

Suppression of early evoked gamma band response in male alcoholics during a visual oddball task

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Abstract

We investigated the early evoked gamma frequency band activity in alcoholics ($n=122$) and normal controls ($n=72$) during a visual oddball task. A time–frequency representation method was applied to EEG data in order to obtain phase-locked gamma band activity (29–45 Hz) and was analyzed within a 0–150 ms time window range. Significant reduction of the gamma band response in the frontal region during target stimulus processing was observed in alcoholic compared to control subjects. In contrast, significantly higher gamma band response for the non-target stimulus was observed in alcoholics compared to controls. It is suggested that the reduction in early evoked frontal gamma band response to targets may be associated with frontal lobe dysfunction commonly observed in alcoholics. This perhaps can be characterized by a deficient top-down processing mechanism.

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1. Introduction

Gamma rhythms are important functional building blocks of brain electrical activity (Basar-Eroglu et al., 1996b). Oscillatory activities in the gamma range form a group of signals with common frequency characteristics but that are functionally related to diverse brain processes (Schurmann et al., 1995, 1997; Sannita et al., 2001). In humans, gamma activity has been observed in a variety of cognitive tasks involving selective attention, mental arithmetic, multistable visual perception, mental rotation, music perception, somatosensory perception, visuo-motor coordination, associative learning, semantic processing, short-term memory, conscious recollection, object representation and induced visual

illusions (Desmedt and Tomberg, 1994; Basar-Eroglu et al., 1996a; Tallon-Baudry et al., 1996, 1999; Miltner et al., 1999; Tallon-Baudry and Bertrand, 1999; Bhattacharya et al., 2001a,b, 2002; Burgess and Ali, 2002; Schack et al., 2002; Chen et al., 2003; Fell et al., 2003; Umeno et al., 2003). Event related oscillations (EROs) in the gamma range 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 activity has been observed following auditory (Marshall et al., 1996; Yordanova et al., 1997a,b; Karakas and Basar, 1998; Haig et al., 1999, 2000a,b; Gurtubay et al., 2001; Kaiser and Lutzenberger, 2001; Muller et al., 2001; Palva et al., 2002; Debener et al., 2003; Karakas et al., 2003), visual (Tallon-Baudry et al., 1996; Herrmann et al., 1999; Herrmann and Mecklinger, 2000b; Braeutigam et al., 2001; Bottger et al., 2002; Senkowski and Herrmann, 2002; Watanabe et al., 2002) or somatosensory stimuli (Desmedt and Tomberg, 1994; Salenius et al., 1996). It has been observed at early (0–150 ms) and later (200–300 ms)

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time intervals (Herrmann et al., 1999). The functional significance of the early evoked gamma activity has been attributed to sensory processing (Karakas and Basar, 1998; Sannita et al., 1999) and is considered to be influenced by bottom-up as well as top-down information processing (Karakas et al., 2001, 2003). However, some researchers have associated this gamma activity to early stimulus selection and attentional processing (Tiitinen et al., 1993, 1997; Debener et al., 2003; Fell et al., 2003).

Abnormalities in gamma band activity have been observed in patients with psychiatric disorders (Lee et al., 2003). Studies in schizophrenic patients have shown abnormalities in amplitude, latency, topography and phase coherence of gamma band responses (Haig et al., 2000a; Green et al., 2003; Spencer et al., 2003). Investigations of other psychiatric disorders have been few in number. However, studies of patients with attention deficit hyperactivity disorder (ADHD), autism, Alzheimer's dementia and epilepsy patients with psychiatric symptoms have revealed aberrations in gamma band responses (Loring et al., 1985; Le Van Quyen et al., 1997; Grice et al., 2001; Yordanova et al., 2001; Green et al., 2003; Spencer et al., 2003).

Although there is a large literature showing the impact of alcoholism on several components of the event related potential (ERP), studies of event related oscillations (EROs) in alcoholics are few. The most commonly reported ERP deficit in alcoholics is the reduced amplitude of P300 for the task relevant target stimuli during oddball tasks (for review, see Porjesz and Begleiter, 1996). It has been suggested that ERP components are the end products of specific superpositions of oscillations in various frequency bands, and P300 consists primarily of delta and theta oscillations (Basar-Eroglu et al., 1992; Yordanova and Kolev, 1996; Basar et al., 1999; Karakas et al., 2000). A significant reduction of evoked delta and theta power has been observed in alcoholics while processing the target stimuli in a visual oddball paradigm, indicating that the reduced P300 amplitudes reported in alcoholics are caused by deficits in theta and delta oscillations that underlie P300 (Porjesz and Begleiter, 2003; Jones et al., in preparation). In a recent study, EROs were investigated using a Go/No-Go paradigm in alcohol dependent individuals (Kamarajan et al., 2004). A significant reduction in delta and theta bands was observed in the frontal region of alcoholics, suggestive of deficient inhibitory control and information processing mechanisms. In another study conducted in our laboratory, a reduction in frontal midline theta activity was observed in alcoholics during a mental arithmetic task (Suresh et al., in preparation).

Acute alcohol administration in normal individuals and investigations of heavy social drinkers has shown that EROs are sensitive to the short-term effects of alcohol. Krause et al. (2002) investigated the effect of alcohol on event related synchronization (ERS) and desynchronization (ERD) of theta and alpha bands during an auditory memory task;

administration of alcohol decreased the early-appearing ERS responses during auditory encoding and increased the later-appearing ERD responses during retrieval in the theta and lower alpha frequency ranges indicating that alcohol has disorganizing effects on brain electric oscillatory systems during cognitive processing. In another study, Jaaskelainen et al. (2000) investigated the dose-related impact of alcohol on auditory transient evoked 40-Hz responses during a selective attention task. They found that higher doses of alcohol significantly suppressed the early evoked gamma responses in both attended and non-attended conditions. As gamma band responses have been associated with several cognitive functions, the authors concluded that this result indicates an alcohol-induced cognitive deficit. This study demonstrated that cognitive processing associated with gamma band activity is affected by alcohol administration. In a recent study, increased EEG synchronization in theta and gamma bands was observed in heavy social drinkers; this finding was similar across the brain areas for resting EEG, as well as during a mental rehearsal task (De Bruin et al., 2004).

Although there are numerous studies showing electrophysiological aberrations in alcoholism, event related gamma band oscillations have not been investigated. It has been demonstrated that gamma oscillations can be generated by GABAergic interneuronal activity (Whittington et al., 2000b). GABAergic receptors have been implicated in mediating the effects of alcohol in the central nervous system (Davies, 2003), suggesting a potential role for gamma oscillations in the electrophysiological processes of the alcoholic brain. Hence, in the present study we examined the early evoked gamma band activity in alcoholics during a visual oddball task, one of the most frequently used methods in ERP research. This task was chosen based on: 1) the consistent electrophysiological findings in alcoholics during visual oddball tasks, and 2) increased early evoked gamma band activity observed during target stimulus processing in visual oddball tasks in healthy individuals (Stefanics et al., 2004). Based on the evidence of electrophysiological deficits observed during target stimulus processing in alcoholics during visual oddball tasks, we hypothesized that the early evoked gamma activity to the target stimuli would be suppressed in alcoholics when compared to controls.

2. Materials and methods

2.1. Subjects

The participants were 194 adult males ranging from 19 to 40 years of age. The demographic and clinical characteristics of the sample are presented in Table 1. The alcoholic subjects ($n=122$; mean age=32.33 years; S.D.=4.28) were recruited from individuals undergoing treatment in the Short Term Alcohol Treatment Unit, Addictive Disease Hospital,

Table 1
Sample characteristics

Variables	Alcoholics (<i>N</i> =122)	Controls (<i>N</i> =72)
Age (year)		
Mean	32.33	25.64
S.D.	4.28	4.29
Range	20–40	19–36
Education (year)		
Mean	11.66	14.58
S.D.	2.04	2.11
Range	4–20	9–18
Age of onset of drinking (year)		
Mean	15.14	NA
S.D.	4.96	NA
Range	8–34	NA
No. of drinking days per month ^a		
Mean	20.62	2.47
S.D.	9.83	2.82
Range	0–35	0–12
No. of drinks ^b per drinking day ^a		
Mean	10.07	1.68
S.D.	7.57	1.93
Range	0–30	0–12

NA=not applicable.

^a Data are for the 6 months prior to treatment in alcoholic group.

^b One drink=1 shot glass of hard liquor; 1 glass of wine; 1 bottle of beer.

Kings County Hospital Center, New York. Alcoholic subjects had been detoxified in a 30-day treatment program and none of the subjects was in the withdrawal phase. The clinical data were obtained using the Bard/Porjesz adult alcoholism battery, a semi-structured clinical assessment schedule based on DSM IV criteria for the evaluation of clinical details of alcohol dependence and alcohol-related medical problems. The control subjects (*n*=72; mean age=25.64 years; S.D.=4.29) were individuals who responded to newspaper advertisements or notices posted in the SUNY Downstate Medical Center. Control individuals were social drinkers with no personal or family history of medical or psychiatric problems, including alcoholism and drug dependence. The control subjects were requested to abstain from alcohol and other central nervous system (CNS)-acting substances for 5 days prior to testing.

Using a questionnaire, all subjects were screened on their own and their relatives' alcohol/drug use and medical/psychiatric histories. Subjects with a history of drug usage in the last 6 months for all drugs except marijuana and cocaine were excluded from the sample. Informed consent was obtained from each individual and they were paid for their services. Exclusion criteria for both groups included major medical conditions or current requirement of medication that could affect the central nervous system (CNS). Breath-analyzer tests were administered prior to recordings, and individuals with nonzero readings were excluded. Experimental procedures were approved by the Institutional Review Board (IRB). Due to the gender differences in cognitive and electrophysiological parameters the study was restricted to include only male alcoholics and controls.

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

The subject was seated comfortably in a dimly lit, temperature regulated, sound-attenuated (Industrial Acoustics Corp., Bronx, NY) room. Each subject was fitted with an electrode cap (Electro-Cap Intl., Inc., Eaton, OH) containing 61 electrodes and was asked to focus his eyes on a fixation target centrally displayed on a computer monitor. The nose served as the reference and the forehead as ground. Both vertical and horizontal eye movements were monitored. Electrical activity was amplified 10 K (Sensorium, Charlotte, VT) and recorded over a bandwidth of 0.02–50.0 Hz at a sampling rate of 256.0 Hz. The recording epoch was 1500 ms long which included a pre-stimulus baseline of 184 ms. Subjects were requested to avoid blinking their eyes and to sit as still as possible. EEG data were recorded from 61 channels, as follows: AF1/2, AF7/8, AFz, F1/2, F3/4, F5/6, F7/8, Fz, FP1/2, FPz, FC1/2, FC3/4, FC5/6, FCz, C1/2, C3/4, C5/6, Cz, CP1/2, CP3/4, CPz, P1/2, P3/4, Pz, PO1/2, PO7/8, POz, O1/2, Oz, FT7/8, CP5/6, P5/6, P7/8, T7/8 and TP7/8. Both vertical and horizontal eye movements were monitored and ocular artifact rejection (>73.3 μV) was performed online.

2.3.1. Data analysis

To obtain reliable estimates of localized power of non-stationary evoked potential time series, we employed the S-transform, a recently developed time–frequency representation method (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:

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

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 $|ST(f, \tau)|$. 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 time–frequency representation via the S-transform. Mean values were calculated from the time–frequency representation amplitude envelope within time–frequency regions of interest (TFROI's) (Lachaux et al., 2003) specified by frequency band ranges and time intervals. Further, a baseline corrected time–frequency representation was obtained by subtracting the average value of the time–frequency representation amplitude envelope in the pre-stimulus time window from the post stimulus time–

frequency representation values. This study focused on TFROI corresponding to the gamma (29–45 Hz) frequency band and 0–150 ms time window range. Fig. 1 shows TFROI's at the F3 electrode for the target and non-target stimuli in the control and alcoholic groups. It can be seen in the figure that while the control group manifests higher gamma response for target stimuli, the alcoholic group manifests higher gamma activity for the non-target stimuli.

2.4. Statistical analysis

Statistical analyses were performed on the evoked gamma activity obtained during the target, non-target and novel stimulus conditions. 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 (alcoholics, controls), condition (target, non-target and novel), electrodes (within a region) and their interactions as fixed effects. Since the alcoholics were significantly older and less educated than the controls ($p < 0.001$), both age and education were also entered in the model. A backward stepwise method was used to remove non-significant effects. 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 univariate analysis of covariance (ANCOVA) and 't' tests.

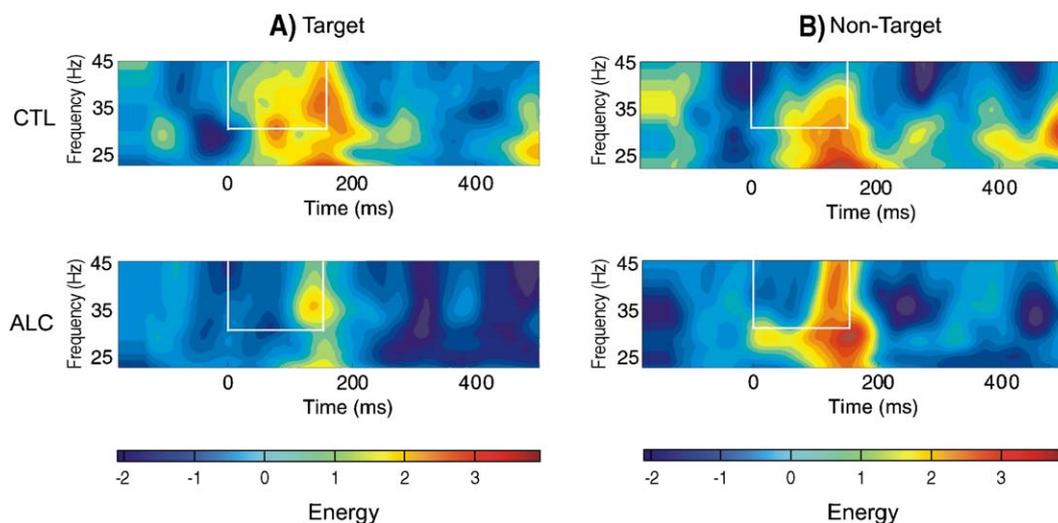


Fig. 1. Time–frequency representation of evoked gamma band energy distribution (29–45 Hz) of target and non-target stimuli at F3 electrode, calculated using the S-transform method. (A) Target stimuli in controls (CTL) and alcoholics (ALC). (B) Non-Target stimuli in controls (CTL) and alcoholics (ALC). The time–frequency region of interest (TFROI) window used for analysis was 0–150 ms (White Square). The time–frequency distribution displayed above was obtained by calculating Z-scores within individual frequencies across the two groups of subjects in each stimulus condition (Target and Non-Target) separately. Significant reduction in early evoked gamma band response is observable in alcoholics (ALC) for the target condition. However, an opposite trend is seen in the non-target condition (higher evoked gamma band response in alcoholics).

3. Results

3.1. Clinical characteristics

Age and education of alcoholic and control groups were compared using *t*-tests. Alcoholics were found to be significantly older ($t = -10.67$; $p < 0.001$) and less educated ($t = 10.06$; $p < 0.001$) than control subjects.

3.2. Behavioral data

The mean reaction time of the two groups were compared using ANCOVA with age as a covariate ($F_{1,220} = 0.643$; $p = 0.424$). Although there was no statistically significant difference between the two groups, the control group had slightly faster reaction times (mean = 462.05 ms; S.D. = 77.52) than the alcoholic group (mean = 473.20 ms; S.D. = 95.48).

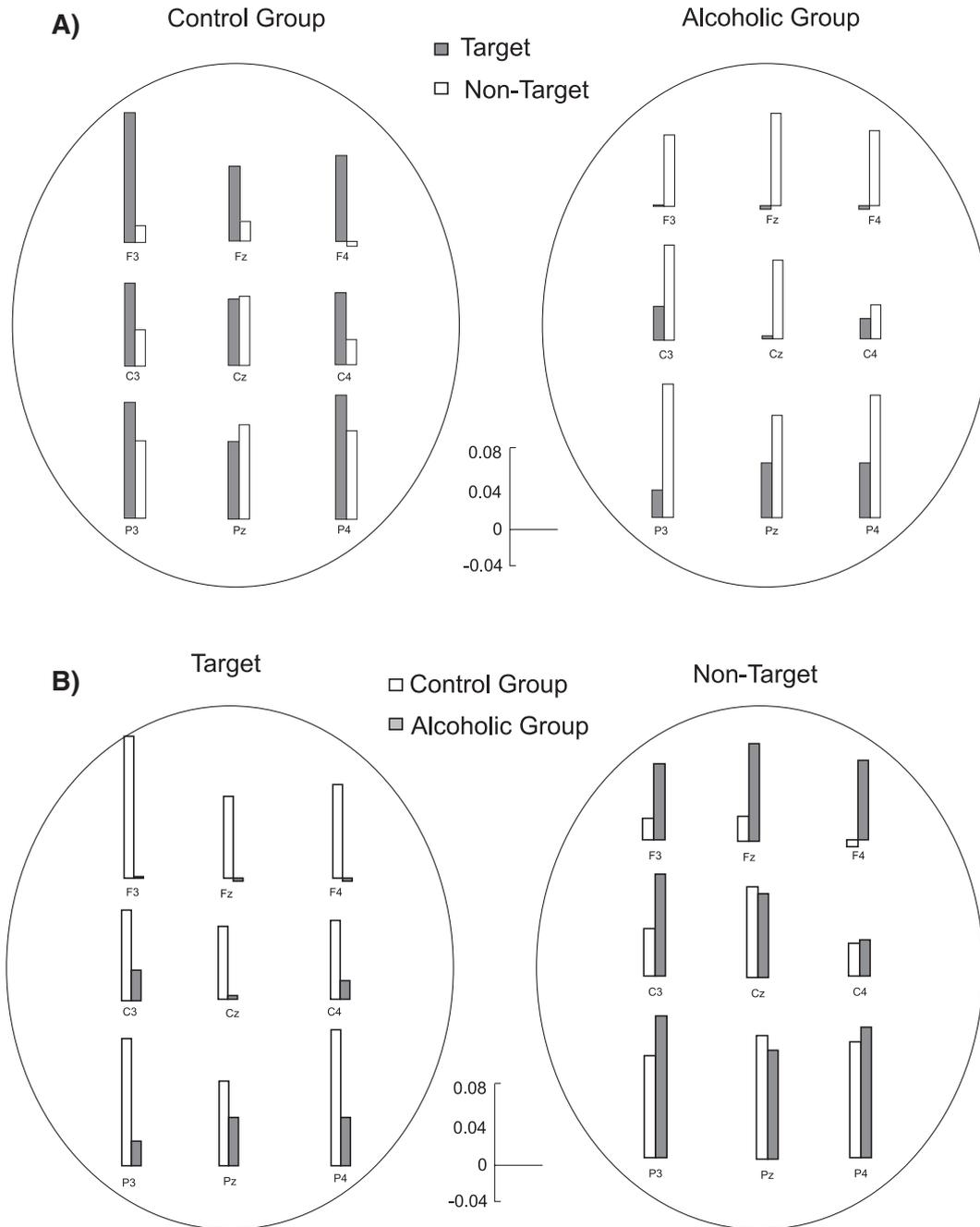


Fig. 2. The bar diagrams within the head plots show mean gamma energy values obtained through baseline corrected TFR (time–frequency representation) calculated using the S-transform for each of the electrodes: (A) Target and non-target stimuli within control and alcoholic groups; note that the controls manifest increased gamma response to target compared to non-target stimuli, while alcoholics manifest decreased gamma response to target stimuli compared to non-target stimuli. (B) Control and alcoholic groups within target and non-target stimulus conditions. The control group manifests increased gamma response to targets compared to the alcoholic group; alcoholics manifest increased gamma compared to controls for non-target stimuli at most leads particularly over frontal regions. Statistically significant differences were obtained only in the frontal region.

Similarly, the mean total error scores (both omission and commission) of the two groups were compared using ANCOVA with age as a covariate ($F_{1,220}=3.12$; $p=0.079$). The alcoholic group had a higher error rate (mean=3.43; S.D.=3.88) than the controls (mean=1.99; S.D.=2.78), but this was not statistically significant.

3.3. Gamma band response

The mean gamma energy during target and non-target stimulus conditions in the control and alcoholic groups is illustrated in Fig. 2. The control group had higher gamma band response for target stimuli at all electrodes compared to the alcoholic group. For the non-target stimuli, the alcoholic group had higher gamma band response at most of the electrodes. The mean and standard deviation of gamma band response in controls and alcoholics in target and non-target conditions are shown in Table 2. Our analysis indicated statistically significant results only in the frontal region. There were no significant main effects or interaction effects in the central or parietal regions. Hence, in the following section we have reported only the significant results obtained in the frontal region.

Statistical analysis yielded a significant Condition \times Group interaction ($F_{(2,384)}=7.10$; $p<0.001$) in the frontal region. The control group obtained significantly higher gamma band response than the alcoholic group in the target condition (Wald t -statistic=2.63, $p<0.01$). In contrast, the alcoholic group had significantly higher gamma band response for the non-target condition compared to the

control group, indicating differential information processing in both groups (Wald t -statistic=-2.51, $p<0.05$). This differential effect is illustrated in Fig. 1. There was no significant difference in gamma band response to novel stimuli between control and alcoholic groups (Wald t -statistic=1.38, $p=0.17$). Although the alcoholic group was significantly older and less educated than the control group, age and education did not yield statistically significant effects on gamma band response. This indicates that the significant group differences in gamma band response obtained during target and non-target stimulus conditions is not due to the effect of age and education variables.

4. Discussion

The present study compared the early evoked gamma band activity in alcoholics and controls during a visual oddball task. The target stimuli elicited increased early evoked gamma band activity in control subjects, and significantly reduced gamma band response in the alcoholic group in the frontal region. In contrast, the non-target stimuli elicited significantly higher gamma band response in alcoholic subjects compared to control subjects. Although there is abundant evidence of frontal lobe dysfunction in alcohol dependent individuals, this is the first study to demonstrate an abnormal gamma band response in alcoholics.

The suppression of gamma band activity to target stimuli observed in the frontal region of alcoholics may be associated with cognitive processes involved in the oddball task used in the present study. This task consisted of visual stimuli that could easily be verbalized. Moreover, it involved stimulus discrimination that necessitated the 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, 1997; Smith and Maes, 1995). In addition, a number of event related fMRI studies have shown frontal activation 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). Further evidence comes from a recent study, similar to the present study that explored the structural correlates of target processing in subjects at risk for developing alcoholism during a visual oddball task using fMRI (Rangaswamy et al., 2004). It was concluded that the absence of activation in the inferior frontal gyrus of high risk subjects was associated with their ineffective rehearsal component of working memory. Based on the abundant evidence of executive function deficits in chronic alcoholics (Giancola and Moss, 1998), it is possible that the reduction in gamma band response reflects frontal lobe dysfunction in our alcoholic group.

Table 2
Mean and standard deviation of evoked gamma band response in controls and alcoholics during target and non-target condition

Electrode	Controls		Alcoholics	
	Mean	S.D.	Mean	S.D.
<i>Target</i>				
F3	0.03925	0.13554	-0.00268	0.14010
FZ	0.02167	0.12740	-0.00179	0.13839
F4	0.02307	0.14331	0.00058	0.14259
C3	0.02230	0.13638	0.00877	0.14190
CZ	0.01711	0.14356	0.00001	0.13824
C4	0.02628	0.13893	0.00418	0.13641
P3	0.04118	0.13355	0.00907	0.13913
PZ	0.02908	0.13411	0.01860	0.13065
P4	0.04526	0.14226	0.02365	0.13533
<i>Non-target</i>				
F3	-0.00205	0.10569	0.03028	0.12085
FZ	0.00289	0.11615	0.03304	0.11423
F4	-0.002	0.11831	0.02146	0.11811
C3	0.00986	0.11298	0.03066	0.11594
CZ	0.01933	0.11638	0.02409	0.11102
C4	0.01044	0.11859	0.01007	0.12033
P3	0.03085	0.14245	0.03939	0.12545
PZ	0.03335	0.12877	0.03155	0.12355
P4	0.03572	0.12466	0.03706	0.13306

Unlike control subjects, alcoholic subjects had higher gamma band response to the non-target stimuli in the frontal region. This increase in gamma band response to the irrelevant stimuli indicates abnormal information processing and a probable reorganization of functional systems in the alcoholic group. Pfefferbaum et al. (2001), in an fMRI study, found that alcoholics have diminished activation in the frontal cortical systems employed by normal subjects during a spatial working memory task. Alcoholic subjects had higher activation in other regions of the frontal lobes suggesting that alcoholic subjects invoke inappropriate brain systems when engaged in a task requiring visuospatial working memory. Similarly, electrophysiological evidence of working memory deficits in different brain regions including frontal lobes have been reported in alcoholics during spatial working memory tasks (Zhang et al., 1997a,b). It has been proposed that the early evoked gamma band response reflects a matching process between the stimulus held in working memory and the incoming, just perceived stimulus (Herrmann and Mecklinger, 2000a; Debener et al., 2003). This template matching in working memory facilitates the discrimination between the target and non-target stimuli. In addition, it has been shown that gamma oscillations play a significant role in working memory processes (Jensen and Lisman, 1998; Burle and Bonnet, 2000; Elliott and Muller, 2000). Hence, it can be assumed that an impaired working memory system in alcoholics leads to an aberrant discriminatory process, resulting in augmented processing of the irrelevant stimuli.

The higher gamma band response for the target stimuli in the frontal region in the control group is consistent with previous reports on visual gamma processing. Increased early evoked gamma activity has been observed in the lateral frontal regions during illusory figure (Kanizsa) perception (Herrmann et al., 1999; Herrmann and Mecklinger, 2000a,b). Karakas et al. (2003) found that early evoked gamma was correlated with neuropsychological functions such as attention, learning, memory and executive functions. In contrast, lack of early gamma band response was related to perseverative responses on Wisconsin Card Sorting Test (WCST). As the presence of early gamma band activity itself is related to higher cognitive functions pertaining to frontal lobes, it was suggested that the early evoked gamma band response reflects top-down information processing. It could be hypothesized that the reduced early evoked gamma activity observed in the alcoholic group in the present study may be due to a deficient top-down information processing mechanism.

Top-down processing occurs in situations when mapping between sensory inputs, thoughts, and actions, are either weakly established or are rapidly changing (Miller and Cohen, 2001). The prefrontal cortex plays a fundamental role in such situations in which the behavior must be guided by internal states or intentions (Cohen and Servan-Schreiber, 1992; Miller, 2000). According to Engel et al. (2001), top-down influences could be defined as intrinsic

sources of contextual modulation of neural processing, which includes the activity of systems involved in goal definition, action planning, working memory and selective attention. Prefrontal cortex plays a major role in mediating these functions (Fuster, 1989; Desimone and Duncan, 1995; Kastner and Ungerleider, 2000; Schultz, 2000; Schall, 2001). It has been suggested that assemblies of neurons that represent action goals in the prefrontal cortex provide modulatory ‘bias signals’ to the sensory motor circuits that have to carry out response selection (Miller, 2000; Miller and Cohen, 2001). This process is executed through the extensive interconnections of prefrontal cortex with other neocortical regions, inclusive of all the sensory systems, cortical and subcortical motor system structures, and also with limbic and midbrain structures involved in affect, memory and reward (Stuss and Benson, 1986; Fuster, 1989). Several studies have suggested the involvement of prefrontal cortex in exerting a top-down influence on visual processing and visual object recognition (Miyashita and Hayashi, 2000; Corbetta and Shulman, 2002; Bar, 2003). Moreover, damage to prefrontal cortex results in disinhibition of input to primary cortical regions (Skinner and Yingling, 1976; Knight et al., 1989, 1999; Yamaguchi and Knight, 1990), indicating its role in the early selection of sensory inputs.

Chronic alcoholism has been linked to a wide range of structural and functional abnormalities in frontal lobes (for review, see Moselhy et al., 2001). Several studies have reported neuropsychological and frontal executive function deficits in alcohol dependent individuals (Jones, 1971; Jones and Parsons, 1972; Tarter, 1973; Acker, 1985; Wilkinson and Poulos, 1987; Sullivan et al., 1993, 2002; Beatty et al., 1996; Nixon and Bowlby, 1996; Ratti et al., 2002). Neuroimaging studies have shown that the executive function deficits of alcohol dependent individuals may be associated with decreased frontal glucose metabolism (Adams et al., 1993; Wang et al., 1993; Gansler et al., 2000) and regional cerebral blood flow in frontal lobes of alcoholics (O’Carroll et al., 1991; Nicolas et al., 1993; Gansler et al., 2000). Furthermore, postmortem and neuro-radiological studies have revealed cortical atrophy and reduction in grey matter and white matter in the frontal lobes of alcoholics (Harper et al., 1985; Pfefferbaum et al., 1997). Evidence from electrophysiological studies have shown frontal abnormalities in alcoholics (Begleiter et al., 1980; Porjesz and Begleiter, 1987; Michael et al., 1993; Rodriguez-Holguin et al., 1999; Hada et al., 2000; Kamarajan et al., 2004). The findings of the present study are consistent with the notion of frontal lobe dysfunction observed in alcoholics. The putative mechanisms underlying these deficits could possibly be related to the biological underpinnings of gamma band activity.

Gamma oscillations are inhibitory rhythms involving GABAergic interneuronal activity (Whittington et al., 2000b). Gamma oscillations have been observed in different areas of the brain including hippocampus, sensory motor

areas, auditory and visual cortices and also in thalamocortical systems (Whittington et al., 2000a). Local or short range gamma synchrony is thought to be generated when metabotropic glutamate receptors activate GABAergic interneurons (GABA_A receptor mediated) leading to an ongoing mutual inhibition of post synaptic interneuron potentials. The synchronous mutual inhibition of the interneurons produces a recurrent feedback loop which forms the basis for the generation of gamma activity (Whittington et al., 1995; Traub et al., 1996). GABA_A receptor antagonists such as bicuculline or picrotoxin have been shown to abolish gamma activity (Stopfer et al., 1997; Whittington et al., 1997; Colling et al., 1998) supporting a role for GABA_A receptor mediation in the generation of synchronous gamma oscillations.

GABA_A receptors occupy a central role in mediating the effects of ethanol in the central nervous system (CNS) (Davies, 2003). Several molecular, cellular and behavioral studies have revealed that GABA_A receptors are involved in the acute actions of ethanol, ethanol intolerance, ethanol dependence and ethanol self administration (Grobin et al., 1998). Moreover, GABA_A receptor activation mediates many of the behavioral and motivational effects of ethanol (Chester and Cunningham, 2002). It has been suggested that chronic alcoholism damages neurons containing GABA_A/Benzodiazepine receptors in the frontal region (Gilman et al., 1996; Lingford-Hughes et al., 1998). Differential expression and distribution of certain subunits of GABA_A receptor in the superior frontal cortex of human alcoholic brain have also been observed (Buckley et al., 2000). Another fast oscillation, namely beta, also mediated by GABAergic mechanisms has been shown to have linkage with a GABA_A receptor gene (Porjesz et al., 2002). In a recent study, the same GABA_A receptor gene (alpha 2) was found to be associated with both beta oscillations and alcohol dependence (Edenberg et al., 2004). It is possible that the reduction in gamma band activity in alcoholics observed during target processing in the present study is associated with dysfunction of GABAergic mechanisms. Moreover, there is evidence that changes in GABA_A receptors reflect processes underlying spatial working memory in the prefrontal cortex (Rao et al., 2000). This supports the findings of the present study, since the oddball task also involves these cognitive components.

In conclusion, the present study demonstrates deficient early evoked gamma band activity in alcohol dependent individuals. This deficit was observed in the frontal region which is consistent with the widely reported frontal brain dysfunction in alcoholics. In addition, these findings suggest a basic deficit in GABAergic mechanisms in alcoholics, given the role of GABAergic interneurons in generating and modulating gamma band activity, as well as the role of GABA in the effects of alcohol on the brain (e.g. tolerance, physical dependence, incoordination). Studies are underway in high risk individuals to determine whether this gamma

deficit observed in alcoholics in the present study is a 'trait' or 'state' variable.

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