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Evoked gamma band response in male adolescent subjects at high risk for alcoholism during a visual oddball task

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Abstract

This study investigates early evoked gamma band activity in male adolescent subjects at high risk for alcoholism (HR; $n=68$) and normal controls (LR; $n=27$) during a visual oddball task. A time–frequency representation method was applied to EEG data in order to obtain stimulus related early evoked (phase-locked) gamma band activity (29–45 Hz) and was analyzed within a 0–150 ms time window range. Significant reduction of the early evoked gamma band response in the frontal and parietal regions during target stimulus processing was observed in HR subjects compared to LR subjects. Additionally, the HR group showed less differentiation between target and non-target stimuli in both frontal and parietal regions compared to the LR group, indicating difficulty in early stimulus processing, probably due to a dysfunctional frontoparietal attentional network. The results indicate that the deficient early evoked gamma band response may precede the development of alcoholism and could be a potential endophenotypic marker of alcoholism risk.

Keywords: EEG; Event-related oscillations; Children of alcoholics; Gamma activity; Alcoholism; Visual oddball task

1. Introduction

Alcoholism is a multifactorial disease which has polygenic influence among biological relatives of alcoholics. A positive family history of alcoholism has been recognized as a consistent predictor of alcoholism risk. A detailed review of family studies indicates that alcoholics are 4 to 6 times more likely to have a parent who is alcohol dependent than are non-alcoholic controls (Cotton, 1979). Children of alcoholics (COAs) are 2 to 10 times more likely to develop alcoholism than non-COAs (Lieberman, 2000). A comprehensive review of the literature on the epidemiology of alcoholism concluded that genetic factors predispose sons of alcoholic fathers to alcoholism (Hesselbrock, 1995).

Electrophysiological abnormalities are one of the most extensively studied markers of high risk for alcoholism. Studies of alcohol naïve offspring of alcoholics at high risk (HR) indicate that the anomalous electrophysiological characteristics observed in alcoholics are already apparent prior to prolonged alcohol exposure (for review, see Porjesz et al., 2005). Several electrophysiological abnormalities have been reported in studies of offspring of alcoholics using electroencephalogram (EEG),

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event-related potentials (ERP) and event-related oscillations (EROs) methods. Reductions in EEG alpha and increases in beta power in male and female offspring of alcoholics have been reported by Finn and Justus (1999). Several studies have shown increased beta power in children of alcoholics (Gabrielli et al., 1982; Bauer and Hesselbrock, 1993; Pollock et al., 1995). In a recent investigation, Rangaswamy et al. (2004b) reported increased beta power in the resting EEG of a large sample of offspring of male alcoholics. In this study, male high risk offspring of alcoholics had elevated slow beta power (12–16 Hz) and female high risk offspring of alcoholics had increased faster beta power (16–28 Hz) when compared to low risk offspring of non-alcoholics. ERP deficits, particularly the reduced P300 component in children of alcoholics have been the most consistent finding in the investigations for a phenotypic marker for alcoholism. Begleiter et al. (1984) reported that male children of alcoholic fathers manifested significantly lower P3 voltages prior to any exposure to alcohol compared with matched males coming from low risk families without first or second degree alcoholic relatives. This finding has been replicated in younger and older male and female offspring of alcoholics (Begleiter et al., 1987; Benegal et al., 1995; Berman et al., 1993; Cohen et al., 1997; Ehlers et al., 2001, 2003; Hesselbrock et al., 1993; Hill and Steinhauer, 1993; Hill et al., 1995; O'Connor et al., 1986, 1987; Porjesz and Begleiter, 1990; Ramachandran et al., 1996; Ratsma et al., 2001; Rodriguez Holguin et al., 1999; van der Stelt et al., 1998; Whipple et al., 1991). In a comprehensive meta analysis, Polich et al. (1994) found that the strongest P300 group differences were obtained in young male offspring with relatively difficult visual tasks and concluded that low voltage P300 may have predictive value as an index of vulnerability for alcoholism.

Several studies have demonstrated that numerous ERP features arise from oscillatory changes due to sensory or cognitive processes which influence the dynamics of ongoing EEG rhythms of different frequency bands (Basar-Eroglu and Basar, 1991; Karakas et al., 2000a,b; Basar et al., 2001; Demiralp et al., 2001). It has been suggested that the P300 component of the ERP consists of superimposed event-related oscillations (EROs) of delta and theta bands (Basar-Eroglu et al., 1992; Yordanova and Kolev, 1996; Schurmann et al., 2001). Similar to the reduced P300 amplitudes observed in alcoholics, deficits in evoked delta and theta ERO amplitudes underlying P300 have been observed in alcoholics while processing the target stimuli during a visual oddball paradigm (Porjesz and Begleiter, 2003; Jones et al., in press). A recent investigation examined high risk children of alcoholics using the same visual oddball paradigm in order to determine whether these deficits in theta and delta oscillations antecede the development of alcoholism (Rangaswamy et al., in preparation). It was found that the 14–17 year old children of alcoholics have reduced delta and theta band ERO amplitude while processing the target stimuli compared to controls. Significant changes in EROs of higher frequency bands have also been observed in alcoholics during visual oddball tasks. In a recent study, significant reductions in early evoked gamma band activity were reported during target stimulus processing in alcoholics in a visual oddball paradigm (Padmanabhapillai et al., 2006).

Event related oscillations in gamma frequency band have been associated with several complex cognitive processes (Basar-Eroglu et al., 1996; Tallon-Baudry and Bertrand, 1999; Schack et al., 2002; Chen et al., 2003; Fell et al., 2003). A recent study that investigated the gamma band activity during multiple cognitive tasks concluded that task complexity augments gamma band power (Fitzgibbon et al., 2004). Event related gamma oscillations can be found as phase-locked (evoked) or non-phase locked (induced) to the onset of the experimental stimuli (Tallon-Baudry et al., 1996). Evoked gamma band activity has been observed following auditory, visual and somatosensory stimuli (Desmedt and Tomberg, 1994; Marshall et al., 1996; Salenius et al., 1996; Tallon-Baudry et al., 1996; Yordanova et al., 1997; Haig et al., 1999; Herrmann and Mecklinger, 2000; Watanabe et al., 2002). It has been observed at early (0–150 ms) and later (200–300 ms) time intervals (Herrmann et al., 1999). The early evoked gamma was found to be insensitive to the stimulus type and was suggested to reflect sensory processing (Karakas and Basar, 1998; Sannita et al., 1999). However, some experiments have shown increased early gamma band activity during target stimulus processing indicating early stimulus selection and attentional processing (Tiitinen et al., 1993, 1997; Debener et al., 2003; Fell et al., 2003). In addition, early evoked gamma band response has been found to be correlated with neuropsychological functions such as attention, learning, memory and executive functions, suggesting that early gamma band response reflects basic sensory (bottom-up) as well as top-down information processing (Karakas et al., 2001, 2003).

The aim of the present study was to investigate early evoked gamma band response in subjects at high risk to develop alcoholism and to determine whether the reduction in gamma band activity observed in alcoholics is a consequence of chronic alcohol abuse or a predisposing factor. Since many of the electrophysiological abnormalities observed in alcoholics have also been observed in high risk subjects, in the present study we investigated the early phase locked gamma band activity in the children of alcoholics using the same task as we had used in alcoholics. For this purpose, early evoked gamma band response elicited during a visual oddball task, in male children of alcoholic parents, was compared to the response in age matched male children of non-alcoholic parents. A similar pattern of deficits in high risk children would indicate that these deficits precede the development of alcoholism; the present study aimed to examine early evoked gamma band response as a potential phenotypic marker for the development of alcoholism.

2. Materials and method

2.1. Subjects

Subjects included in this study were participants in the Collaborative Study on the Genetics of Alcoholism (COGA), a large multi-center study investigating the genetic predisposition to develop alcohol dependence and related disorders. The six participating centers are located at: SUNY-Downstate Medical Center, University of Connecticut Health Center, Washington University School of Medicine in St. Louis, University of California at San Diego, University of Iowa and Indiana University

School of Medicine. The details of the COGA recruitment procedures have been described elsewhere (Begleiter et al., 1995). Alcoholic probands were recruited from inpatient and outpatient treatment facilities, and they met the criteria for DSM-IIIR alcohol dependence and the criteria established by Feighner et al. (1972) for 'definite' alcoholism. Probands were excluded from the COGA study if they were habitual intravenous drug users, known to be HIV positive, or have non-alcohol related terminal illness. All probands and their first-degree relatives were interviewed with the SSAGA, a semi-structured diagnostic psychiatric interview schedule developed specifically for COGA (Bucholz et al., 1994; Hesselbrock et al., 1999). Subjects under the age of 18 years were administered the child/adolescent version of SSAGA, called the CSSAGA-A for adolescents aged 13 to 17 and the CSSAGA-C for children aged 7 to 12 (Kuperman et al., 1999). Families with three or more alcohol-dependent members were studied further with a more extensive protocol that included drawing blood for genetic analysis, neuropsychological and neurophysiological assessments. Control families were recruited from HMOs, drivers' license records, and dental clinics, with the objective of being representative of the general population at each center. Individuals with alcoholism and other psychiatric illnesses were not excluded from the control sample in order to reflect prevalence rates that are similar to those of the population at large. All control subjects were interviewed with the SSAGA and they underwent blood drawing, neuropsychological and neurophysiological assessments. The institutional review board at each site approved the research procedures in the COGA study and written consent was obtained from each individual prior to participation.

Subjects were excluded from the neurophysiological assessment if presence of alcohol was detected with the breath-analyzer prior to testing. Subjects with hepatic encephalopathy/cirrhosis of the liver, acute/chronic illness, a significant history of head injury, seizures or neurosurgical procedures, tested positive for HIV or were on medication that affects/influences brain functioning were excluded. Subjects who manifested uncorrected sensory deficits and subjects who had used any psychoactive substances in the past 5 days were also excluded.

For the present study, male adolescent subjects within the age range of 14–17 years were culled from the COGA database. Subjects younger than 14 years of age were not included in the study due to the inadequate number of subjects in the control group. All subjects were administered the CSSAGA-A, the child/adolescent version of SSAGA. The high risk (HR) sample consisted of 68 male children from densely affected alcoholic families where at least one parent had alcohol dependence. The low risk (LR) subjects were 27 male offspring of non-alcoholics from population based control families. The sample was limited to the male children owing to the gender differences in cognitive and electrophysiological parameters. Clinical characteristics of the sample are described in Table 1.

Table 1
Sociodemographic, clinical (DSM III R) diagnoses of the low risk and high risk male subjects

	Low risk	High risk
Number of subjects (n)	27	68
Mean age (years)	15.43	15.31
% Alcohol dependence	0	4.4
% Cocaine dependence	0	2.9
% Marijuana dependence	3.7	1.5
% ADHD	0	5.9
% Conduct disorder	11.1	16.2
% Oppositional defiant disorder	0	4.4
% Obsessive compulsive disorder	0	2.9

2.2. Stimuli

The visual oddball paradigm employed in the present study has been previously described (Cohen et al., 1994; Porjesz et al., 1998). It consisted of the presentation of three types of visual stimuli (n=280), 60 ms duration, subtending a visual angle of 2.5°, with an interstimulus interval of 1.625 s. The rare target stimulus (n=35) was the letter X, to which the subject was required to press a button as quickly as possible; the responding hand was alternated across subjects to counterbalance any laterality effects due to responding. Speed was emphasized, but not at the cost of accuracy. The frequently occurring non-target stimuli (n=210) were squares and the novel stimuli (n=35) consisted of colored geometric polygons that were different on each trial; the subject was not required to respond to the non-target and novel stimuli. The probabilities of occurrences of the trials were 0.125 for the target trials, 0.75 for the non-target trials, and 0.125 for the novel trials. The stimuli were presented pseudorandomly with the constraints that neither targets nor novels could be repeated consecutively. The experiment terminated automatically when a minimum number of artifact-free trials had been acquired for each stimulus category: 25 target, 25 novel and 150 non-target.

2.3. Data recording

Identical experimental procedures and EEG acquisition hardware/software were used in all six collaborating sites. Subjects were seated comfortably in a dimly lit sound-attenuated temperature-regulated booth (Industrial Acoustics Company; Bronx, NY), and instructed to keep their eyes closed and remain relaxed before the visual oddball experiment. Subjects were also instructed not to fall asleep. Each subject wore a fitted electrode cap (Electro-Cap International Inc.; Eaton, OH) using the 19-channel montage as specified according to the 10–20 International system [FP1, FP2, F7, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, O1, O2]. The nose served as reference and the forehead as ground. Electrode impedances were always maintained below 5 kohms. Electrooculogram (EOG) was recorded from electrodes placed supraorbitally and at the outer canthus of the left eye. Vertical and horizontal eye movements were monitored to perform ocular artifact correction. In the present study, EEG was acquired during the performance of the visual oddball paradigm described in Section 2.2. Electrical activity was amplified 10 K (Sensorium EPA-2 Electrophysiology amplifiers, Charlotte, VT), with a bandpass between 0.02 Hz and 50 Hz at a sampling rate of 256.0 Hz and digitized on a Concurrent 5550 computer (Concurrent Computer Corp.; Atlanta, GA).

2.3.1. Data analysis

To obtain reliable estimates of localized power of nonstationary evoked potential time series we employed a recently developed time–frequency representation method: the S-transform (Chu, 1996; Stockwell et al., 1996; Theophanis and Queen, 2000). The S-transform is a generalization of the Gabor transform (Gabor, 1946) and an extension to the continuous wavelet transform. The S-transform generates a time–frequency representation (TFR) of a signal by integrating the signal at each time point with a series of windowed harmonics of various frequencies as follows:

$$\mathrm{ST}(f,\tau) = \int_{-\infty}^{\infty} h(t)\frac{|f|}{\sqrt{2\pi}}\mathrm{e}^{\frac{(\tau-t)^2 f^2}{2}} e^{i2\pi ft}\mathrm{d}t,$$

where $h(t)$ is the signal, f is frequency, τ is a translation parameter, the first exponential is the window function, and the second exponential is the harmonic function. The S-transform TFR is computed by shifting the window function down the signal in time by τ across a range of frequencies. The window function is Gaussian with $1/f^2$ variance and scales in width according to the examined frequency. This inverse dependence of the width of the Gaussian window with frequency provides the frequency-dependent resolution. The amplitude envelope of the complex-valued S-transform TFR is calculated by taking the absolute value $|\mathrm{ST}(f,\tau)|$. This method has been previously described in a genetic linkage study of delta and theta EROs during the same visual oddball paradigm employed in the present study (Jones et al., 2004).

The electrophysiological data used in the analyses were derived from trial-averaged visual oddball event related data for target, non-target, and novel cases to obtain the evoked TFR via the S-transform. In order to reduce the effects of large differences between the number of stimuli in target/novel and non-target conditions, an upper limit of 35 trials was maintained for the non-target condition, for inclusion into the S-transform method. Mean values were calculated from the TFR amplitude envelope within time–frequency regions of interest (TFROI's) specified by frequency band ranges and time intervals (Lachaux et al., 2003). Further, a baseline corrected TFR was obtained by subtracting the average value of the TFR amplitude envelope in the pre-stimulus time window from the post stimulus TFR values. This study focused on TFROI corresponding to the gamma (29–45 Hz) frequency band during the 0–150 ms time window range. The same procedure was used in a previous study for this frequency band and time window (Padmanabhapillai et al., 2006).

2.4. Statistical analysis

Statistical analyses were performed on the evoked gamma activity obtained during the target, non-target and novel stimulus conditions. Co-morbid psychiatric conditions were not included in the main analysis.

Mean energy values of the evoked gamma data (time window 0–150 ms) from 9 electrodes (F3, F4, Fz, C3, C4, Cz, P3, P4, Pz) were analyzed by a linear mixed-effects model. These 9 electrodes were divided into three topographical regions, frontal (F3/F4/Fz), central (C3/C4/Cz) and parietal (P3/P4/Pz). Frontal, central and parietal regions were analyzed separately by linear mixed-effects models using SAS Proc Mixed procedure (SAS 9, SAS Institute Inc., NC, USA). The mixed-effects model included group (HR, LR), condition (target, non-target and novel), electrodes (within a region) and their interactions as fixed effects. The model was designed to deal with the effects of unequal sample sizes. A backward stepwise method was used to remove non-significant effects (Rawlings et al., 1998). In the backward selection procedure, the non-significant covariates were removed from the model in a stepwise manner until all remaining covariates were significant (i.e., at each step, the most insignificant covariate was removed). However, the main effects or lower level interaction terms were retained in the model (even if they are not significant) if the higher-level interaction was significant. Further exploration of main effects and interactions were performed using Wald's tests (Kenward and Roger, 1997). The behavioral data and clinical characteristics were analyzed using *t* tests.

3. Results

3.1. Demographic and behavioral data

The socio-demographic and clinical characteristics of the sample are presented in Table 1. The percentage of occurrence of co-morbid psychiatric conditions (DSM IIIR diagnoses of Axis I conditions) in each of the groups are also given. The HR group had a higher percentage of co-occurring psychiatric conditions than the LR group, which is consistent with the previous reports of higher incidence of psychopathology in children of alcoholics (Sher et al., 1991; Kuperman et al., 1999).

The mean reaction time of the two groups were compared using *t* tests (t [1,93]=1.656; p=0.101) and there was no statistically significant difference between the two groups. Similarly, the mean total error scores (both omission and commission) of the two groups (t [1,93]=0.896; p=0.373) did not yield statistically significant results.

3.2. Gamma band response

Evoked gamma band activity was significantly different between LR and HR groups in frontal and parietal regions. In the frontal region, evoked gamma band response was significantly higher in the LR group than in the HR group (Condition × Group; F (2, 182)=4.70; p<0.05). Fig. 1 illustrates the difference between the two groups during target, non-target and novel stimulus conditions at the F4 electrode. In the target condition there is higher evoked gamma band activity in the LR group than in the HR group (Wald *t*-statistic=2.45; p<0.05). Within the LR group, target stimuli elicited significantly higher evoked gamma band response than non-target (Wald *t*-statistic=4.26; p<0.0001) and novel stimuli (Wald *t*-statistic=2.24; p<0.05). Within the HR group there was no significant difference between the stimulus conditions indicating difficulty in differentiating relevant and irrelevant stimuli.

In the parietal region, there was a significant Condition × Group × Electrode interaction (F (4, 546)=2.41; p<0.05),

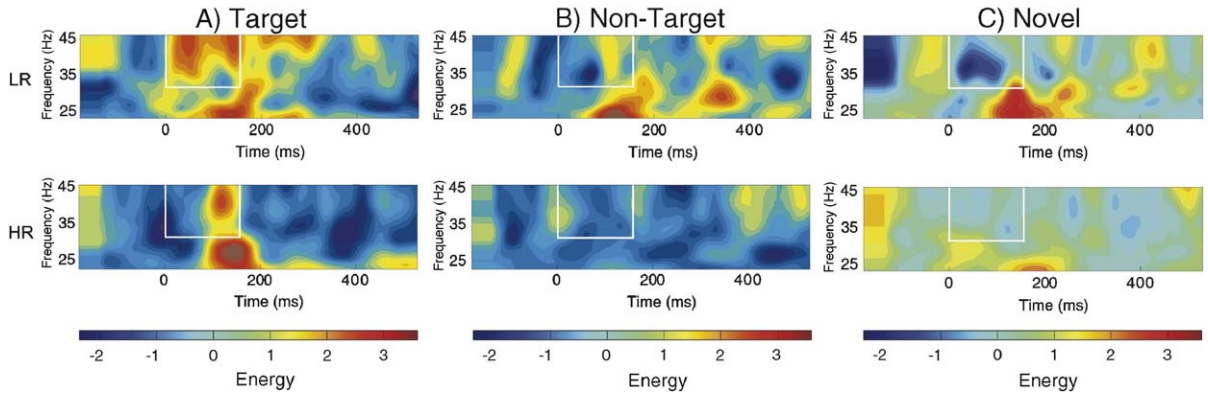

Fig. 1. Time–frequency representation of evoked gamma band energy distribution (29–45 Hz) of target, non-target and novel stimuli at the F4 electrode, calculated using the S-transform method. The time–frequency region of interest (TFROI) window used for analysis was 0–150 ms (White Square outline). The time–frequency distributions displayed above show increases (Red) or decreases (Blue) of evoked power from the baseline levels, and are represented as *Z*-scores within individual frequencies across the two groups of subjects for each stimulus condition (Target, Non-Target and Novel) separately. (A) Time–frequency responses to target stimuli in the low risk (LR) and high risk (HR) groups. (B) Responses to non-target stimuli in the LR and HR groups. (C) Responses to novel stimuli in the LR and HR groups. Increased early evoked gamma band response is observable in the target condition in the LR group.

which showed increased evoked gamma band activity at all three parietal electrodes for the target condition (highest at Pz) in the LR group. The higher evoked gamma band activity for the target stimuli in the LR group is illustrated in Fig. 2. Evoked gamma band activity was significantly higher for the target condition in the LR group compared to the HR group (Wald *t*-statistic = 2.02; $p < 0.05$). There was no significant difference between the groups for non-target and novel stimulus conditions. Within the LR group there was a significant difference between the target and non-target conditions (Wald *t*-statistic = 2.33; $p < 0.05$). However, in the HR group there was no difference between any of the three stimulus conditions.

There was no difference between the LR group and the HR group in the central region. However, there was a significant condition main effect (F (2, 182) = 7.23; $p < 0.001$) indicating a significantly higher evoked gamma band response for target condition compared to non-target condition (Wald *t*-statistic = 3.79; $p < 0.001$) in both the groups. Novel stimuli also elicited significantly higher gamma band response than the non-target stimuli in both the groups (Wald *t*-statistic = 2.11; $p < 0.05$).

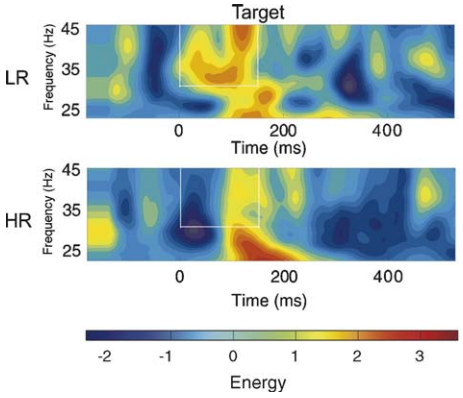

Fig. 2. Time–frequency representation of evoked gamma band energy distribution (29–45 Hz) recorded to target stimuli at the Pz electrode in low risk (LR) and high risk (HR) groups, calculated using the S-transform method. The time–frequency region of interest (TFROI) window used for analysis was 0–150 ms (White Square outline). The time–frequency distribution displayed above was obtained by calculating *Z*-scores within individual frequencies across the two groups of subjects. The LR group has higher gamma band response in the target condition than the HR group.

4. Discussion

This study investigated the early evoked gamma band response (0–150 ms) in male adolescent subjects at high risk (HR) for alcoholism and subjects at low risk (LR) for alcoholism during a visual oddball task. Reduced early evoked gamma band response was observed in HR subjects compared to LR subjects to target stimuli and the difference was significant over frontal and parietal regions. While the early gamma band response was higher for target stimuli than the non-target stimuli in the LR group, there was a lack of differentiation between the target and non-target stimulus conditions in the HR group.

The difference between target and non-target stimuli in the frontal and parietal regions in the LR group indicates that the early evoked gamma band response is sensitive to stimulus conditions. Moreover, target stimuli also elicited higher gamma band response than non-target and novel stimuli in the central region. The higher gamma band response for the target stimuli is consistent with previous reports on visual gamma processing. Increased early evoked gamma activity has been observed during illusory figure (Kanizsa) perception (Herrmann et al., 1999; Herrmann and Mecklinger, 2000). The cognitive processes involved in visual oddball tasks lead to an increase in gamma band response for target stimuli in the fronto-central and parietal regions. Oddball tasks involve stimulus discrimination that requires selective attention and maintenance of information in working memory. The same neural system that has been found to be activated during working memory tasks in both humans and animals is also involved in the processing of infrequent targets in oddball tasks (Friedman and Goldman-Rakic, 1994; McCarthy et al., 1994, 1996). A number of event related fMRI studies have shown activations in frontal and

parietal regions to the target stimuli during the visual oddball task (McCarthy et al., 1997; Yoshiura et al., 1999; Clark et al., 2000; Ardekani et al., 2002). Neuropsychological and functional neuroimaging studies have shown that fronto-parietal networks subserve both attentional processes and working memory (Awh and Jonides, 2001).

It has been proposed that visual attention is controlled by two partially segregated neural systems (Corbetta and Shulman, 2002). The ventral system is centered on the temporoparietal and ventral frontal cortex, and is involved in the detection of behaviorally relevant stimuli, particularly when they are salient or unexpected. The ventral frontoparietal network is involved in bottom-up selection as a 'circuit breaker' for the dorsal system. The ventral frontoparietal network is also engaged in the detection of rare (or low frequency) events such as target stimuli in an oddball task. The dorsal system which includes superior frontal cortex and posterior parietal regions is involved in preparing and applying goal-directed (top-down) selection for stimuli and responses. Both dorsal and ventral attentional networks interact during cognitive processes.

The reduced gamma band response observed in the frontal and parietal regions in the HR group may be due to a dysfunctional frontoparietal circuit. The difference between target and non-target stimuli in the HR group was significantly lower in the frontal and parietal region compared to the LR group. The reduced differentiation between stimulus conditions in the HR group is indicative of a difficulty in discriminating relevant from irrelevant stimuli. It has been shown that the task relevance of the rare stimulus increases activation in the temporoparietal junction (Downar et al., 2001). The reduced differentiation between relevant and irrelevant stimuli in the HR group indicates a dysfunctional ventral fronto-parietal circuit, which is recruited for bottom up processes. The HR group may be processing both relevant and irrelevant stimuli with equal amount of attentional resources, whereas the LR group allocates more resources to the relevant stimuli. A defective early sensory discrimination would lead to a defective interaction between bottom-up (ventral) and top-down (dorsal) fronto-parietal networks. As the oddball tasks involve both bottom-up as well as top-down processes, it is possible that the defective interaction between the fronto-parietal networks would lead to the decreased gamma band response in the HR group. Moreover, the early evoked gamma band activity has been considered to be involved in both top-down and bottom up processes, since it was correlated with early sensory stimulation as well as to higher mental functions (Karakas et al., 2003). A recent neuroimaging study explored the structural correlates of target processing in subjects at risk for developing alcoholism during a visual oddball task (Rangaswamy et al., 2004a). It was found that the high risk subjects had reduced activation in the bilateral frontal and parietal regions indicating a dysfunctional fronto-parietal circuit.

The early evoked gamma band activity reduction in the HR group indicates that this deficit antecedes the development of alcoholism. In a recent study, using the same visual oddball task, significant reduction in early evoked gamma band response was observed in alcoholics in the frontal region (Padmanabhapillai et al., 2006). However, in the present study the reduction in gamma band response was observed in both frontal and parietal regions. This differential effect could possibly be due to the age related differences in the functional maturation of frontoparietal networks (Kwon et al., 2002) or the long term effects of alcohol usage in the functional brain anatomy of alcoholics. Developmental changes in cognitive functions has been shown to affect event related gamma oscillations and its functional reactivity. A study that compared 9–12 year old children and 13–16 year old adolescents using a bilateral auditory attention task found that the younger group had higher early evoked gamma band activity for the target stimuli in the frontal region; the older group showed higher early event related gamma activity lateralized to the attended side of the parietal region that is associated with the maintenance of attentional focus to the stimulus location (Yordanova et al., 2002). It was concluded that this age dependent reactivity of gamma band responses to different task variables reflected a transition in processing strategies emerging at approximately 12–13 years in relation to the maturation of cognitive and executive brain functions.

Gamma oscillations are inhibitory rhythms that are thought to be generated due to the synchronous mutual inhibition of GABAergic interneurons (Whittington et al., 1995; Traub et al., 1996). Several molecular, cellular and behavioral studies have revealed that GABAA receptors play a central role in mediating the acute effects of alcohol, alcohol intolerance, alcohol dependence and alcohol self administration (Grobin et al., 1998). Several neuroimaging studies have shown specific deficits in GABA benzodiazepine receptors in the brains of alcoholics (Abi-Dargham et al., 1998; Lingford-Hughes et al., 1998) and individuals at risk (Volkow et al., 1995). Beta oscillations, which are also mediated by GABAergic mechanisms have been shown to have significant linkage and linkage disequilibrium with a GABAA receptor gene on chromosome 4 (Porjesz et al., 2002). In a recent study, the GABAA receptor gene (alpha 2) was found to be associated with beta oscillations and DSM-IV diagnosis of alcohol dependence (Edenberg et al., 2004). Other studies also have replicated this finding indicating that the genes encoding GABA-alpha 2 receptors influence the risk of developing alcohol dependence (Covault et al., 2004; Xu et al., 2004). Based on the GABAergic origins of gamma oscillations, it is possible to assume that the reduction in gamma band activity in children of alcoholics observed in the present study is associated with a dysfunction in GABAergic mechanisms. This would suggest that the deficient evoked gamma band activity of children of alcoholics in the present study may reflect genetic influences that antecede the development of alcoholism. It also indicates that the early evoked gamma band response can be considered as a potential endophenotypic marker for alcoholism.

Although we have found a reduction in early gamma band response in alcoholics as well as high-risk subjects, this phenomenon is not specific to alcoholism. Abnormalities in gamma band activity have been observed in patients with neuropsychiatric disorders including schizophrenia, attention deficit hyperactivity disorder (ADHD), Alzheimer's Dementia and epilepsy (Herrmann and Demiralp, 2005). Gamma band

abnormalities have also been observed in heavy tobacco smokers and morphine dependent primates (Crawford et al., 2002; Liu et al., 2005). However, most of these studies have focused on spontaneous and induced gamma activity rather than evoked gamma activity. Few studies that investigated evoked gamma band activity have reported significant reduction in evoked gamma band response in schizophrenia, and an increase of evoked gamma band response has been reported in ADHD (Haig et al., 2000; Spencer et al., 2003; Yordanova et al., 2001). Unlike other studies on gamma band activity in neuropsychiatric disorders, this is the first study that investigated evoked gamma band response in a vulnerable population of offspring, using the same method employed in the alcoholic patients. Although the gamma band abnormality is not specific to alcoholism, it is observed in both alcoholic and high-risk population indicating a major role for evoked gamma band activity in mediating the biological underpinnings of alcoholism.

In conclusion, the present study demonstrates that the subjects at high risk for alcoholism have a deficient early evoked gamma band response. The reduction in gamma band response was observed in the frontal and parietal regions characterized by a lesser differentiation between the relevant and irrelevant stimuli, indicating a dysfunctional frontoparietal network. Similar findings were reported in abstinent alcoholics using the same paradigm indicating that the gamma band deficit perhaps antecedes the development of alcoholism. In addition, these findings suggest a basic deficit in GABAergic mechanisms and their genetic underpinnings, owing to the role of GABAergic interneurons in the generation of gamma band activity, as well as the role of GABA in mediating the effects of alcohol in the brain. Thus the deficient early evoked gamma band activity in high risk subjects may reflect the influence of genetic factors that precede the onset of alcoholism and could be a potential endophenotypic marker for its development.

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