feedback of either loss or gain for each trial (i.e., the epochs following colored frames in Fig. 1).

2.4. EEG data acquisition and signal analysis

Identical experimental procedures and EEG acquisition systems were used at all neurophysiology collection sites of COGA (Begleiter et al., 1995; Porjesz and Begleiter, 1995) with 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 Systems (Chatrian et al., 1985; Chatrian et al., 1988; Oostenveld and Praamstra, 2001) (Fig. 2), with a reference electrode at the tip of the nose and with a ground electrode at the forehead. The electrooculogram (EOG) was recorded by a supra-orbital vertical electrode and by a horizontal electrode on the external canthus of the left eye. Electrode impedances were maintained below 5 k Ω . Electrical activity was amplified 10,000 times using SynAmps2 amplifiers (Compumedics USA, Charlotte, NC) and was recorded continuously over a bandwidth of DC–100.0 Hz on a Neuroscan system (Versions 4.3–4.5; Compumedics USA, Charlotte, NC) at sampling rate of 500 Hz. All EEG data were resampled offline at 256 Hz for the analyses. Artifact rejection threshold during preprocessing was set at ± 100 μ V.

ERP waveforms were filtered at 0.03–16.0 Hz and the P3 amplitude was measured as the voltage difference from the pre-stimulus baseline window (0–100 ms) to the largest positive going peak within the post-stimulus time window (275–600 ms) after the onset of an outcome stimulus. A semi-automatic computerized algorithm developed in our laboratory identified the P3 peak as a time point on the P3 wave with maximum amplitude within the 275–600 ms post-stimulus time window (Cohen et al., 2002; Kamarajan et al., 2009). Further, ERP waveforms were visually analyzed for the correctness of peak identification and morphology of the waveforms. Since the P3 topography for smaller and larger amounts (10¢ and 50¢) were similar (Kamarajan et al., 2009, 2010), trials for the two amounts (10¢ and 50¢) were combined for the loss condition (loss 10¢ + loss 50¢) as well as for the gain condition (gain 10¢ + gain 50¢) in order to have more trials per subject and more subjects per group. Mean trial numbers across the risk groups in each condition are: LR = 39.12 and HR = 36.51 for the loss condition; LR = 42.24 and HR = 40.53 for the gain condition. Although signal-to-noise-ratio (SNR) and minimum number of trials needed for the stability P3 in gambling paradigm have not been determined in the current study, trial numbers for each condition seem to be adequate. In view of the findings that the SNR did not differ when the trial numbers

Table 1
Number of participants categorized by age group, gender, and risk group.

Age group	Gender	Risk group		Total
		Low-risk (LR)	High-risk (HR)	
12–15 years	Male	70	317	387
	Female	96	329	425
	Total	166	646	812
16–25 years	Male	64	452	516
	Female	65	471	536
	Total	129	923	1052
Total	Male	134	769	903
	Female	161	800	961
	Total	295	1569	1864

Table 2

Prevalence rates in counts and percentage (in parentheses) for the diagnoses of externalizing disorders (EXT) in LR and HR groups in the total sample and within gender. Note that the HR group had higher prevalence rates in all the diagnoses than the LR group. Significance levels based on Chi-square test have been marked with asterisks (in HR columns). Diagnosis of SUD is based on DSM-IV criteria for dependence or abuse. Empty cell (with a dash) represents the count of zero.

Diagnosis	Male (affected cases)		Female (affected cases)		Total (affected cases)	
	LR	HR	LR	HR	LR	HR
Alcohol	9 (6.98)	112 (14.95)**	5 (3.16)	90 (11.49)***	14 (4.88)	202 (13.19)***
Tobacco	5 (3.88)	64 (8.54)*	2 (1.27)	62 (7.92)***	7 (2.44)	126 (8.22)***
Marijuana	9 (6.98)	123 (16.55)**	2 (1.27)	75 (9.59)***	11 (3.85)	198 (12.98)***
Cocaine	–	9 (1.20)	–	8 (1.02)	–	17 (1.11)*
Stimulant	–	6 (0.80)	–	13 (1.66)*	–	19 (1.24)*
Sedative	–	3 (0.40)	–	4 (0.51)	–	7 (0.46)
Opiate	–	5 (0.67)	–	9 (1.15)	–	14 (0.92)*
Other drugs	–	8 (1.07)	–	12 (1.53)*	–	20 (1.30)**
ASPD	3 (8.33)	40 (15.56)	1 (2.56)	25 (8.31)	4 (5.33)	65 (11.65)
CD	5 (3.88)	81 (10.81)**	5 (3.16)	45 (5.76)	10 (3.48)	126 (8.24)**
ADHD	3 (2.33)	27 (3.63)	2 (1.27)	13 (1.66)	5 (1.75)	40 (2.62)
ODD	1 (0.78)	21 (2.94)	1 (0.64)	13 (1.70)	2 (0.70)	34 (2.30)*
Any SUD	15 (11.63)	189 (25.17)***	8 (5.06)	154 (19.52)***	23 (8.01)	343 (22.27)***
Any EXT	20 (15.50)	239 (31.82)***	14 (8.86)	186 (23.57)***	34 (11.85)	425 (27.60)***

* $p < 0.05$.** $p < 0.01$.*** $p < 0.001$.

exceeded eight for the ERN/Pe components (Olvet and Hajcak, 2009), and that the components can be reliably measured with 8 trials for ERN (Olvet and Hajcak, 2009) and with 20 trials for the FRN (Marco-Pallares et al., 2011), it is very unlikely that SNR-related issues may confound the results of the current study given the higher number of trials in each condition.

2.5. Current source density mapping

The recorded EEG potential at each electrode does not represent brain sources solely adjacent to the electrode location (Nunez, 1981), because of two limitations (Kayser and Tenke, 2015): (i) EEG is measured as a potential difference between the recorded electrode and

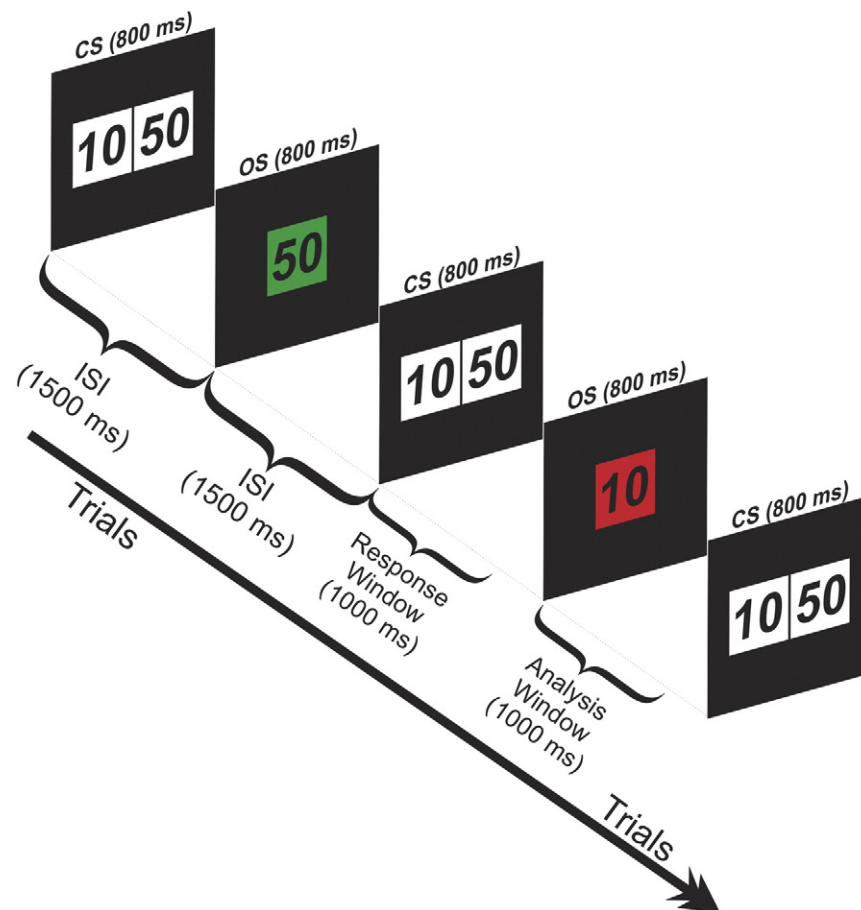


Fig. 1. Schematic illustration of the monetary gambling task. Each trial starts with a choice stimulus (CS) which lasts for 800 ms and displays two amounts (10¢ or 50¢) to bet with. The participant selects one of the amounts and receives an outcome of either gain (green box) or loss (red box) for the 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.

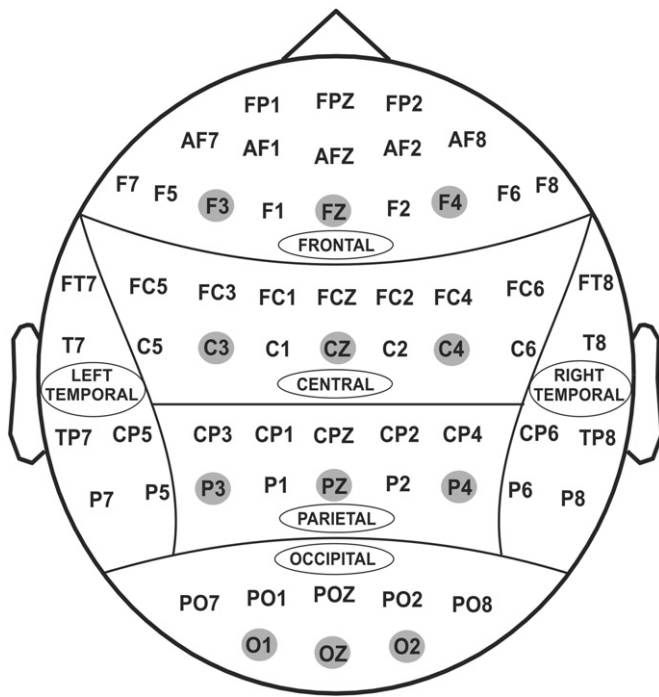


Fig. 2. Sixty-one electrodes as recorded in the current study from the surface of the scalp. Twelve electrodes (F3, FZ, F4, C3, CZ, C4, P3, PZ, P4, O1, OZ, O2) representing frontal, central, parietal and occipital regions were selected for statistical analyses.

the reference electrode, and (ii) the EEG signal is a mixture of propagated neuroelectric activity from multiple local and distal brain sources and is smeared by volume conduction. Both of these limitations can be mitigated by use of the surface Laplacian algorithm (Hjorth, 1975), which is a simple mathematical transformation applied to the EEG surface potentials (for a tutorial review on this topic, see Kayser and Tenke, 2015). The CSD provides information about local radial current density representing components of the primary neural activity in the scalp region (Nunez and Pilgreen, 1991). Thus, the CSD topographic map is a spatially enhanced representation of current generators with more sharply localized peaks than those of the scalp potential, while eliminating volume-conducted contributions from distant regions and sources (Tenke and Kayser, 2012). CSD topography thus represents reference-free estimates of radial current flow at the scalp represented in positive and negative polarities (Kayser and Tenke, 2015). The positivity or “source” represents current flow from the brain toward the scalp (i.e., outward flow), while the negativity or “sink” indicates current flow toward the brain from the scalp (i.e., inward flow) (Nunez and Srinivasan, 2006). CSD methods have been successfully implemented in several neuropsychiatric disorders (Kamarajan et al., 2015) including alcoholism (Ramachandran et al., 1996; Ji et al., 1999; Hada et al., 2000; Kamarajan et al., 2005a, 2012) in order to understand possible brain sources underlying scalp-recorded potentials. In the present study, CSD maps were constructed from the Laplacian transformed grand averaged data of P3 amplitudes, for each group and condition, as described by Wang and Begleiter (1999). Z-scored maps for P3 amplitude as well as CSD were plotted so that topographic patterns could be compared across groups regardless of the magnitude of amplitude/CSD. Topographic activation patterns of sources and sinks between LR and HR groups were compared.

2.6. Statistical analyses

Statistical analyses were performed using SPSS 21.0 (IBM Corporation, Armonk, NY). Prevalence rates of externalizing diagnoses were compared between HR and LR groups in each gender as well as total

samples using Chi-square test with significance testing for Likelihood Ratio (see Table 2). P3 amplitudes from 12 electrodes (F3, FZ, F4, C3, CZ, C4, P3, PZ, P4, O1, OZ, O2) were analyzed using a repeated measures analysis of variance (RM-ANOVA) of the general linear model involving Risk Group (HR and LR), Age Group (12–15 and 16–25 years), and Gender (male and female) as between-subjects factors, and Task condition (Loss and Gain) and Region (frontal, central, parietal, and occipital) as within-subjects factors. Four scalp regions with three electrodes per region (Frontal: F3, FZ, F4; Central: C3, CZ, C4; Parietal: P3, PZ, P4; Occipital: O1, OZ, O2) were included in the model. Although affected status (i.e., individuals with any externalizing diagnosis as shown in Table 2) was initially used as a covariate in the RM-ANOVA model, it was removed from the later analysis which is presented here, as the covariate (i.e., externalizing factor) showed neither a main effect nor any interaction effect with any factors in the model. As the electrophysiology data for the within-subjects factors in the current study did not adhere to the sphericity assumption (i.e., the equality of the variances of the differences between levels of repeated measures factor, such as region), we used multivariate test statistics, which are not dependent on the assumption of sphericity (O'Brien and Kaiser, 1985; Field, 1988). Hence this provides an appropriate alternative method to analyze EEG data with repeated-measures multivariate analyses of variance, which does not assume sphericity and therefore does not require any corrections (cf. Bell and Cuevas, 2012). Bonferroni adjusted pairwise comparisons within each significant main and interaction effects were analyzed using estimated marginal means (EMM) and standard errors (SE). The BIS scores between LR and HR groups were analyzed using one-way ANOVA. The relationship between P3 amplitudes and BIS scores was examined using Pearson correlation coefficients.

3. Results

3.1. Prevalence rates of externalizing disorders

Table 2 shows comparison of prevalence rates of externalizing (EXT) disorders, which includes DSM-IV lifetime diagnosis for SUD (dependence/abuse) and other related disorders, such as anti-social personality disorder (ASPD), conduct disorder (CD), attention deficit hyperactivity disorder (ADHD), and oppositional defiant disorder (ODD). “Other drugs” refers to the substances other than those mentioned in the list. Significant differences in the prevalence rates between LR and HR subjects were observed in several diagnoses for all three comparisons: (i) *Males*: alcohol, tobacco, marijuana, CD, any SUD, and any EXT; (ii) *Females*: alcohol, tobacco, marijuana, stimulant, other drugs, any SUD, and any EXT; and (iii) *All subjects*: alcohol, tobacco, marijuana, cocaine, stimulant, opiate, other drugs, CD, ODD, any SUD, and any EXT. The diagnoses that were significant in all the comparisons were: alcohol, tobacco, marijuana, any SUD, and any EXT.

3.2. Mean P3 values across the subgroups

Qualitative comparison of mean P3 values for each subgroup during loss and gain conditions are illustrated in Fig. 3. Section 3.2 describes the statistical comparison of P3 amplitudes across factors with RM-ANOVA. Lower P3 amplitudes in HR compared to LR subjects (solid vs. broken lines within each panel in Fig. 3) was more evident in both younger and older male subjects only during the loss condition (top left panel), as well as in younger female subjects during both loss and gain conditions (orange lines in right-side panels). Further, a comparison between genders (left-side vs. right-side panels in Fig. 3), indicates that younger males during both loss and gain conditions showed higher P3 amplitudes than their female counterparts (cyan vs. orange lines). Furthermore, older subjects showed increased P3 amplitudes in anterior sites and a decrease in posterior regions compared to younger subjects (darker vs. lighter colored lines within each panel in Fig. 3), reflecting brain maturation during development (“frontalization”).

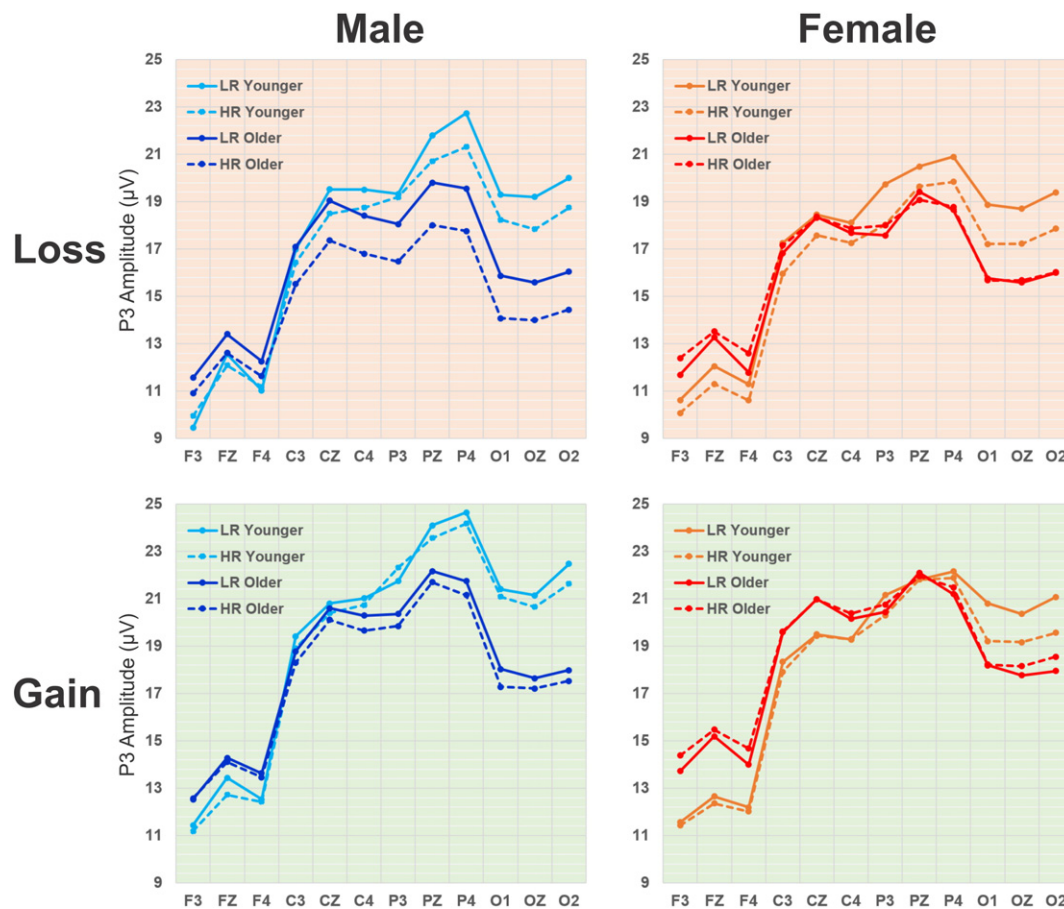


Fig. 3. Qualitative comparison of mean P3 values for each subgroup during loss and gain conditions across 12 electrodes representing 4 regions (frontal: F3, FZ, F4; central: C3, CZ, C4; parietal: P3, PZ, P4; occipital: O1, OZ, O2). HR offspring display markedly lower P3 amplitude than LR subjects in both younger and older male subgroups during loss condition as well as in younger female subjects during both loss and gain conditions.

3.3. RM-ANOVA results

Table 3 lists the main and interaction effects in the RM-ANOVA model, and Fig. 4 illustrates the pairwise comparisons of the estimated marginal means of the P3 amplitude between the levels of risk groups, gender, and age groups at each scalp region for the loss and gain conditions. P3 amplitude showed significant main effects for age group, condition, and region along with the following 2-way and 3-way interaction effects: (i) age group \times gender, (ii) age group \times region, (iii) gender \times region, (iv) condition \times region, (v) risk group \times condition \times region, (vi) gender \times condition \times region (Table 3). These results are explained for each major factor (risk group, gender, and age group) in the order of higher order (complex) to lower order (simpler) effects in the subsections below.

3.3.1. Risk group

A higher order interaction (risk group \times condition \times region) was found for risk group, suggesting that P3 amplitudes between risk groups varied in specific regions and conditions. Follow-up analysis revealed that HR offspring had significantly lower P3 amplitudes in parietal and occipital regions only during loss condition. Further, Bonferroni corrected multiple pairwise comparisons (see Fig. 4, panels A1–A2) revealed that risk group differences in P3 amplitudes (HR < LR) was significant in older males (in central and parietal regions) as well as in younger females in occipital region during the loss condition (see Fig. 5).

3.3.2. Gender

In terms of gender effects, the 3-way interaction gender \times condition \times region interaction revealed that males displayed significantly higher P3 amplitude than females only at the parietal region during the gain condition. Significant gender \times age group interaction indicated that males showed higher P3 amplitude than females only in the younger age group. Gender \times region effect showed that overall P3 amplitudes were higher for males (than females) in central, parietal, and occipital regions, while the frontal region showed the opposite pattern (females > males). Comparison between males and females across other factors (see Fig. 4, panels B1–B2) revealed that males displayed higher P3 amplitudes (with significant differences mainly among younger subjects) than females in all but the older HR subgroup.

3.3.3. Age group

The age group \times gender effect showed that younger male subjects manifested significantly higher P3 amplitude, but this pattern (younger > older) was not statistically significant in female subjects. In terms of gender differences across scalp regions, the younger age group showed significantly higher P3 amplitude in parietal and occipital regions while the older group showed significant increases in the frontal region as revealed by age group \times region effect. Overall, younger subjects displayed significantly higher P3 amplitude than older subjects as shown by the main effect of age group. Comparisons between age groups across other factors (see Fig. 4, panels C1–C2) confirm that this pattern (younger > older) is true in several subgroups except for the

anterior regions in older females, where the opposite pattern (older > younger) was observed.

3.3.4. Within-subjects factors

Effects of within-subjects factors (condition \times region, condition, and region) were highly significant ($p < 0.001$). Condition \times region interaction indicated that P3 was larger in the gain compared to the loss condition in all regions, and this observation was further confirmed by the condition main effect. The region main effect showed that overall P3 amplitude was highest in the parietal region, followed by central, occipital and frontal regions (i.e., parietal > central > occipital > frontal), thus indicating that P3 scalp voltage has a posterior topography.

3.4. Current source density

Topographic maps of CSD for each subgroup during loss and gain conditions are shown in Fig. 6 (panels A1, A2, B1, and B2). Differences across conditions and groups have been observed in sources (positivity) and sinks (negativity). Overall, the results showed that the loss condition had predominant left and right frontal sources, while the gain condition had an additional mid-frontal source as well. Younger and older male HR offspring displayed weaker source activation at the left and right frontal regions during both loss and gain conditions in comparison their LR counterparts. Among females, the right frontal source was weaker during both loss and gain conditions in younger HR subjects compared to their LR counterparts. Further, a weaker prefrontal sink activation was found in younger male HR offspring compared to male LR subjects during both loss and gain conditions and only during the loss condition in females. Central and posterior sinks were almost comparable across groups.

3.5. BIS impulsivity

3.5.1. Impulsivity scores between LR and HR subjects

Comparisons of impulsivity scores between LR and HR groups are shown in Fig. 7. Overall, in the total sample, the HR offspring displayed significantly increased impulsivity on each of the scores: non-planning ($F = 26.47$; $p < 0.0001$), motor ($F = 34.21$; $p < 0.0001$), attentional ($F = 28.47$; $p < 0.0001$), and total ($F = 45.44$; $p < 0.0001$). Specifically, younger HR males exhibited significantly higher impulsivity in non-planning ($F = 6.87$; $p = 0.0091$), motor ($F = 15.01$; $p = 0.0001$), attentional ($F = 5.35$; $p = 0.0213$), and total impulsivity ($F = 13.64$; $p = 0.0003$) than their LR counterparts. On the other hand, older HR males showed increased impulsivity only in motor ($F = 5.44$; $p = 0.0202$) and total impulsivity ($F = 5.56$; $p = 0.0188$) compared to older LR males. Among females, younger HR offspring had significantly higher impulsivity on all the scores than the LR subjects: non-planning ($F = 13.36$; $p = 0.0003$), motor ($F = 16.21$; $p = 0.0001$), attentional ($F = 28.49$; $p < 0.0000$), and total impulsivity ($F = 27.80$; $p < 0.0001$). Similarly, older HR females showed significantly increased BIS scores for non-planning ($F = 7.52$; $p = 0.0063$), motor ($F = 6.21$; $p = 0.0130$), and total impulsivity ($F = 8.85$; $p = 0.0031$) compared to older LR females.

3.5.2. Correlations between BIS scores and P3 amplitudes

The relationship between P3 amplitude and impulsivity has been summarized in Table 4. Gain-related P3 amplitudes had significant negative correlations with BIS scores, while there was no such relationship observed for the loss condition. The significant correlations during the gain condition were: FZ with non-planning, attentional, and total scores, CZ with attentional and total scores, and both PZ and OZ with attentional score. Although these correlations were statistically significant, the values of the coefficients (r) are much smaller, and therefore these results should be interpreted with caution. Correlations within the groups (risk group, gender and age group) were not significant.

4. Discussion

The goal of the present study was to elucidate reward processing deficits as indexed by P3 amplitude and CSD topography in the HR offspring from high density alcoholism families in contrast to the LR individuals from the comparison families, in the context of brain maturation across age groups and gender. Impulsivity scores were compared between the risk groups, and the relationship between P3 amplitude and impulsivity in the context of age and gender was also examined. The current study has yielded several findings:

- (1) HR offspring from older male and younger female subgroups showed significantly lower P3 amplitude than LR comparison subgroups during the loss condition;
- (2) Lower CSD activity at frontal sources in the HR older male and younger female subgroups compared to the comparison LR groups was observed;
- (3) Males had higher P3 amplitude than females in both younger and older LR groups as well in the younger HR group, while the opposite pattern (female > male) was observed in the older HR subjects;
- (4) Younger subjects produced significantly higher P3 amplitudes than older subjects during loss and gain conditions in both LR and HR groups;
- (5) HR subjects as a whole and in each subgroup showed increased BIS impulsivity scores compared to their LR counterparts;
- (6) P3 amplitudes (during gain condition) were negatively correlated with impulsivity scores.

Table 3

The main and interaction effects of the RM-ANOVA of P3 amplitude (dependent variable) with several between-subjects and within-subjects factors. Degrees of Freedom, F value, and p value are shown. Significant effects have been highlighted with bold font.

Effect	df	F	p
Risk-group	1	1.70	0.1926
Gender	1	0.82	0.3646
Age-group	1	7.53	0.0061**
Risk-group \times gender	1	1.70	0.1927
Risk-group \times age-group	1	0.72	0.3973
Gender \times age-group	1	4.31	0.0381*
Risk-group \times gender \times age-group	1	1.14	0.2863
Condition	1	234.77	< 0.0001***
Condition \times risk-group	1	2.66	0.1034
Condition \times gender	1	1.53	0.2161
Condition \times age-group	1	2.73	0.0984
Condition \times risk-group \times gender	1	0.01	0.9302
Condition \times risk-group \times age-group	1	0.19	0.6638
Condition \times gender \times age-group	1	2.96	0.0854
Condition \times risk-group \times gender \times age-group	1	2.17	0.1407
Region	3	1165.91	< 0.0001***
Region \times risk-group	3	2.21	0.0851
Region \times gender	3	4.33	0.0047**
Region \times age-group	3	38.79	< 0.0001***
Region \times risk-group \times gender	3	0.74	0.5263
Region \times risk-group \times age-group	3	0.79	0.5021
Region \times gender \times age-group	3	0.54	0.6560
Region \times risk-group \times gender \times age-group	3	0.15	0.9289
Condition \times region	3	24.34	< 0.0001***
Condition \times region \times risk-group	3	2.93	0.0327*
Condition \times region \times gender	3	2.99	0.0301*
Condition \times region \times age-group	3	1.99	0.1128
Condition \times region \times risk-group \times gender	3	1.43	0.2321
Condition \times region \times risk-group \times age-group	3	1.24	0.2935
Condition \times region \times gender \times age-group	3	0.46	0.7116
Condition \times region \times risk-group \times gender \times age-group	3	0.87	0.4538

* $p < 0.05$.

** $p < 0.01$.

*** $p < 0.001$.

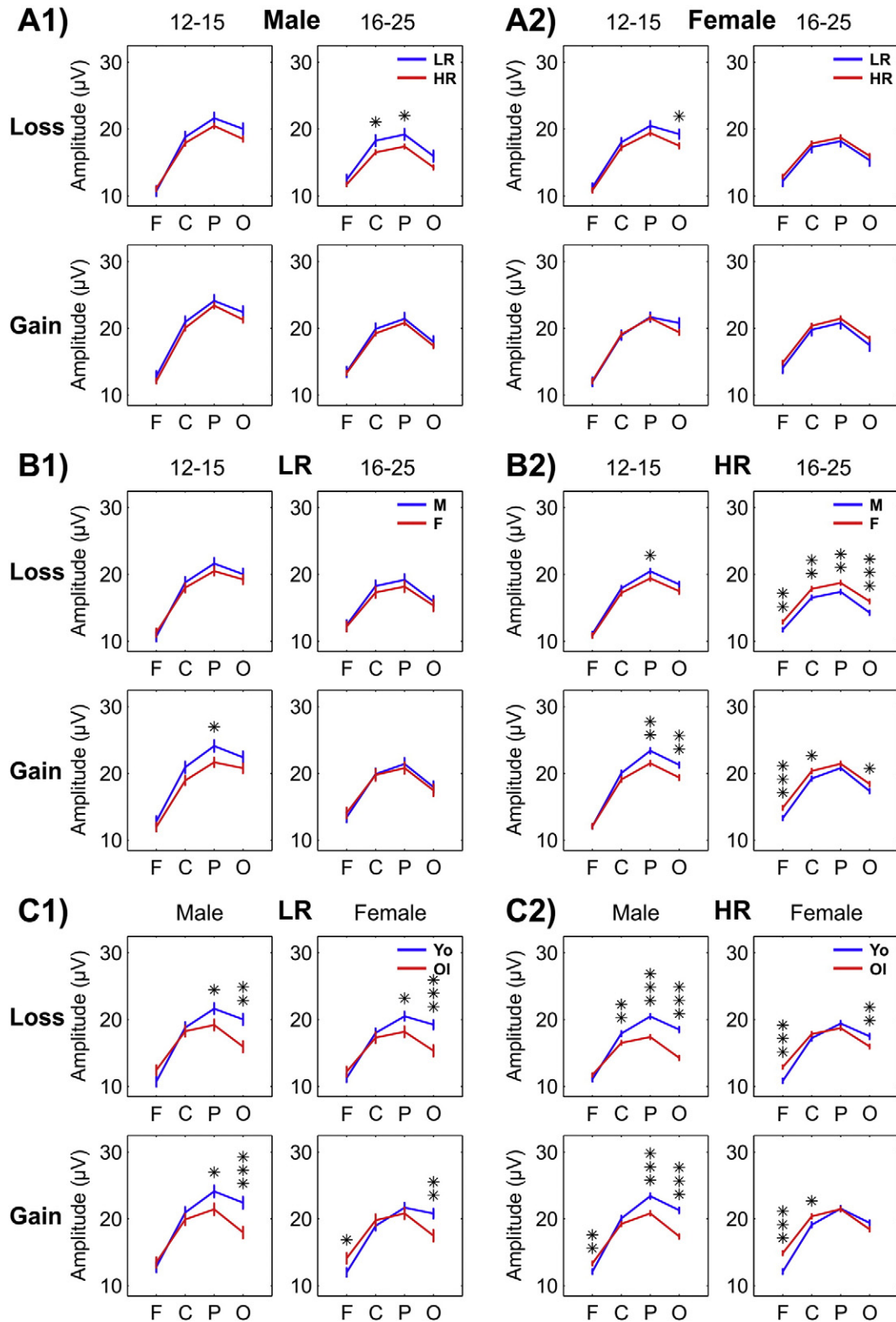


Fig. 4. Multiple comparisons across different groups during loss and gain conditions. Estimated marginal means and standard error (± 1 SE) of pairwise comparisons between the levels of risk groups (panel-sets A1 and A2), gender (panel-sets B1 and B2), and age groups (panel-sets C1 and C2) in loss and gain condition have been plotted for each scalp region (F: frontal; C: central; P: parietal; and O: occipital). Bonferroni adjusted level of significance for each comparison is shown in asterisks (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$).

4.1. P3 deficits and risk for alcoholism

4.1.1. P3, cognitive function and reward processing

In the current study, HR older male and younger female subgroups exhibited significantly lower P3 amplitude during reward processing

than the comparison LR subgroups. In stimulus discrimination paradigms, P3 amplitude has been theorized to reflect a capacity or set of brain resources related to mental processes (Kok, 1997, 2001), or subjective probability, stimulus meaning, and information transmission (Johnson, 1986). On the other hand, in the reward paradigms, P3

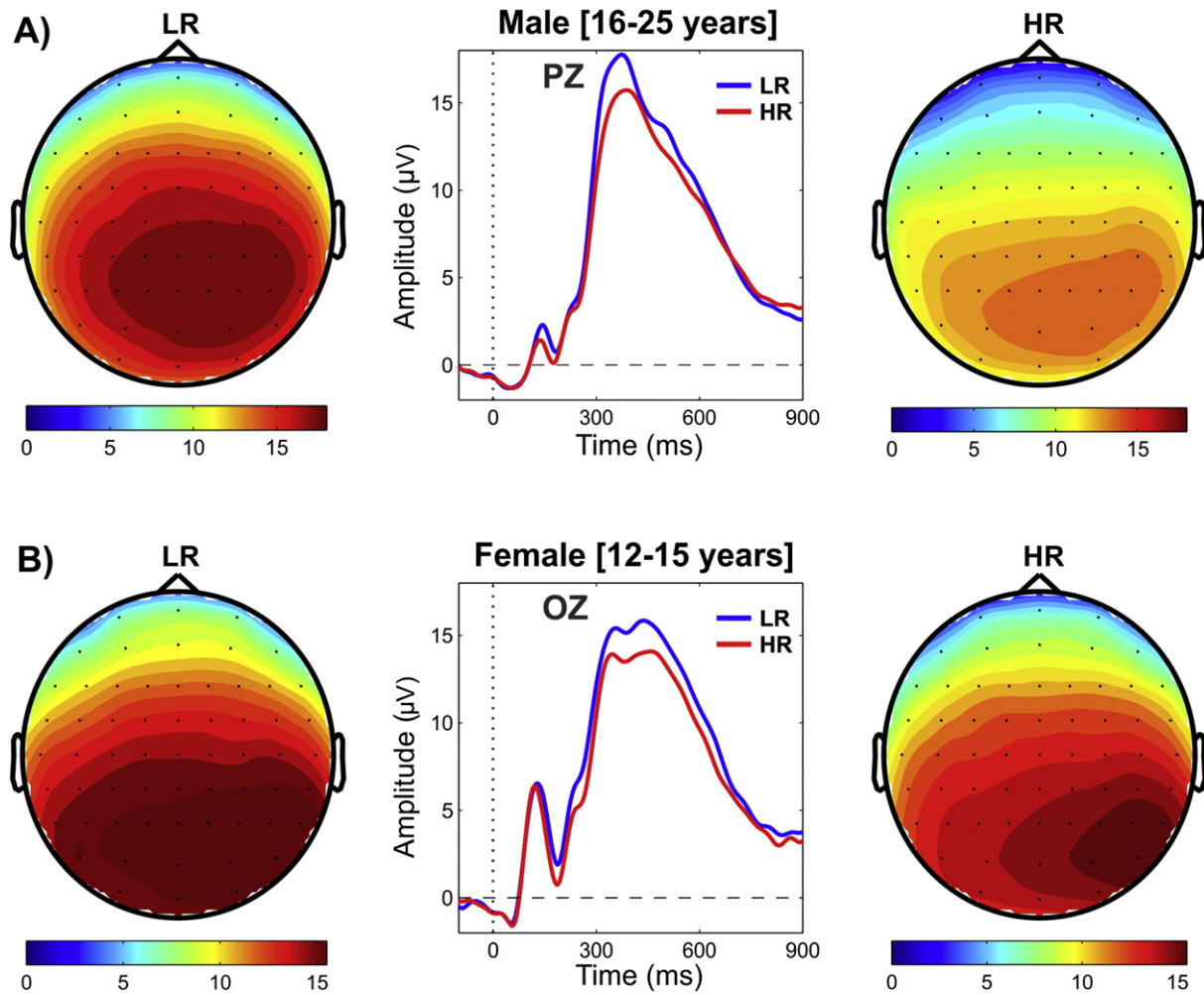


Fig. 5. Topographic maps and waveforms showing significant difference in P3 amplitude between HR and LR subjects in older males (panel A) and younger females (panel B) during the loss condition. The vertical dotted line in the waveform plots (middle subpanels) represents the onset of outcome stimulus, and the horizontal dashed line indicates the baseline (0 μV). The color scales for the topographic maps (left and right subpanels) represent P3 amplitude in μV .

amplitude has been shown to index both valence and/or magnitude of the reward (e.g., Homberg et al., 1981; Begleiter et al., 1983; Otten et al., 1995; Yeung and Sanfey, 2004; Goldstein et al., 2006). Distinct topographic patterns and specific brain sources for different outcomes (i.e., loss and gain) have also been reported (Kamarajan et al., 2009, 2010). This suggests that lower P3 amplitude in a monetary gambling paradigm may be due to dysfunctional reward processing at the neural level.

4.1.2. Lower P3 in HR offspring

The major finding of the present study was that older male HR offspring and younger female HR offspring showed significantly lower P3 amplitudes during the loss condition. Although the present study is the first to report P3 deficits during reward processing in a monetary gambling paradigm in HR offspring, similar reward-related P3 deficits have been previously reported in alcoholics (Porjesz et al., 1987; Kamarajan et al., 2010) and their offspring (Ramsey and Finn, 1997). Since, reward related P3 amplitude has been found to be sensitive to both the valence (loss/gain) and magnitude (larger/smaller) of the outcomes (Toyomaki and Murohashi, 2005a; Kamarajan et al., 2009, 2010), it can be taken as an index of reward processing. Hence, low P3

amplitudes manifested by HR offspring may represent dysfunctional or suboptimal reward processing.

4.2. Topographic differences in P3

Although P3 differences between the risk groups were significant at central and parietal regions for the loss condition in older males and at occipital region in younger females, the source analysis using surface Laplacian (CSD maps) revealed weaker current density in HR offspring at the frontal sources. These frontal deficits or 'hypofrontality' of HR subjects as demonstrated in CSD maps may explain the lower P3 in these individuals (as discussed in detail in the following sections). Further, imaging studies in adolescent subjects who were vulnerable for and/or diagnosed with substance use disorders (SUDs) (Bava et al., 2009, 2010; Bava and Tapert, 2010; Casey and Jones, 2010; Dayan et al., 2010; Feldstein Ewing et al., 2014) and other externalizing disorders (Rubia et al., 1999; Rubia et al., 2000) have shown evidence for frontal lobe dysfunction, possibly due to a "dysmaturational pathogenesis for hypofrontality" as phrased by Rubia et al. (2000) in their work on ADHD children.

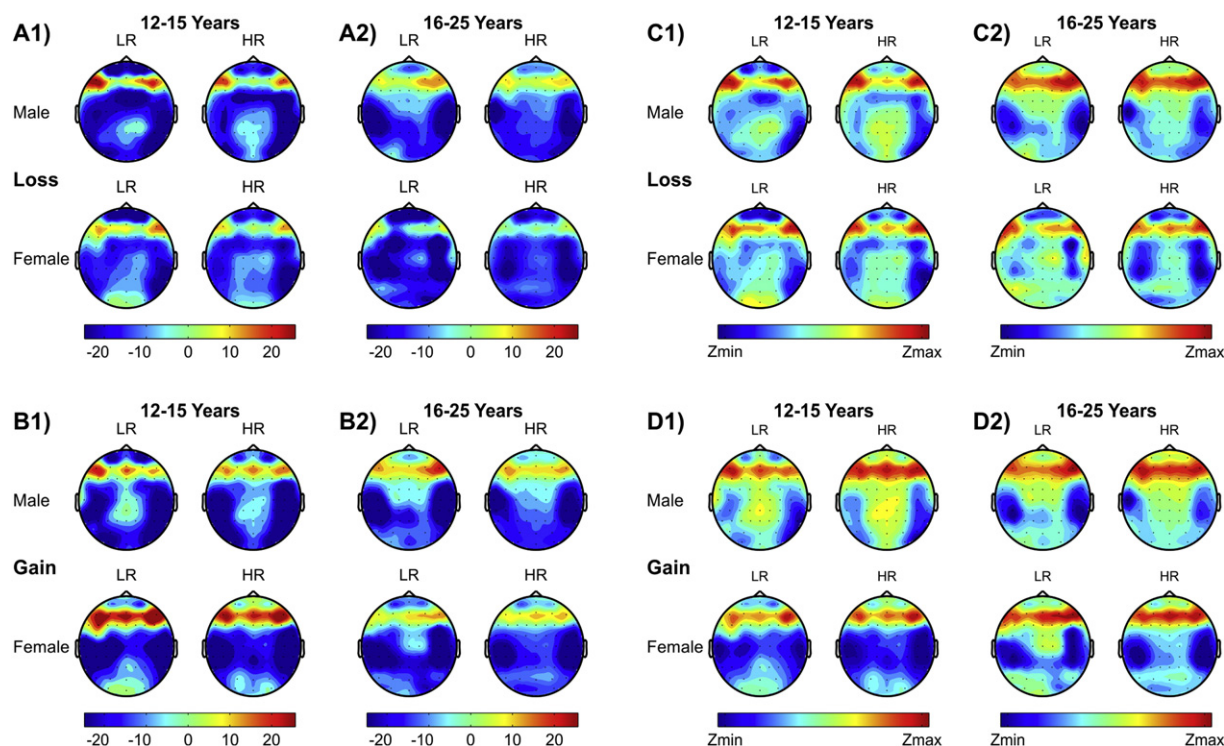


Fig. 6. Topographic maps of CSD activity [panels A1, A2, B1, B2], and Z-scores [panels C1, C2, D1, D2]. Lower CSD activations of frontal sources and sinks are seen in HR offspring (more prominently among males) than LR group. Z-score maps are shown to highlight the topographic patterns more clearly across the different groups, but the magnitudes between the Z-score maps cannot be compared.

4.2.1. P3 differences between risk groups in each gender

It should be noted that statistically significant P3 differences between HR and LR subjects were specific to age group, gender and task condition (Fig. 4, panels A1 and A2). In males, the P3 difference between the risk groups was statistically significant solely in the older age group at the central and parietal regions and only in the loss condition (Fig. 4, panel A1). In females, on the other hand, statistically significant P3 differences were observed only in the younger group at the occipital region during the loss condition (Fig. 4, panel A2). This finding suggests that although both male and female HR children/adolescents manifest lower P3 amplitudes, this deficit becomes augmented in males as they age during development while it gets attenuated in females as they age into late adolescence and young adulthood. This gender specific finding is in line with previous findings indicating that low P3 amplitudes in high risk offspring of alcoholics have been reported more often in males (Begleiter et al., 1984, 1987; O'Connor et al., 1986; O'Connor et al., 1987; Whipple et al., 1991; Berman et al., 1993; Benegal et al., 1995; Ramachandran et al., 1996; Cohen et al., 1997a; Ramsey and Finn, 1997; Rodriguez Holguin et al., 1999b) than in females (Porjesz et al., 1996; Van der Stelt et al., 1998), while there are only a few studies showing P3 differences (between risk groups) in both males and females (e.g., Van der Stelt et al., 1998). Further, lower P3 has been shown to be more robust in high risk male than female offspring (e.g., Polich et al., 1994; Hill et al., 1999). It should also be noted that P3 differences (between HR and LR subjects) in both younger and older males is in line with previous studies which have reported lower P3 amplitude in samples of 'at risk' children/adolescents (Begleiter et al., 1984, 1987; Berman et al., 1993) as well as in young adults (O'Connor et al., 1986, 1987; Ramachandran et al., 1996; Cohen et al., 1997a; Ramsey and Finn, 1997; Kamarajan et al., 2005b). A meta-analytic study revealed that P3 reduction was more robust in younger male subjects with family history of alcoholism

and showed higher effect sizes for younger ages than for older subjects (Polich et al., 1994). There are a host of factors that can affect the trajectory of gender-specific development including sexual dimorphism of brain maturation (De Bellis et al., 2001; Lenroot et al., 2007; Lenroot and Giedd, 2010), which can be influenced by both genetic and environmental factors (Lenroot and Giedd, 2008; Lenroot et al., 2009a,b).

4.2.2. P3 differences between male and female groups

Comparison between male and female subjects within age groups and risk groups (Fig. 4, panels B1 and B2) shows that the pattern of higher P3 amplitudes shown by males during 12–15 years becomes less prominent in the LR individuals as they aged into 16–25 years (Fig. 4, panel B1) while the gender difference in younger age (male > female) switched to the opposite direction in the older age group (female > male) in the HR offspring (Fig. 4, panel B1). This finding may suggest that the developmental and maturational changes in the P3 activity could be different in LR and HR subjects, although this interpretation has to be confirmed by further studies with a larger/comparable sample sizes of LR and HR subjects. Further, it is rather surprising that P3 amplitude between male and female subjects did not differ significantly in the LR group except in the gain condition in the younger group (Fig. 4, panel B1), although all comparisons of gender in HR subjects were significant. Although previous studies have shown that females produced higher amplitude than males in visual paradigms (Orozco and Ehlers, 1998; Guillem and Mograss, 2005; Proverbio et al., 2006) including the gambling paradigm (Kamarajan et al., 2009), the age range was not compatible with our current study (i.e., the sample in these studies were adults with 18–45 years of age, while our study has samples of children/adolescents and young adults with 12–25 years of age range). However, except in older females, there is a pattern in the current study that males produced higher P3 amplitudes than females.

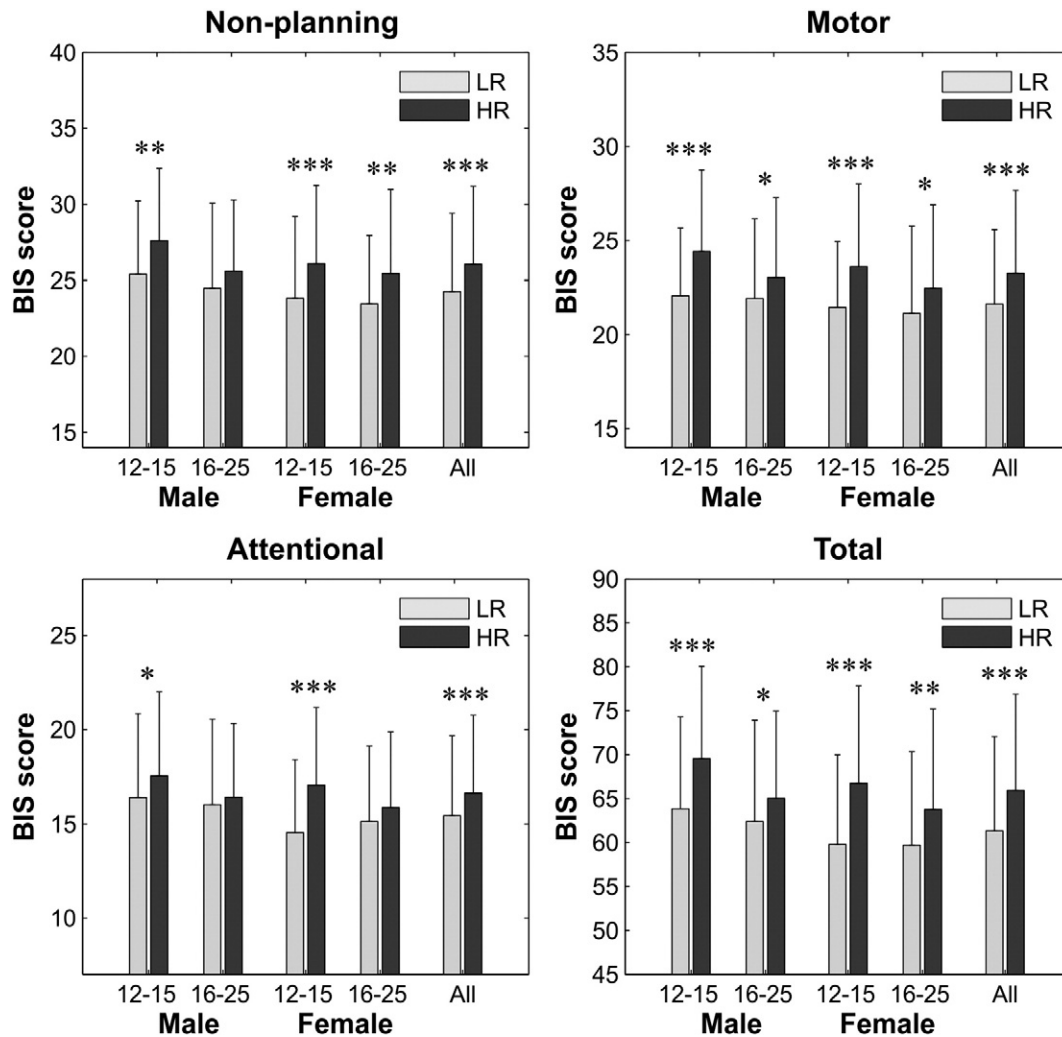


Fig. 7. Comparison of BIS scores between LR and HR subjects across subgroups and all subjects. HR offspring in each subgroup showed increased impulsivity in the BIS subscales and the total score. Error bars represent 1 standard deviation. Significance level for each comparison is shown by asterisks (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$).

These gender differences in P3 within age groups can be understood in the context of brain development. As noted earlier, there is evidence for sexual dimorphism of brain maturation (De Bellis et al., 2001; Lenroot et al., 2007; Lenroot and Giedd, 2010). Further, there is a substantial evidence of gender differences in brain connectivity that may account for gender-related cognitive differences (for a review, see Gong et al., 2011). For example, gender related connectivity differences within prefrontal cortex (PFC) showed that males exhibited stronger connectivity in the PFC regions with leftward dominance, while bilateral

dominance was observed in females (Chuang and Sun, 2014). It is possible that individuals with familial/genetic risk for alcoholism may have a different developmental patterns within each gender than the normal/healthy individuals (Bava and Tapert, 2010), although this issue needs further exploration.

4.2.3. P3 differences between age groups (younger vs. older group)

The P3 differences between age groups (Fig. 4, panels C1 and C2) are worth elaborating. It was observed that younger (12–15 years) subjects

Table 4
Correlations (r) and level of significance (p) between BIS scores and P3 amplitudes are shown.

Condition	Electrode	Non-planning		Motor		Attentional		Total	
		r	p	r	p	r	p	r	p
Loss	FZ	−0.046	0.0599	−0.029	0.2363	−0.033	0.1859	−0.046	0.0636
	CZ	−0.036	0.1386	−0.023	0.3603	−0.018	0.4555	−0.033	0.1798
	PZ	−0.033	0.1787	−0.016	0.5163	−0.020	0.4242	−0.029	0.2334
	OZ	−0.030	0.2288	−0.023	0.3435	−0.024	0.3242	−0.032	0.1886
	FZ	−0.051	0.0359*	−0.043	0.0748	−0.066	0.0065**	−0.066	0.0066**
Gain	CZ	−0.043	0.0741	−0.033	0.1747	−0.071	0.0032**	−0.060	0.0129*
	PZ	−0.025	0.3090	−0.014	0.5725	−0.062	0.0103*	−0.040	0.0951
	OZ	−0.012	0.6277	−0.007	0.7688	−0.048	0.0469*	−0.026	0.2741

* $p < 0.05$.

** $p < 0.01$.

showed significantly higher P3 amplitudes in the posterior regions than their older (16–25 years) counterparts. Further, a reverse pattern (i.e., older > younger) was observed in the frontal region, although the posterior differences were more robust than the frontal differences. The finding of larger P3 in children (compared to adolescents/young adults) is in keeping with well-known developmental findings of P3 and EEG. For example, the amplitude of visual P3 decreased gradually from childhood to adulthood (e.g., Johnson, 1989; Courehesne, 1990), and this amplitude reduction can also be explained by the findings from other developmental studies which found a gradual reduction of slower rhythms (which constitute P3 response) in children's EEG during development as they mature into adolescence/adulthood (Matousek and Petersen, 1973a; John et al., 1980; Gasser et al., 1988b; Wackermann and Matousek, 1998; Dustman et al., 1999; Clarke et al., 2001; Boord et al., 2007). In a developmental study of error-related negativity (ERN), a related component to feedback negativity, Davies et al. (2004) demonstrated that the amplitude of the ERN increased from 7 to 17 years of age and the waveforms did not reach optimal level to those of young adults until mid-teens. Further, similar to our finding, Ladouceur et al. (2007) found that P3 amplitude during error-processing was greater in the adolescent group compared to the adult group. These studies lend support to our finding of P3 differences between age groups.

Compared to the younger age group, the older subjects showed relatively higher P3 amplitudes at frontal regions, while the younger group showed relatively higher P3 amplitudes at parietal and occipital regions. The anterior–posterior modulation (“frontalization”) during brain development has been well-documented in the EEG literature. Maturational patterns of EEG activity follow gray matter reduction during development, as there is a redistribution of relative EEG power as a function of age with posterior regions maturing earlier than anterior regions (cf. Segalowitz et al., 2010). During development, theta-alpha maturation occurs first in occipital regions and then progresses gradually to frontal regions (Matousek and Petersen, 1973b; Gasser et al., 1988a; Dustman et al., 1999). Yordanova and Kolev (1996) demonstrated similar age effects in EROs by demonstrating that adults showed ERO alpha maxima at mid-central regions in contrast to the parietal maxima in children, reflecting perhaps a gradual “frontalization” with growth (cf. Segalowitz et al., 2010). These studies support our finding related to anterior–posterior differences in younger and older groups.

Our finding of increased anterior P3 activity coupled with decreased posterior activity from adolescence to adulthood corresponds with recent imaging data showing a posterior to frontal progression of cortical development from childhood through adolescence and adulthood (Gogtay et al., 2004; Gogtay and Thompson, 2010). During brain development with advancing age, the prefrontal activity becomes progressively more focal and specialized (Tamm et al., 2002; Brown et al., 2005; Durston et al., 2006). This phenomenon is termed “frontalization” or the maturational process of frontal lobes during development, whereby frontal lobes gradually take control of higher-order cognitive functions, such as executive functions and inhibitory control (Rubia et al., 2000; Yurgelun-Todd and Killgore, 2006; Segalowitz et al., 2010; Arain et al., 2013). Furthermore, imaging findings showing late maturation of prefrontal cortex (Fuster, 2002; Gogtay et al., 2004) may explain the higher P3 activity at frontal regions (and lower P3 activity in the posterior regions) in the older subjects compared to the younger group.

4.3. P3 amplitude, impulsivity, and externalizing disorders

Two important findings regarding impulsivity have been observed in the current study: (i) increased impulsivity in all subscales and total score of the BIS in the HR offspring compared to the LR

group in each subgroup of gender and age (Fig. 7); and (ii) significant negative correlations between P3 amplitudes during gain condition and impulsivity scores, showing decreased P3 amplitude in individuals with higher impulsivity (Table 4). In light of the established view that impulsivity is a critical factor in the pathophysiology and/or risk propensity for alcoholism and related disorders (Petry, 2001; Finn et al., 2002; Moeller et al., 2002; Chen et al., 2007; Dom et al., 2007; Kamarajan et al., 2007; Rubio et al., 2007, 2008; Hanson et al., 2008; Verdejo-Garcia et al., 2008; von Diemen et al., 2008; Crews and Boettiger, 2009; Rogers et al., 2010), our finding that HR offspring showed increased impulsivity may provide further evidence for the notion that etiological connections exist between impulsivity and alcoholism and other SUDs (for reviews, see Sher and Trull, 1994; Verdejo-Garcia et al., 2008; Dick et al., 2010). In a review, Kamarajan and Porjesz (2012) have outlined electrophysiological abnormalities in impulsivity spectrum disorders, which include AUD and other related disorders. Studies have also shown that psychometrically measured impulsivity, as done in our study, was associated with externalizing disorders in general and substance use disorder in particular (Saunders et al., 1973; O'Boyle and Barratt, 1993; Krueger et al., 2002; Romer et al., 2009). It may be worth noting that prevalence rates of externalizing disorders were significantly higher in the HR group than in the LR group, suggesting that the HR group is susceptible not only to alcoholism but also to other externalizing disorders (see Table 2). Further, our finding of a negative correlation between P3 amplitude and impulsivity scores suggests that individuals with lower P3 amplitudes have higher impulsivity, lending further support to the notion that P3 abnormalities are intrinsically related to impulsivity traits (Justus et al., 2001; McGue et al., 2001; Moeller et al., 2004; Potts et al., 2006; Chen et al., 2007; Kamarajan et al., 2009) as well as to externalizing conditions (Justus et al., 2001; McGue et al., 2001; Moeller et al., 2004; Chen et al., 2007; Kamarajan et al., 2010). It is possible that P3 deficits and high impulsivity may have common underlying brain mechanisms. Recent fMRI studies have found differences between high and low impulsive individuals in terms of engagement and activation patterns of frontal lobe structures (Sripada et al., 2011; Davis et al., 2013; Diekhof et al., 2012). Frontal lobe structures have also been implicated in several disorders involving impulsivity and externalizing traits (Vollm et al., 2004; Lee et al., 2005; Vollm et al., 2007; Wolf et al., 2011; Costa Dias et al., 2013; Cyders et al., 2014). Taken together, these findings add support to the view that P3 amplitude, impulsivity, and externalizing disorders are etiologically related (Iacono et al., 2003; Iacono and McGue, 2006; Chen et al., 2007; Carlson et al., 2009; Gao and Raine, 2009; Young et al., 2009; Gilmore et al., 2010a; Lejuez et al., 2010). It is important to note that BIS score differences between HR and LR groups varied according to the age group and gender (Fig. 7). Among males, the younger age group showed more robust differences ($p < 0.001$) between LR and HR groups in non-planning, motor, cognitive and total scores, while the older males displayed a modest level of significance ($p < 0.05$) only in motor and total scores. While our finding on age and gender differences in impulsivity are similar to the findings in the literature (Steinberg et al., 2008; Stoltenberg et al., 2008), impulsivity as such may mediate the association between gender and risk for alcohol problems (Stoltenberg et al., 2008). While there was a correlation between P3 amplitude and BIS scores during the gain condition, the lack of correlation during the loss condition in our study may warrant further exploration in similar samples. Interestingly, Bernat et al. (2011) reported that while delta-P3 amplitude was found to be reduced among individuals high in externalizing proneness, theta-FRN (N2) response was unrelated to externalizing. Further studies are needed to establish the relationship between various facets of impulsivity and neurophysiological measures, such as the P3.

4.4. Source activations of P3, reward processing, and risk for alcoholism

In this study, CSD topographic analysis yielded three key findings: i) loss condition showed bilateral frontal sources while the gain condition additionally had a prominent midfrontal source; ii) HR offspring (younger males and females as well as older males) displayed weaker CSD sources at the frontal regions in comparison their LR counterparts; and iii) a weaker prefrontal sink activation was found in younger HR offspring compared to the LR group during both loss and gain conditions in males and only during loss condition in females.

During the evaluation of monetary loss and gain, the common features of the CSD topography observed across groups were the sources (positivities) in left-frontal, right-frontal and mid-frontal regions (Fig. 6). Our finding that prominent CSD sources were located at the frontal regions corroborates existing evidence that cognitive tasks requiring evaluations of reward outcomes recruit the frontal lobes (Wallis and Miller, 2003; Glascher et al., 2010; Rangel and Hare, 2010). There is also a strong literature support for the major involvement of frontal lobes (connecting a network of other subcortical structures) during reward processing and decision making (Haber and Knutson, 2010; Rushworth et al., 2011; Economides et al., 2014; Forbes et al., 2014). Specifically, medial prefrontal cortex (mPFC) involving ACC has been shown to be involved in the processing of the reward values of the reinforcers (O'Doherty et al., 2001; Shidara and Richmond, 2002; Knutson et al., 2003; Rogers et al., 2004; Knutson et al., 2005; Shidara et al., 2005; Taylor et al., 2006; Sallet et al., 2007; Fujiwara et al., 2009; Xue et al., 2009; Economides et al., 2014).

HR offspring also showed weaker CSD activations (of the sources and sinks) in the frontal and prefrontal regions. Specifically, the lower activations in both P3 amplitude and CSD were found in both younger and older age groups in males but only in younger age groups in females. Neuroimaging studies have found pathophysiological alterations in the brain's reward system (Diekhof et al., 2008; Park et al., 2010; Tomasi et al., 2010; Muller-Oehring et al., 2013) including altered white matter integrity in individuals with SUD (Bava et al., 2009; Jacobus et al., 2009; McQueen et al., 2009; Bava et al., 2010), and deficient functional connectivity between frontal lobes and other key structures in subjects who are at high risk for alcoholism (Weiland et al., 2012, 2013; Wetherill et al., 2012). Forbes et al. (2014) reported that young adults with family history of alcohol dependence exhibited lower medial PFC response. Taken together, all these findings support our hypothesis that suppressed CSD features at the frontal regions during reward processing in the HR group may represent dysfunctional reward circuitry as well as a 'hypofrontality', which may mediate or predispose toward risk for developing AUD and/or related disorders in these subjects.

4.5. Genetic factors underlying P3 and risk for alcoholism and related disorders

The development of alcoholism is influenced by underlying biological susceptibility factors, environmental factors, and complex interactions among genes and environment (Porjesz et al., 2005; Dick and Kendler, 2012). There is a large literature indicating that low P3 amplitude can be considered to be an important genetic marker for the development of alcoholism (Begleiter et al., 1984; Goldman, 1993; Porjesz et al., 2005; Porjesz and Rangaswamy, 2007) and other externalizing disorders (Iacono et al., 2002; Iacono and McGue, 2006). Several genes have been found to be associated with delta and theta EROs underlying P3 (Jones et al., 2004, 2006; Chen et al., 2009, 2010; Zlojutro et al., 2011; Kang et al., 2012), and several of these genes have also been associated with alcoholism (Wang et al., 2004; Luo et al., 2005; Dick et al., 2007; Chen et al., 2009, 2010) and related externalizing disorders as well (Dick, 2007; Dick et al., 2008). Quantitative electrophysiological phenotypes, such as

EEG, P3, and related EROs, have served as effective endophenotypes for gene identification in psychiatric genetics (for recent reviews, see Porjesz and Rangaswamy, 2007; Rangaswamy and Porjesz, 2008, 2014; Iacono and Malone, 2011; Chen et al., 2012; Euser et al., 2012; Pandey et al., 2012; Kamarajan and Porjesz, 2015). These heritable neurophysiological biomarkers (Begleiter and Porjesz, 2006; Anokhin, 2014) have been very successful in identifying susceptibility genes for alcohol dependence and related disorders (Rangaswamy and Porjesz, 2008; Chen et al., 2012) as they are directly associated with human information processing and cognitive functions (Porjesz and Rangaswamy, 2007). Interestingly, several of the same genes associated with electrophysiological phenotypes and alcoholism in adults have been found to be related to precursor phenotypes in children and adolescents, such as conduct disorder (Dick et al., 2004), onset of regular drinking (Chorlian et al., 2013), and trajectories of drunkenness (Dick et al., 2014). While heritability of the reward-related P3 is yet to be determined, it may be another promising endophenotype, as both alcoholics (Kamarajan et al., 2010) and HR offspring (in the current study) manifest lower P3 amplitude.

4.6. Limitations of the present study and suggestions for future studies

The present study has extended our previous research in alcoholics, in order to confirm whether reward related ERP deficits observed in alcoholics are also found in children of alcoholics, and has successfully revealed differences in P3 amplitude and CSD across risk groups. However, there are some limitations in the current study, which could not be completely eliminated. For example, (i) the sample sizes for the LR groups are relatively smaller than the HR groups, and hence the findings have to be interpreted with caution; (ii) the trials involving both bet amounts (10¢ and 50¢) have been combined within loss and gain conditions respectively, in order to maximize trial numbers and sample size, while the analysis of each condition may have offered more detailed findings; (iii) the N2 component, which was difficult to measure and has not been analyzed in the current study, may have yielded additional information about reward processing deficits in HR offspring; (iv) although the mean trial numbers across the groups in each condition [LR = 42.24 and HR = 40.53 for the gain condition; LR = 39.12 and HR = 36.51 for the loss condition] seems to be sufficient and optimal for the reward-P3 (in view of the findings from earlier studies), further assessments regarding the SNR and minimum/optimal number of trials for component stabilization may have confirmed or improved the validity of current findings; and (v) complex, predictive analytic models, which have not been done in the current study, may be essential to assess the degree to which the factors of genetic risk, substance use, and impulsivity contribute independently as well as relatively contribute to the P3 deficits and CSD profile. Despite these limitations, the study has provided important findings that may have considerable implications for the use of reward related electrophysiological phenotypes to characterize neurocognitive dysfunction in alcoholism and risk status.

Future studies, while avoiding the limitations of the present study, may further consider examining: (i) the oscillations underlying P3 component (e.g., delta and theta bands) along with ERP measures, (ii) the trajectories of reward-related P3 amplitude comparing the LR and HR subjects; (iii) longitudinal changes associated with P3 and ERO measures in HR offspring by analyzing the data on multiple assessments over a period of time, (iv) brain circuitries underlying reward/outcome processing in high risk individuals by using coherence/synchrony measures of electrophysiology and by using functional connectivity measures of neuroimaging, (v) externalizing disorders along with substance use disorders, (vi) new strategies to statistically or methodologically disentangle the underlying genetic risk (in those at high risk for alcoholism) from the manifested symptoms or characteristics (e.g., externalizing disorders) that may influence the phenotype

(e.g., P3) under study, (vii) the utility of reward related ERP/ERO measures as endophenotypes in genetic studies, and (viii) a more systematic study with multiple measures of impulsivity and externalizing disorders in AUD and HR offspring to further elucidate the complex interactions among these factors.

5. Conclusions

The present study has elucidated reward processing deficits in younger and older high risk offspring from dense alcoholism families of COGA. Older male and younger female HR subgroups have shown significantly lower P3 amplitude and reduced CSD activation at frontal sources during reward processing compared to their LR counterparts. High risk subjects were also found to be more impulsive than LR subjects. Negative correlation between P3 amplitudes and impulsivity scores suggested that reduced P3 amplitude and increased impulsivity (as manifested by HR offspring) may predispose toward risk for alcoholism and related disorders. Further, gender- and age-specific findings of the present study may have several implications for future research on alcoholism and risk. Lastly, it is suggested that using electrophysiological endophenotypes, such as P3 and its oscillatory components, to identify genes involved in risk for alcoholism and related disorders may serve as sensitive biomarkers that are physiologically closer to gene functions, that may shed light on novel prevention, diagnosis and treatment options.

Conflict of interest

None of the authors have potential conflicts of interest to be disclosed.

Acknowledgments

The Collaborative Study on the Genetics of Alcoholism (COGA), Principal Investigators B. Porjesz, V. Hesselbrock, H. Edenberg, L. Bierut, includes eleven different centers: University of Connecticut (V. Hesselbrock); Indiana University (H.J. Edenberg, J. Nurnberger Jr., T. Foroud); University of Iowa (S. Kuperman, J. Kramer); SUNY Downstate (B. Porjesz); Washington University in St. Louis (L. Bierut, J. Rice, K. Bucholz, A. Agrawal); University of California at San Diego (M. Schuckit); Rutgers University (J. Tischfield, A. Brooks); University of Texas Health Science Center at San Antonio (L. Almasy), Virginia Commonwealth University (D. Dick), Icahn School of Medicine at Mount Sinai (A. Goate), and Howard University (R. Taylor). Other COGA collaborators include: L. Bauer (University of Connecticut); D. Koller, J. McClintick, S. O'Connor, L. Wetherill, X. Xuei, Y. Liu (Indiana University); G. Chan (University of Iowa; University of Connecticut); D. Chorlian, N. Manz, C. Kamarajan, A. Pandey (SUNY Downstate); J.-C. Wang, M. Kapoor (Icahn School of Medicine at Mount Sinai) and F. Aliev (Virginia Commonwealth University). A. Parsian and M. Reilly are the NIAAA Staff Collaborators.

We continue to be inspired by our memories of Henri Begleiter and Theodore Reich, founding PI and Co-PI of COGA, and also owe a debt of gratitude to other past organizers of COGA, including Ting-Kai Li, currently a consultant with COGA, P. Michael Conneally, Raymond Crowe, and Wendy Reich, for their critical contributions. This study is supported by NIH grant U10AA008401 from the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and the National Institute on Drug Abuse (NIDA), and by AA05524 (PI: Bernice Porjesz) from the NIAAA.

Appendix I. Mean (M) and standard deviation (SD) of P3 amplitudes for each subgroup

Condition	Electrode	LR								HR							
		Male				Female				Male				Female			
		Younger		Older		Younger		Older		Younger		Older		Younger		Older	
		M	SD	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD
Loss	F3	9.45	6.38	11.56	5.30	10.62	6.03	11.68	6.19	9.94	6.01	10.90	5.85	10.07	5.99	12.39	5.69
	FZ	12.56	6.64	13.40	5.56	12.05	6.96	13.26	6.80	12.08	6.33	12.61	6.19	11.30	6.48	13.52	6.11
	F4	11.02	6.53	12.25	5.25	11.29	7.14	11.78	5.86	11.19	6.11	11.63	5.67	10.61	6.16	12.59	5.73
	C3	16.98	6.86	17.10	5.99	17.25	7.04	16.82	6.68	16.43	6.62	15.52	6.10	15.96	6.58	17.15	6.19
	CZ	19.52	7.82	19.04	6.83	18.45	7.29	18.36	7.14	18.50	7.32	17.36	6.53	17.57	7.13	18.32	6.73
	C4	19.51	7.68	18.40	6.49	18.11	7.46	17.68	6.57	18.75	6.86	16.80	6.26	17.26	6.80	17.87	6.25
	P3	19.33	6.16	18.05	6.89	19.73	6.61	17.57	7.25	19.19	6.98	16.47	6.12	18.02	6.60	18.00	6.18
	PZ	21.79	6.98	19.80	7.26	20.48	7.03	19.42	7.54	20.71	7.13	18.01	6.37	19.64	6.84	19.07	6.48
	P4	22.73	7.28	19.55	7.00	20.89	7.08	18.65	7.04	21.31	7.27	17.76	6.52	19.84	6.86	18.78	6.31
	O1	19.29	7.42	15.87	7.67	18.87	6.22	15.76	7.45	18.23	7.12	14.07	6.20	17.21	6.62	15.67	6.27
	OZ	19.20	7.25	15.59	7.89	18.70	6.13	15.59	8.18	17.84	7.30	13.99	6.26	17.22	6.62	15.68	6.31
	O2	19.99	7.65	16.04	8.08	19.39	6.33	15.99	7.74	18.74	7.77	14.44	6.47	17.86	6.69	16.02	6.51
Gain	F3	11.43	6.26	12.53	5.42	11.56	6.09	13.72	6.66	11.18	6.24	12.57	6.17	11.42	5.96	14.38	6.12
	FZ	13.43	5.90	14.28	6.01	12.65	6.53	15.19	7.46	12.72	6.63	14.11	6.56	12.35	6.71	15.47	6.76
	F4	12.53	5.93	13.63	5.81	12.19	6.74	13.99	6.53	12.42	6.61	13.46	6.07	12.01	6.70	14.68	6.24
	C3	19.41	7.36	18.78	5.83	18.33	6.57	19.59	7.09	18.92	6.74	18.30	6.75	17.92	6.31	19.62	6.79
	CZ	20.80	7.63	20.60	6.99	19.50	7.39	20.99	8.18	20.39	7.42	20.11	7.18	19.44	7.17	20.97	7.58
	C4	21.02	7.37	20.29	6.64	19.28	6.87	20.15	7.26	20.74	6.90	19.66	6.92	19.29	7.03	20.38	6.91
	P3	21.75	7.54	20.36	6.73	21.15	6.73	20.44	7.10	22.32	7.24	19.85	6.62	20.30	6.77	20.76	6.67
	PZ	24.10	7.86	22.17	7.33	21.82	7.09	22.10	8.09	23.57	7.63	21.70	7.00	21.81	7.05	21.95	7.20
	P4	24.64	7.57	21.75	7.40	22.15	7.03	21.20	7.40	24.18	7.66	21.16	6.90	21.88	7.04	21.49	6.92
	O1	21.41	8.17	18.03	7.77	20.80	7.41	18.19	7.32	21.09	7.70	17.28	6.70	19.21	6.84	18.22	6.48
	OZ	21.14	7.85	17.64	7.86	20.36	7.43	17.77	7.81	20.65	7.63	17.21	6.56	19.16	6.85	18.15	6.64
	O2	22.47	8.36	17.98	8.05	21.08	7.12	17.95	7.59	21.63	8.02	17.53	6.66	19.56	6.86	18.55	6.78

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