Available online at www.sciencedirect.com

SCIENCE DIRECT®

International Journal of Psychophysiology 60 (2006) 304 – 314

INTERNATIONAL JOURNAL OF PSYCHOPHYSIOLOGY

www.elsevier.com/locate/ijpsycho

Moderate-to-heavy alcohol intake is associated with differences in synchronization of brain activity during rest and mental rehearsal

Eveline A. de Bruin [a,*], Cornelis J. Stam [b], Suzanne Bijl [a], Marinus N. Verbaten [a], J. Leon Kenemans [a,c]

[a] *Utrecht Institute of Pharmaceutical Sciences, Department of Psychopharmacology, Utrecht University, Sorbonnelaan 16, NL-3584 CA Utrecht, The Netherlands*

[b] *Department of Clinical Neurophysiology, VU University Medical Center, Amsterdam, The Netherlands*

[c] *Helmholtz Institute, Department of Psychonomics, Utrecht University, Utrecht, The Netherlands*

Received 9 December 2004; received in revised form 17 February 2005; accepted 11 July 2005
Available online 8 September 2005

Abstract

In alcohol-dependent individuals, synchronization of brain activity is different from that in non-alcohol-dependent individuals as reflected by EEG differences at alpha and beta frequencies (8–30 Hz). These EEG differences may not only be related to long-term alcohol intake but also to genetic factors that are associated with alcohol dependence. Thus, it is not known what the pure effect of long-term alcohol intake on synchronization of brain activity is. Therefore, we investigated whether EEG synchronization differs between light (0.5–6 drinks per week), moderate (7–20 drinks per week), and heavy (21–53 drinks per week) drinkers. All participants (49 males and 47 females) were free of a personal and family history of alcohol dependence. Eyes-closed EEG was recorded at rest and during mental rehearsal of pictures. EEG synchronization was determined by computing Synchronization Likelihood for six frequency bands (0.5–4 Hz, 4–8 Hz, 8–12 Hz, 12–20 Hz, 20–30 Hz, 30–45 Hz). Both male and female heavy drinkers displayed a loss of lateralization in alpha (8–12 Hz) and slow-beta (12–20 Hz) synchronization. In addition, moderately and heavily drinking males had lower fast-beta (20–30 Hz) synchronization than lightly drinking males. It is concluded that both male and female drinkers who drink 21 alcoholic drinks per week or more have impaired synchronization of brain activity during rest and mental rehearsal at alpha and beta frequencies as compared to individuals who drink less. As individuals with a personal or family history of alcohol dependence were excluded, the confounding effects of genetic factors related to alcohol dependence on synchronization of brain activity were minimized.

Keywords: EEG; Synchronization; Alcohol; Moderate drinking; Heavy drinking; Alpha; Beta; Lateralization

1. Introduction

Cognitive functioning is impaired in alcohol-dependent individuals (Ciesielski et al., 1995; Horner et al., 1999; Ratti et al., 2002). The impairments reported are non-specific and range from basic processes, such as reduced perceptual and motor speed, to complex processes, like diminished cognitive flexibility (e.g. Di Sclafani et al., 1995; Parsons, 1994). Heavy drinkers (defined by Parsons, 1998 as people consuming 21 drinks per week or more who are not alcohol-dependent) also have cognitive deficits as compared to light and moderate drinkers (Parker and Noble, 1977; Parsons, 1998; Parsons and Nixon, 1998), but these deficits are smaller than in alcoholics.

Complex cognitive tasks require coordination of activity between different neural assemblies. This coordination is achieved by synchronization of brain activity between spatially remote neurophysiological events. This synchronization, or 'functional connectivity' is reflected by temporal correlations between the electrical activities in the different brain regions involved (Fingelkurts et al., 2005; Lee et al., 2003). Even basic cognitive processes,

* Corresponding author. Tel.: +31 30 253 1599; fax: +31 30 253 7900.
E-mail address: E.A.deBruin@pharm.uu.nl (E.A. de Bruin).

0167-8760/$ - see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpsycho.2005.07.007

such as random episodic silent thought during rest (Andreasen et al., 1995), involve synchronization of brain activity characterized by temporal correlations between spatially remote events in complex brain networks (Greicius et al., 2003).

The finding that alcohol-dependent individuals have cognitive deficits suggests that functional brain activity, which underlies cognition, is also different in alcohol-dependent patients. A good technique to study functional brain activity is electroencephalography (EEG), having a high time resolution and an extensive theoretical foundation regarding the underlying processes (Salek-Haddadi et al., 2003). Theta activity (4–8 Hz), for example, is associated with encoding of new information in memory (Basar et al., 2001; Klimesch, 1999). Alpha activity (8–12 Hz) plays a role in retrieving information from memory, and in attention (Basar et al., 1997; Klimesch, 1999). Beta activity (12–30 Hz) and gamma activity (30–45 Hz) are associated with perception, attention, and learning (Engel and Singer, 2001; Fell et al., 2003; Neuper and Pfurtscheller, 2001).

Alcohol-dependent individuals have different synchronization of brain activity than light drinkers as reflected by differences in resting EEG coherence (Kaplan et al., 1985; Michael et al., 1993; Winterer et al., 2003a) and power (e.g., Bauer, 2001; Enoch et al., 2002; Rangaswamy et al., 2002; Saletu-Zyhlarz et al., 2004). Most differences in EEG coherence and power are found at alpha (8–12 Hz), slow-beta (12–20 Hz), and fast-beta (20–30 Hz) frequencies. Relatives of alcohol-dependent individuals, who are not alcohol-dependent themselves, also have EEG differences in alpha and beta coherence (Michael et al., 1993) and power (Bauer and Hesselbrock, 2002; Ehlers and Schuckit, 1991; Finn and Justus, 1999; Rangaswamy et al., 2004) as compared to light drinkers without alcohol-dependent relatives. This indicates that differences in functional brain activity as measured with EEG in alcohol-dependent patients not only relate to the impact of long-term alcohol intake, but possibly also to genetic factors related to alcohol dependence.

Both alcohol dependence (Enoch, 2003; Schuckit, 2000) and EEG patterns (Van Beijsterveldt and Van Baal, 2002) are highly heritable. In addition, some genes coding for GABA receptors in the brain, which mediate the effects of alcohol, are related to certain EEG patterns (e.g., Porjesz et al., 2002; Winterer et al., 2003c). Moreover, some GABA-receptor genes that are related to EEG patterns are also associated with the risk to develop alcohol dependence. For example, genes that code for the receptor $GABA_AR2$ are strongly associated with alcohol dependence as well as with EEG oscillations in the beta range (Edenberg et al., 2004). Furthermore, genes coding for the receptor $GABA_BR1$ are associated with alpha amplitude in healthy participants, but not in alcohol-dependent individuals (Winterer et al., 2003b). These associations again suggest that genetic factors play a major role in the EEG differences associated with alcohol dependence.

To investigate the pure effects of alcohol intake on synchronization of brain activity, while minimizing the confounding influence of genetic factors related to alcohol dependence, different groups of drinkers who are not alcohol-dependent, and who do not have alcohol-dependent relatives either, can be compared. Ehlers et al. (1989) contrasted lightly drinking students (1 to 8 drinks per week) with moderately drinking students (10 to 18 drinks per week), all with a negative family history of alcohol dependence. Moderate drinkers had higher slow-beta power (12–20 Hz) than light drinkers did; theta (4–7 Hz) and alpha (7.5–12 Hz) power were not affected. In another study, heavily drinking students (on average, 54 drinks per week) with a negative family history, had stronger EEG synchronization at theta (4–8 Hz) and gamma (30–45 Hz) frequencies than lightly drinking students (21 drinks per week) with a negative family history (De Bruin et al., 2004). These studies suggest that, in students, heavy alcohol intake has an impact on functional brain activity, even in the absence of genetic factors related to alcohol dependence. It remains to be investigated whether these effects of alcohol intake on synchronization of brain activity persist in older adults with a longer drinking history.

In alcohol research, EEG is commonly analyzed with linear measures such as power or coherence. However, there is increasing evidence that non-linear components are also relevant to the interpretation of EEG. For example, a study on Alzheimer's disease showed that patients have lower EEG and MEG synchronization in the alpha, beta, and gamma band than control subjects, while EEG coherence did not differ between the groups (Stam et al., 2002b). For this reason, methods that describe both linear and non-linear parts of EEG, such as Synchronization Likelihood (Stam and Van Dijk, 2002), are preferred (David et al., 2003; Fingelkurts et al., 2005).

Two other advantages of Synchronization Likelihood over power and coherence methods are its sensitivity to changes in synchronization in the absence of amplitude changes, and its insensitivity to changes in signal amplitude that are not related to changes in synchronization (Stam and De Bruin, 2004). Synchronization Likelihood can measure differences between patient groups (Babiloni et al., 2004; Ferri et al., 2001; Pijnenburg et al., 2004) but is also able to pick up subtle task effects in healthy participants (Micheloyannis et al., 2003, 2005; Stam et al., 2002a, 2003). For example, with Synchronization Likelihood, it was repeatedly shown that theta synchronization is higher during mental rehearsal of pictures than during rest (e.g. Stam et al., 2002a).

Alcohol intake is highly associated with smoking (Romberger and Grant, 2004). Smokers have smaller volumes and lower densities of gray matter in the brain than non-smokers (Brody et al., 2004). Although some in vitro animal studies suggest that nicotine protects the brain against alcohol-induced damage (e.g. Tizabi et al., 2003), a

human study measuring brain metabolism in alcohol-dependent individuals in vivo concluded that smoking exacerbates alcohol-induced brain damage (Durazzo et al., 2004). To investigate the possible influence of smoking in non-alcohol-dependent individuals in the current study, smoking habits were included in the statistical analyses.

In the present study, we investigated whether alcohol intake is associated with differences in synchronization of brain activity in light, moderate, and heavy male and female older adult drinkers with a negative personal and family history of alcoholism. Multi-channel EEG was recorded with eyes closed, both while at rest and during mental rehearsal of pictures. EEG synchronization was assessed with Synchronization Likelihood (Stam and Van Dijk, 2002). Main effects of group (light, moderate, and heavy drinkers), and interactions with gender, condition, and/or area were investigated in the alpha (8–12 Hz), slow-beta (12–20 Hz), and fast-beta (20–30 Hz) band. In addition, in extension of the findings in heavily drinking students by De Bruin et al. (2004), specific hypotheses regarding group effects in the theta (4–8 Hz) and gamma bands (30–45 Hz) were tested.

2. Methods

2.1. Participants

Participants were recruited via newspaper advertisements, and were paid for their participation. After written and oral explanation of the study, they signed the informed consent and filled out an extensive questionnaire on physical and mental health. Eligible subjects were invited for a 3-h screening consisting of a physical check-up and a structured interview (the Composite International Diagnostic Interview; Robins et al., 1988) assessing for the presence of psychopathological symptoms based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). From about 1500 applications, 96 non-alcohol-dependent drinkers (49 men, 47 women) drinking from one standard drink (i.e. 100 cm^3 wine, 250 cm^3 beer, or 30 cm^3 spirits, equivalent to 12 g of alcohol per drink) per 2 weeks up to 53 standard drinks per week were selected to participate in the study.

Each participant was right-handed as determined with the Edinburgh Handedness Inventory, had normal hearing and (corrected-to-) normal sight, was not colour-blind, and had a blood pressure, body mass index, and resting heart rate within normal limits. The electrocardiogram, hematology and blood chemistry were screened for abnormalities by a medical specialist. Premorbid IQ was estimated with the Dutch Adult Reading Test (*Nederlandse Leestest voor Volwassenen*, the Dutch version of the National Adult Reading Test; Schmand et al., 2003). The participants were matched on age, gender, Mini Mental State Examination (MMSE) score, and body mass index. The participants had no (history of) chronic somatic or neurological disease, head trauma or loss of consciousness for more than 10 min. Neither did they have a psychiatric disease (including alcohol dependence) at any time in life. Other exclusion criteria were: use of psychoactive medication within the past month, drug use (besides alcohol or cigarettes) for more than three times in life, total alcohol abstinence, and first- or second-degree relatives with neurological or psychiatric deficits. Every effort was made to ensure via the questionnaire and the interview that all participants had a negative family history of alcohol dependence up to the second degree.

Lifetime alcohol intake (cumulative alcohol intake in kg) and duration of the drinking history (in years) were assessed by a questionnaire in Dutch, based on the Lifetime Drinking History interview (Lemmens et al., 1997; Skinner and Sheu, 1982). To estimate current alcohol intake, subjects filled out a diary during a 2-week period in which they recorded the number of alcoholic drinks and the type of glass, bottle, or can on a daily basis. Reported alcohol intake was converted into number of standard drinks (i.e. units containing 12 g of alcohol) per week. The following groups were defined: light drinkers (0.5–6 drinks per week; 13 men, 16 women), moderate drinkers (7–20 drinks per week; 17 men, 16 women), and heavy drinkers (21–60 alcoholic drinks per week; 19 men, 15 women). The cut-off between the

Table 1
Demographics (mean, standard deviation in brackets)

	Light		Moderate		Heavy	
	Males	Females	Males	Females	Males	Females
n	13	16	17	16	19	15
Age (years)	46.4 (9.6)	49.5 (7.8)	49.3 (8.5)	50.8 (7.6)	51.9 (8.0)	48.1 (5.5)
IQ	107.5 (9.2)	106.5 (7.8)	105.0 (7.0)	101.7 (10.1)	110.3 (5.2)	102.1 (9.8)
Smoking (# cigarettes smoked per day)	0.0 (0.0)	0.4 (1.1)	1.2 (4.9)	4.0 (6.6)	4.6 (9.7)	0.3 (0.8)
Body mass index (kg/m^2)	24.1 (3.2)	25.0 (2.9)	24.7 (1.6)	24.7 (3.6)	26.0 (2.7)	24.8 (3.5)
Lifetime alcohol intake (kg)	67.9 (71.0)	48.7 (34.7)	195.6 (142.7)	131.3 (89.5)	398.9 (179.5)	324.4 (141.1)
Duration of drinking history (year)	29.9 (8.3)	32.1 (8.1)	32.8 (7.7)	33.5 (7.2)	35.8 (7.4)	31.2 (6.6)
Mean lifetime alcohol intake (kg/year)	2.2 (2.1)	1.5 (1.0)	5.8 (3.7)	3.8 (2.1)	11.4 (5.1)	10.1 (3.0)
Mean lifetime alcohol intake (units per week)[a]	3.5 (3.3)	2.4 (1.6)	9.3 (5.9)	6.1 (3.4)	18.2 (8.1)	16.2 (4.9)
Current alcohol intake (units per week)[a]	3.2 (1.6)	3.6 (1.5)	14.6 (4.1)	10.3 (3.8)	36.9 (8.7)	33.4 (8.7)

[a] Number of standard drinks per week; a standard drink contains about 12 g of pure alcohol.

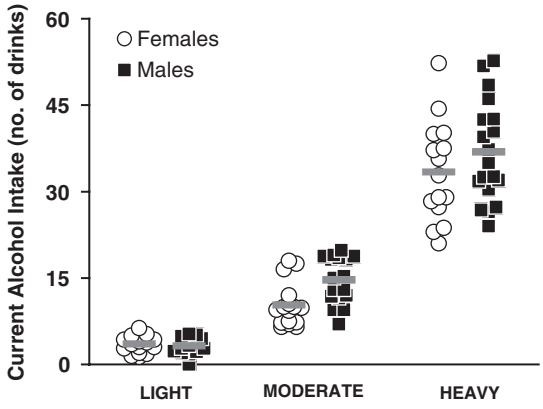

Fig. 1. Current alcohol intake in the light, moderate and heavy drinkers. The circles and squares represent the individual current alcohol intake (in standard units per week) in females and males, respectively; the gray dashes illustrate the mean current alcohol intake per group and per gender.

moderate and heavy drinkers was based on the results of the meta-analysis of neuropsychological studies by Parsons (1998). For a summary of the demographics, see Table 1. See Figs. 1 and 2 for an illustration of current and lifetime alcohol intake in the three groups.

This study was approved by the Utrecht University medical ethics committee, and all participants were treated in accordance with the Helsinki Declaration and amendments.

2.2. Procedure

On arrival at the lab, the participants performed a breath test for alcohol (Alcotest, Dräger Medical, Lübeck, Germany) and a urine test for tetrahydrocannabinol, cocaine, barbiturates, benzodiazepines and morphine (Rapid Drug Testing Services, Inc., Key Largo, USA) to confirm abstinence of these drugs. After that, the participants were prepared for EEG recording, and seated in a comfortable chair in a sound-attenuated and electrically shielded testing chamber with a monitor in front of them at a distance of 1 m. EEG with eyes closed was recorded continuously during two conditions: at rest and during mental rehearsal of a set of pictures. In the rest condition, subjects were instructed to keep their eyes closed and to remain in a relaxed and awake state. After this, the subjects were asked to open their eyes, and were presented with twelve pictures of common neutral animate and inanimate objects (e.g., a car, a book, a hot drink) that were displayed simultaneously on the monitor for 10 s (see De Bruin et al., 2004; Pijnenburg et al., 2004; Stam et al., 2002a for more examples; see Stam et al., 2002a for an analysis of the effects of mental rehearsal on EEG synchronization in healthy volunteers). Next, they were instructed to close their eyes and mentally rehearse the pictures that had been presented (mental-rehearsal condition). After 1 min, they were asked to open their eyes and verbally recall as many pictures as possible.

2.3. EEG recording and analysis

The EEG was recorded from 62 tin electrodes placed according to the international 10–10 system with the left mastoid as a reference (QuikCap, Neurosoft, El Paso, USA). Vertical and horizontal EOG were recorded bipolarly to monitor eye-movement artifacts. A maximum electrode impedance of 10 kΩ was allowed. Filters were set at 0.15 and 70 Hz, and signals were digitized at a rate of 500 Hz and a gain of 2500. SynAmps amplifiers with 16-bit A/D resolution (0.033 μV/bit), 10 MΩ input impedance, and 100 dB common mode rejection were used for acquisition with Neuroscan software version 4.1 (Neurosoft, El Paso, USA).

Two consecutive artifact-free epochs of 16.4 s (each containing 4096 samples after down sampling to 250 Hz) were selected at the start of each condition for every subject. Artifacts were defined as epochs containing EEG with a peak-to-peak amplitude of more than 75 μV. Synchronization Likelihood was calculated with an average reference including all electrodes except the midline (i.e. 54 electrodes) in the following frequency bands: delta: 0.5–4 Hz, theta: 4–8 Hz, alpha: 8–12 Hz, slow-beta: 12–20 Hz, fast-beta: 20–30 Hz, and gamma: 30–45 Hz. SL was averaged over two epochs (covering 32.8 s of EEG) and six areas (see Fig. 3 for the division of the 54 channels into six areas). As some studies conclude that heavy alcohol intake impairs cognitive functioning particularly in the frontal regions (Dao-Castellana et al., 1998; Di Sclafani et al., 1995; Ratti et al., 2002), whereas other studies report evidence for a selective right-side impairment (Ellis and Oscar-Berman, 1989), the electrodes were grouped in such a way that both hypotheses could be tested.

The Synchronization Likelihood (SL) is a general measure of the correlation between two time series, for instance two EEG signals. In the SL estimation, two dynamic systems, *X* and *Y*, are considered. These systems can be conceived of as representations of neural networks that give rise to EEG signals. The dynamic systems *X* and *Y*

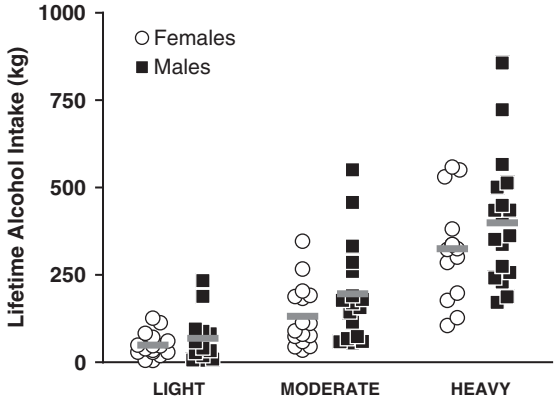

Fig. 2. Lifetime alcohol intake in the light, moderate and heavy drinkers. The circles and squares represent the individual lifetime alcohol intake (in kg) in females and males, respectively; the gray dashes illustrate the mean lifetime alcohol intake per group and per gender.

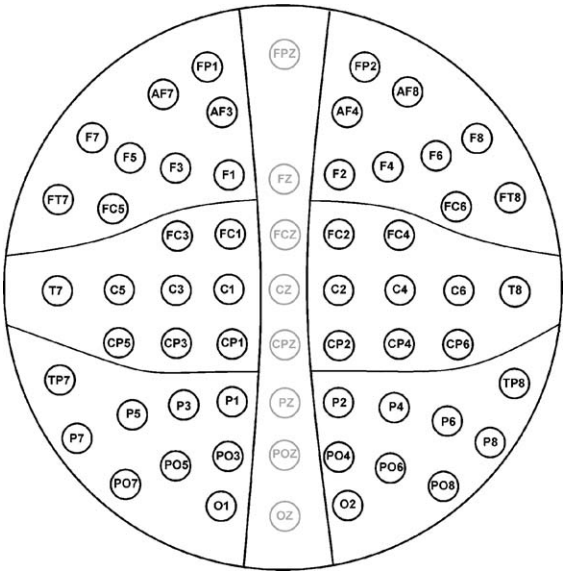

Fig. 3. Division of the 54 channels into six areas.

are represented by the vectors X_i and Y_i in their respective state spaces, which are obtained from the time series by time-delay embedding. SL is the possibility (likelihood) that, when system X is in a particular state at two different times i and j, system Y will be in the same state at those times. "Being in the same state" is operationalized by computing the distance between the vectors X_i and X_j. SL is then averaged over all times i, resulting in a description of the resemblance of a particular time series to another time series in a particular epoch (Stam and De Bruin, 2004; Stam and Van Dijk, 2002). For each channel, one SL value was computed by calculating the mean SL of the time series of that channel compared with the time series of all other 53 channels (i.e. the mean of 53 pair-wise comparisons). For an explanation of the mathematical background of SL, see the Appendix.

2.4. Statistical analyses

Possible group differences in demographics and memory performance were analyzed with multiple univariate analyses of variance (ANOVAs) with Group (3 levels: light, moderate, and heavy) and Gender (2 levels: male, female) as between-subjects factors. Alpha, slow-beta and fast-beta SL were analyzed with omnibus ANOVAs containing the between-subjects factors Group and Gender, and Condition (2 levels: rest versus mental rehearsal), Frontality (3 levels: anterior, central, posterior), and Lateralization (2 levels: left, right) as within-subjects factors. F-tests were Greenhouse–Geisser-corrected. Significant effects involving the factor Group were analyzed with post hoc Bonferroni-corrected t-tests. In addition, preplanned Bonferroni-corrected Group comparisons of theta and gamma SL were carried out.

To examine the possible effects of smoking, Pearson's Chi-square tests were carried out to check whether the number of smokers was similar across groups. In addition, the number of cigarettes smoked per day was added as a covariate to the ANOVAs. Statistical analyses were performed with SPSS 11.0.1 for Windows.

3. Results

The participants remembered on average 7.0±.2 items (range from 3 to 11) correctly from the 12 pictures presented. The number of smokers was similar across groups (Pearson's $\chi^2=5.22$, n.s.) and gender (Pearson's $\chi^2=0.39$, n.s.). Moderately drinking females smoked more cigarettes per day than lightly and heavily drinking females (Group × Gender interaction: $F_{2,90}=3.59$, $p=.032$; post hoc Bonferroni-corrected t-tests: moderately vs. lightly drinking females: $t_1=2.57$, $p=.040$; moderately vs. heavily drinking females: $t_1=2.60$, $p=.038$; all other t-tests n.s.). There were no Group or Group × Gender effects on other demographic variables or memory performance.

In the alpha band (8–12 Hz), a significant Group × Condition × Lateralization interaction effect was found ($F_{2,90}=3.34$, $p=.040$). Post hoc Bonferroni-corrected t-tests revealed that heavy drinkers did not show the lateralization in alpha SL (left>right) during rest ($t_1=1.10$, n.s.) that was present in the light ($t_1=2.77$, $p=.010$) and moderate ($t_1=6.46$, $p<.001$) drinkers, and in all groups during mental rehearsal (light: $t_1=5.02$, $p<.001$; moderate: $t_1=2.53$, $p=.017$; heavy: $t_1=2.73$, $p=.010$), because the heavy drinkers had relatively low SL in the left hemisphere (see Fig. 4).

In the slow-beta band (12–20 Hz), a significant Group × Lateralization interaction effect was found ($F_{2,90}=4.83$, $p=.010$). Post hoc Bonferroni-corrected t-test showed a lack of lateralization in slow-beta SL (left>right) during rest ($t_1=0.44$, n.s.) and mental rehearsal ($t_1=0.47$, n.s.) in the heavy drinkers, and during mental rehearsal in the moderate drinkers ($t_1=1.65$, n.s.). This contrasted with the hemispheric asymmetry in SL in the light drinkers during rest

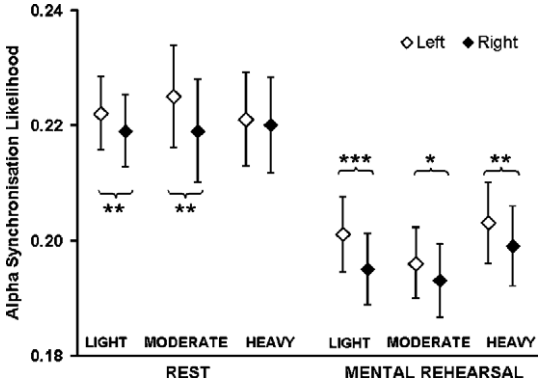

Fig. 4. Lack of lateralization of alpha (8–12 Hz) Synchronization Likelihood during rest in heavy drinkers. Diamonds represent mean SL; error bars denote standard errors; asterisks indicate the level of significance in post hoc Bonferroni-corrected t-tests: *$p<0.05$, **$p\leq0.01$, ***$p<0.001$.

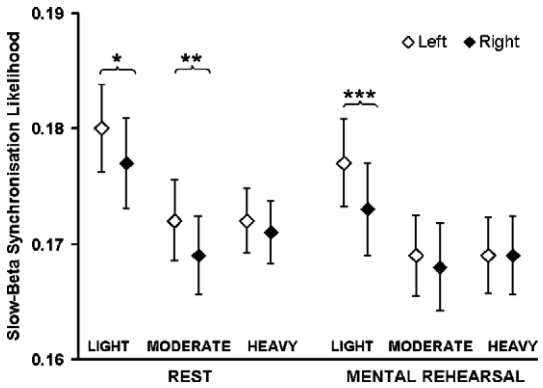

Fig. 5. Lack of lateralization of slow-beta (12–20 Hz) Synchronization Likelihood in heavy drinkers during both rest and mental rehearsal and in moderate drinkers during mental rehearsal only. Diamonds represent mean SL; error bars denote standard errors; asterisks indicate the level of significance in post hoc Bonferroni-corrected *t*-tests: $*p<0.05$, $**p<0.01$, $***p=0.001$.

($t_1=2.34$, $p=.027$) and mental rehearsal ($t_1=3.72$, $p=.001$), and during rest in the moderate drinkers ($t_1=2.84$, $p=.008$). The lack of lateralization was due to a relatively low SL in the left hemisphere in the heavy drinkers in both conditions, and in the moderate drinkers during mental rehearsal only (see Fig. 5).

In the fast-beta band (20–30 Hz), moderate and heavy male drinkers had lower SL than light male drinkers (Group × Gender interaction effect: $F_{2,90}=5.35$, $p=.006$; post hoc Bonferroni-corrected *t*-tests: light male drinkers vs. moderate male drinkers: $t_2=2.81$, $p=.022$; light male drinkers vs. heavy male drinkers: $t_2=2.97$, $p=.014$, moderate male drinkers vs. heavy male drinkers: $t_2=0.09$, n.s.), whereas the female drinkers did not differ across groups (all $|t|\leq 1.35$; n.s.; see Fig. 6). See Table 2 for an overview of the group differences in Synchronization Likelihood in the alpha and beta bands.

There were no interactions between the factor Group and the factor Frontality. Unlike the study with student drinkers, no main Group effects in the theta band (4–8 Hz: $F_{2,90}=0.01$, n.s.) or gamma band (30–45 Hz: $F_{2,90}=1.02$, n.s.) were found. Additional exploratory omnibus ANOVAs in the delta, theta and gamma bands did not demonstrate any main or interaction effect involving the factor Group. Adding the number of cigarettes smoked per day as a covariate marginally lowered the significance of the interactions (alpha: $F_{2,89}=3.03$, $p=.054$; slow-beta: $F_{2,89}=4.50$, $p=.014$; fast-beta: $F_{2,89}=5.18$, $p=.007$).

4. Discussion

In the present study, heavy alcohol intake of 21 alcoholic drinks per week or more was associated with differences in synchronization of brain activity in healthy individuals who are not alcohol-dependent. Both male and female heavy drinkers displayed a loss of lateralization in the alpha (8–12 Hz) and slow-beta (12–20 Hz) band. In addition, males consuming 7 drinks per week or more showed lower synchronization in the fast-beta band (20–30 Hz) as compared to males who drink less, while in the females, this effect was not found. As individuals with a personal or family history of alcohol dependence were excluded, the confounding effects of genetic factors related to alcohol dependence on EEG synchronization were minimized.

Light and moderate drinkers showed lateralization of alpha and slow-beta synchronization, but heavy drinkers did not display this hemispheric asymmetry. In both frequency bands, this lack of lateralization was due to relatively low synchronization in the left hemisphere of heavy drinkers. Local alpha and beta synchronization are thought to reflect dynamic integrative processes regulating cortical activation and deactivation (Basar et al., 1997; Klimesch, 1996; Neuper and Pfurtscheller, 2001). Possibly, the relatively low alpha and slow-beta synchronization in the left hemisphere in male and female heavy drinkers may be a sign of weaker coupling in different networks implicated in these rhythms.

Only one study investigated the relationship between risk factors for alcohol dependence and EEG asymmetry (Ehlers et al., 2001). In this study, parental history of alcohol dependence was unrelated to alpha asymmetry in children of native Americans. In addition, a higher degree of native-American heritage (which is associated with a higher prevalence of a positive family history of alcohol dependence) was associated with greater alpha asymmetry. The fact that risk factors for alcohol dependence such as a family history of alcohol dependence or degree of native-American heritage were either unrelated to, or associated with *greater* alpha asymmetry, whereas our family history negative heavy drinkers had a *lower* alpha asymmetry, supports the hypothesis that the differences in alpha EEG activity in our sample of heavy drinkers are relatively unrelated to genetic factors.

The finding of concurrent differences in the alpha and slow-beta band are in agreement with the results of studies on the effects of alcohol dependence on EEG coherence. Kaplan et al. (1985) reported lower frontal alpha and slow-beta coherence in alcohol-dependent males and females.

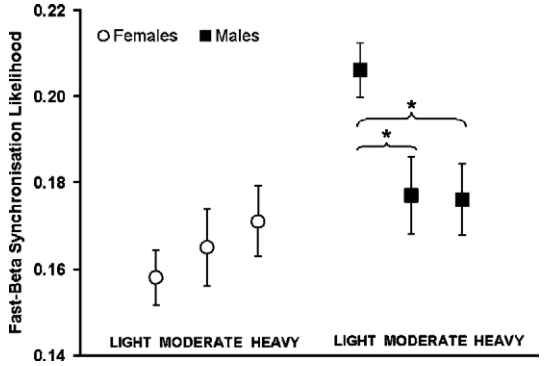

Fig. 6. Lower fast-beta (20–30 Hz) Synchronization Likelihood in moderate and heavy male drinkers but not in female drinkers. Diamonds represent mean SL; error bars denote standard errors; asterisks indicate the level of significance in post hoc Bonferroni-corrected *t*-tests: $*p<0.05$.

Table 2
Group differences in Synchronization Likelihood

	df[a]	Alpha (8–12 Hz)		Slow-beta (12–20 Hz)		Fast-beta (20–30 Hz)	
		F	p	F	p	F	p
Group	2,90	0.04	0.965	1.55	0.217	1.37	0.259
Group × Frontality	4,180	0.09	0.953	0.91	0.452	2.14	0.082
Group × Gender	2,90	0.30	0.739	1.13	0.327	**5.35**	**0.006**
Group × Condition	2,90	0.38	0.687	0.04	0.964	0.06	0.940
Group × Lateralization	2,90	1.79	0.174	**4.83**	**0.010**	2.56	0.083
Group × Gender × Lateralization	2,90	0.70	0.501	0.79	0.455	1.49	0.231
Group × Condition × Lateralization	2,90	**3.34**	**0.040**	0.97	0.383	1.17	0.315

Significant effects involving the factor Group are highlighted in boldface.
[a] Uncorrected degrees of freedom.

Michael et al. (1993) found higher central alpha and slow-beta coherence, but lower parietal alpha and slow-beta coherence in males with alcohol dependence. Winterer et al. (2003a,b,c) described higher left-temporal alpha and slow-beta coherence and higher slow-beta coherence at right-temporal and frontal electrode pairs in alcohol-dependent males and females.

On the other hand, the present results do not support hypotheses from cognitive research that alcohol intake particularly affects the frontal regions of the brain (Dao-Castellana et al., 1998; Di Sclafani et al., 1995; Ratti et al., 2002). No interactions between alcohol intake and brain activity measured along the front-to-back axis (i.e. the factor Frontality) were found. Neither did the results support that the right hemisphere was particularly affected as suggested by Bertera and Parsons (1978) and Miglioli et al. (1979), as the present results suggest that the lack of lateralization in heavy drinkers was due to relatively low synchronization in the left hemisphere. In addition, adding the number of cigarettes smoked per day as a covariate reduced the statistical significance of the interactions only marginally. This suggests that, in contrast to the findings of Durazzo et al. (2004) in alcoholics, in non-alcohol-dependent drinkers, the additive effect of smoking is negligible as compared to that of alcohol intake alone. The discrepancies between our findings and those reported in the literature may be related to the absence of the confounding effects of genetic factors related to alcohol dependence in the present study.

Moderate and heavy male drinkers additionally displayed low fast-beta synchronization as compared to light male drinkers. The interaction between group and gender, illustrated in Fig. 6, can be interpreted in two ways. One interpretation is that women are more susceptible to the effects of alcohol, and that, despite the slightly lower alcohol intake in females, alcohol intake affects fast-beta synchronization even in light female drinkers. Alternatively, females may have a generally lower fast-beta synchronization than males regardless of alcohol intake, suggesting that male moderate and heavy drinkers are particularly affected. To our knowledge, there are no publications about gender differences in lateralization of fast-beta synchronization.

Additional support for the latter hypothesis that male drinkers are more vulnerable for the negative effects of alcohol than the females comes from brain MRI scans made in the same sample of non-alcohol-dependent drinkers. These scans revealed that alcohol intake only affected brain structure in the male and not in the female drinkers (De Bruin et al., 2005a,b). In the males, a higher alcohol intake was associated with a decrease in gray matter, whereas in the females, no relationship between alcohol intake and gray or white matter was found (De Bruin et al., 2005b). Furthermore, behavioral studies show that light and moderate alcohol intake have a more beneficial effect on cognition in females than in males (Britton et al., 2004; Dufouil et al., 2001). Possible mechanisms behind these gender differences are different drinking patterns (Green et al., 2004), different alcohol metabolism (Mumenthaler et al., 1999), lower sensitivity of brain metabolism to acute alcohol effects in females (Wang et al., 2003), or a possible neuroprotective effect of estrogen against alcohol toxicity in the brain (Singer et al., 1996).

In the present study, participants were rigorously screened to exclude people with (a history of) alcohol dependence, or with first- or second-degree relatives who were alcohol-dependent. Nevertheless, the EEG differences in heavy drinkers were found in the same frequency bands as in previous studies in alcohol-dependent individuals (e.g., Kaplan et al., 1985; Michael et al., 1993; Winterer et al., 2003a), although in those studies synchronization was assessed with amplitude measures instead of the currently employed Synchronization Likelihood analysis.

Synchronization Likelihood assesses the similarity between system states reconstructed from EEG time series by calculating temporal correlations (Stam and Van Dijk, 2002). In this way, temporal correlations between spatially remote neurophysiological events, or 'functional connectivity' (Friston, 2000; Lee et al., 2003), can be determined. Functional connectivity reflects the coordination of activity between different neural assemblies that are needed to achieve a perceptual process or cognitive task (Fingelkurts et al., 2005). In contrast to effective connectivity, the characterization of brain activity in terms of

functional connectivity is essentially model-free and does not involve topographical qualifications (Ramnani et al., 2002).

Studies in lightly drinking relatives of alcohol-dependent individuals reporting similar EEG differences as in alcoholics (Bauer and Hesselbrock, 2002; Ehlers and Schuckit, 1991; Finn and Justus, 1999; Michael et al., 1993; Rangaswamy et al., 2004) suggested that these EEG differences were related to genetic factors involved in alcohol dependence. However, in the present study, again the same frequencies were affected in participants without alcohol dependence and without alcohol-dependent relatives, indicating that alcohol intake has a pure effect on brain activity, also in the absence of those genetic factors. Thus, in alcohol-dependent patients, EEG differences may reflect a combination of the influence of genetic factors related to alcohol dependence and the pure effects of long-term alcohol intake. To verify that these EEG differences are indeed the result of heavy alcohol intake, and not a reflection of pre-existing differences in brain activity, a longitudinal study should be performed.

A positive family history of alcohol dependence is associated with a lower level of response to alcohol as measured by self-reported feelings of intoxication after an acute alcohol challenge (Schuckit, 1994). The level of response to alcohol may contribute to a transition from lighter to heavier drinking in individuals in a relatively heavy-drinking environment (Schuckit et al., 2004). In an initial 8-year follow-up study of males with a positive or negative family history of alcohol dependence (Schuckit and Smith, 1996), the level of response to alcohol was associated with alcohol dependence independently of family history, although a mediating role could not be ruled out. However, the subsequent 20-year follow-up of the same sample demonstrated that the level of response rather acted as an intermediate phenotype of the association between a family history of alcohol dependence and alcohol use disorders (Schuckit et al., 2004).

Similar to the previous study in student drinkers (De Bruin et al., 2004), the groups did not differ in performance on the mental-rehearsal task, but only in EEG synchronization. Combined with the observation of Parsons (1998) that the effects of heavy drinking on neuropsychological test results are subtle, this suggests that EEG synchronization is a more sensitive measure of brain dysfunction. In contrast to the previous study, no evidence of stronger theta and gamma synchronization in heavy drinkers was found. This may be related to differences in age, which is strongly related to EEG coherence (Duffy et al., 1996), which may also be the case for Synchronization Likelihood. Furthermore, the students had a higher alcohol intake than the older adults, and started to drink at an earlier age. There are indications that the brains of adolescents are more vulnerable to the long-term effects of alcohol than the brains of older adults, particularly during the development of the memory system involving the hippocampus (Hill, 2004; White and Swartzwelder, 2004). This hypothesis is supported by the fact that the frequencies affected in the heavy student drinkers were theta and gamma, which are associated with hippocampal–neocortical activity during memory formation (Buzsáki, 1996).

In conclusion, moderate-to-heavy alcohol consumption is associated with differences in synchronization of brain activity during rest and mental rehearsal. Both male and female heavy drinkers displayed a loss of hemispheric asymmetry of EEG synchronization in the alpha and slow-beta band. Moderately and heavily drinking males additionally showed lower fast-beta band synchronization. These findings may reflect altered coupling between different networks implicated in the resting state of the brain and during mental rehearsal in relation to heavy drinking. The presently reported differences in functional brain activity are probably relatively purely associated with alcohol intake. The confounding effects of genetic factors related to alcohol dependence were minimized by selecting participants who were not alcohol-dependent and had a negative family history of alcohol dependence up to the second degree. We agree with Parsons (1998) that drinking 21 or more alcoholic drinks per week may affect brain functioning.

Acknowledgements

The authors gratefully acknowledge the assistance of William Verheul, Hanneke Palmen, and Simone Scherpenisse. This study was supported by the Dutch Foundation for Scientific Research (NWO/ZONMw) grant 960-40000-39.

Appendix A

Synchronization Likelihood (SL) is a measure of the generalized synchronization between two dynamical systems $\boldsymbol{X}$ and $\boldsymbol{Y}$ (Stam and Van Dijk, 2002; Posthuma et al., in press). Generalized synchronization (Rulkov et al., 1995), that exists between $\boldsymbol{X}$ and $\boldsymbol{Y}$ of the state of the response system, is a function of the driver system: $\boldsymbol{Y}=\boldsymbol{F}(\boldsymbol{X})$. The first step in the computation of SL is to convert the time series $\boldsymbol{x_i}$ and $\boldsymbol{y_i}$ recorded from $\boldsymbol{X}$ and $\boldsymbol{Y}$ as a series of state space vectors using the method of time delay embedding (Takens, 1981):

$$X_i = \left(x_i, x_{i+L}, x_{i+2\times L}, x_{i+3\times L}, \ldots, x_{i+(m-1)\times L}\right), \quad (1)$$

where L is the time lag, and m the embedding dimension. From a time series of N samples, $N-(m\times L)$ vectors can be reconstructed. State space vectors Y_i are reconstructed in the same way.

Synchronization Likelihood is defined as the conditional likelihood that the distance between Y_i and Y_j will be smaller than a cutoff distance r_y, given that the distance

between X_i and X_j is smaller than a cutoff distance r_x. In the case of maximal synchronization, this likelihood is 1; in the case of independent systems, it is a small but nonzero number, namely P_{ref}. This small number is the likelihood that two randomly chosen vectors Y (or X) will be closer than the cut-off distance r. In practice, the cut-off distance is chosen such that the likelihood of random vectors being close is fixed at P_{ref}, which is chosen the same for X and for Y. To understand how P_{ref} is used to fix r_x and r_y we first consider the correlation integral:

$$C_r = \frac{2}{N(N-w)} \sum_{i=1}^{N} \sum_{j=i+w}^{N-w} \theta\left(r - |X_i - X_j|\right). \quad (2)$$

Here, the correlation integral C_r is the likelihood that two randomly chosen vectors X will be closer than r. The vertical bars represent the Euclidean distance between the vectors. N is the number of vectors, which is the Theiler correction for autocorrelation (Theiler, 1986), and θ is the Heaviside function: $\theta(X)=0$ if $X \geq 0$ and $\theta(X)=1$ if $X<0$. Now, r_x is chosen such that $C_{rx}=P_{\text{ref}}$ and r_y is chosen such that $C_{ry}=P_{\text{ref}}$. The SL between X and Y can now be formally defined as:

$$\text{SL} = \frac{2}{N(N-w)P_{\text{ref}}} \times \sum_{i=1}^{N} \sum_{j=i+w}^{N-w} \theta\left(r_x - |X_i - X_j|\right)\theta\left(r_y - |Y_i - Y_j|\right). \quad (3)$$

Synchronization Likelihood is a symmetric measure of the strength of synchronization between X and Y ($\text{SL}_{XY}=\text{SL}_{YX}$). In Eq. (3), the averaging is done over all i and j; by doing the averaging only over j SL can be computer as a function of time i. Furthermore, from (3) it can be seen that in the case of complete synchronization, SL=1; in the case of complete independence, $\text{SL}=P_{\text{ref}}$. In the case of intermediate levels of synchronization $P_{\text{ref}}<\text{SL}<1$.

References

Andreasen, N.C., O'Leary, D.S., Cizadlo, T., Arndt, S., Rezai, K., Watkins, G.L., Ponto, L.L., Hichwa, R.D., 1995. Remembering the past: two facets of episodic memory explored with positron emission tomography. Am. J. Psychiatry 152, 1576–1585.

Babiloni, C., Ferri, R., Moretti, D.V., Strambi, A., Binetti, G., Dal Forno, G., Ferreri, F., Lanuzza, B., Bonato, C., Nobili, F., Rodriguez, G., Salinari, S., Passero, S., Rocchi, R., Stam, C.J., Rossini, P.M., 2004. Abnormal fronto-parietal coupling of brain rhythms in mild Alzheimer's disease: a multicentric EEG study. Eur. J. Neurosci. 19, 2583–2590.

Basar, E., Schürmann, M., Basar-Eroglu, C., Karakas, S., 1997. Alpha oscillations in brain functioning: an integrative theory. Int. J. Psychophysiol. 26, 5–29.

Basar, E., Basar-Eroglu, C., Karakas, S., Schürmann, M., 2001. Gamma, alpha, delta, and theta oscillations govern cognitive processes. Int. J. Psychophysiol. 39, 241–248.

Bauer, L.O., 2001. Predicting relapse to alcohol and drug abuse via quantitative electroencephalography. Neuropsychopharmacology 25, 332–340.

Bauer, L.O., Hesselbrock, V.M., 2002. Lateral asymmetries in the frontal brain: effects of depression and a family history of alcoholism in female adolescents. Alcohol., Clin. Exp. Res. 26, 1662–1668.

Bertera, J.H., Parsons, O.A., 1978. Impaired visual search in alcoholics. Alcohol., Clin. Exp. Res. 2, 9–14.

Britton, A., Singh-Manoux, A., Marmot, M., 2004. Alcohol consumption and cognitive function in the Whitehall II Study. Am. J. Epidemiol. 160, 240–247.

Brody, A.L., Mandelkern, M.A., Jarvik, M.E., Lee, G.S., Smith, E.C., Huang, J.C., Bota, R.G., Bartzokis, G., London, E.D., 2004. Differences between smokers and nonsmokers in regional gray matter volumes and densities. Biol. Psychiatry 55, 77–84.

Buzsáki, G., 1996. The hippocampo-neocortical dialogue. Cereb. Cortex 6, 81–92.

Ciesielski, K.T., Waldorf, A.V., Jung, R.E., 1995. Anterior brain deficits in chronic alcoholism. Cause or effect? J. Nerv. Ment. Dis. 183, 756–761.

Dao-Castellana, M.H., Samson, Y., Legault, F., Martinot, J.L., Aubin, H.J., Crouzel, C., Feldman, L., Barrucand, D., Rancurel, G., Feline, A., Syrota, A., 1998. Frontal dysfunction in neurologically normal chronic alcoholic subjects: metabolic and neuropsychological findings. Psychol. Med. 28, 1039–1048.

David, O., Cosmelli, D., Hasboun, D., Garnero, L., 2003. A multitrial analysis for revealing significant corticocortical networks in magnetoencephalography and electroencephalography. NeuroImage 20, 186–201.

De Bruin, E.A., Bijl, S., Stam, C.J., Böcker, B.E., Kenemans, J.L., Verbaten, M.N., 2004. Abnormal EEG synchronisation in heavily drinking students. Clin. Neurophysiol. 115, 2048–2055.

De Bruin, E.A., Hulshoff Pol, H.E., Bijl, S., Schnack, H.G., Fluitman, S., Bocker, K.B., Kenemans, J.L., Kahn, R.S., Verbaten, M.N., 2005a. Associations between alcohol intake and brain volumes in male and female moderate drinkers. Alcohol., Clin. Exp. Res. 29, 656–663.

De Bruin, E.A., Hulshoff Pol, H.E., Schnack, H.G., Janssen, J., Bijl, S., Evans, A.C., Leon, K.J., Kahn, R.S., Verbaten, M.N., 2005b. Focal brain matter differences associated with lifetime alcohol intake and visual attention in male but not in female non-alcohol-dependent drinkers. NeuroImage 26, 536–545.

Di Sclafani, V., Ezekiel, F., Meyerhoff, D.J., MacKay, S., Dillon, W.P., Weiner, M.W., Fein, G., 1995. Brain atrophy and cognitive function in older abstinent alcoholic men. Alcohol., Clin. Exp. Res. 19, 1121–1126.

Duffy, F.H., McAnulty, G.B., Albert, M.S., 1996. Effects of age upon interhemispheric EEG coherence in normal adults. Neurobiol. Aging 17, 587–599.

Dufouil, C., Kersaint-Gilly, A., Besancon, V., Levy, C., Auffray, E., Brunnereau, L., Alperovitch, A., Tzourio, C., 2001. Longitudinal study of blood pressure and white matter hyperintensities: the EVA MRI Cohort. Neurology 56, 921–926.

Durazzo, T.C., Gazdzinski, S., Banys, P., Meyerhoff, D.J., 2004. Cigarette smoking exacerbates chronic alcohol-induced brain damage: a preliminary metabolite imaging study. Alcohol., Clin. Exp. Res. 28, 1849–1860.

Edenberg, H.J., Dick, D.M., Xuei, X., Tian, H., Almasy, L., Bauer, L.O., Crowe, R.R., Goate, A., Hesselbrock, V., Jones, K., Kwon, J., Li, T.K., Nurnberger Jr., J.I., O'Connor, S.J., Reich, T., Rice, J., Schuckit, M.A., Porjesz, B., Foroud, T., Begleiter, H., 2004. Variations in GABRA2, encoding the a2 subunit of the GABA_A receptor, are associated with alcohol dependence and with brain oscillations. Am. J. Hum. Genet. 74, 705–714.

Ehlers, C.L., Schuckit, M.A., 1991. Evaluation of EEG alpha activity in sons of alcoholics. Neuropsychopharmacology 4, 199–205.

Ehlers, C.L., Wall, T.L., Schuckit, M.A., 1989. EEG spectral analysis characteristics following ethanol administration in young men. Electroencephalogr. Clin. Neurophysiol. 73, 179–187.

Ehlers, C.L., Wall, T.L., Garcia-Andrade, C., Phillips, E., 2001. EEG asymmetry: relationship to mood and risk for alcoholism in Mission Indian youth. Biol. Psychiatry 50, 129–136.

Ellis, R.J., Oscar-Berman, M., 1989. Alcoholism, aging, and functional cerebral asymmetries. Psychol. Bull. 106, 128–147.

Engel, A.K., Singer, W., 2001. Temporal binding and the neural correlates of sensory awareness. Trends Cogn. Sci. 5, 16–25.

Enoch, M.A., 2003. Pharmacogenomics of alcohol response and addiction. Am. J. Pharmacogenomics 3, 217–232.

Enoch, M.A., White, K.V., Harris, C.R., Rohrbaugh, J.W., Goldman, D., 2002. The relationship between two intermediate phenotypes for alcoholism: low voltage alpha EEG and low P300 ERP amplitude. J. Stud. Alcohol 63, 509–517.

Fell, J., Fernandez, G., Klaver, P., Elger, C.E., Fries, P., 2003. Is synchronized neuronal gamma activity relevant for selective attention? Brain Res. Brain Res. Rev. 42, 265–272.

Ferri, R., Elia, M., Musumeci, S.A., Stam, C.J., 2001. Non-linear EEG analysis in children with epilepsy and electrical status epilepticus during slow-wave sleep (ESES). Clin. Neurophysiol. 112, 2274–2280.

Fingelkurts, A.A., Fingelkurts, A.A., Kahkonen, S., 2005. Functional connectivity in the brain: is it an elusive concept? Neurosci. Biobehav. Rev. 28, 827–836.

Finn, P.R., Justus, A., 1999. Reduced EEG alpha power in the male and female offspring of alcoholics. Alcohol., Clin. Exp. Res. 23, 256–262.

Friston, K.J., 2000. The labile brain: I. Neuronal transients and nonlinear coupling. Philos. Trans. R. Soc. Lond., B Biol. Sci. 355, 215–236.

Green, C.A., Perrin, N.A., Polen, M.R., 2004. Gender differences in the relationships between multiple measures of alcohol consumption and physical and mental health. Alcohol., Clin. Exp. Res. 28, 754–764.

Greicius, M.D., Krasnow, B., Reiss, A.L., Menon, V., 2003. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. Proc. Natl. Acad. Sci. U. S. A. 100, 253–258.

Hill, S.Y., 2004. Trajectories of alcohol use and electrophysiological and morphological indices of brain development: distinguishing causes from consequences. Ann. N.Y. Acad. Sci. 1021, 245–259.

Horner, M.D., Waid, L.R., Johnson, D.E., Latham, P.K., Anton, R.F., 1999. The relationship of cognitive functioning to amount of recent and lifetime alcohol consumption in outpatient alcoholics. Addict. Behav. 24, 449–453.

Kaplan, R.F., Glueck, B.C., Hesselbrock, M.N., Reed, H.B., 1985. Power and coherence analysis of the EEG in hospitalized alcoholics and nonalcoholic controls. J. Stud. Alcohol 46, 122–127.

Klimesch, W., 1996. Memory processes, brain oscillations and EEG synchronization. Int. J. Psychophysiol. 24, 61–100.

Klimesch, W., 1999. EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. Brain Res. Rev. 29, 169–195.

Lee, L., Harrison, L.M., Mechelli, A., 2003. A report of the functional connectivity workshop, Dusseldorf 2002. NeuroImage 19, 457–465.

Lemmens, P.H., Volovics, L., De Haan, Y., 1997. Measurement of lifetime exposure to alcohol: data quality of a self-administered questionnaire and impact on risk assessment. Contemp. Drug Probl. 24, 581–600.

Michael, A., Mirza, K.A., Mukundan, C.R., Channabasavanna, S.M., 1993. Interhemispheric electroencephalographic coherence as a biological marker in alcoholism. Acta Psychiatr. Scand. 87, 213–217.

Micheloyannis, S., Vourkas, M., Bizas, M., Simos, P., Stam, C.J., 2003. Changes in linear and nonlinear EEG measures as a function of task complexity: evidence for local and distant synchronization. Brain Topogr. 15, 239–247.

Micheloyannis, S., Sakkalis, V., Vourkas, M., Stam, C.J., Simos, P.G., 2005. Neural networks involved in mathematical thinking: evidence from linear and non-linear analysis of electroencephalographic activity. Neurosci. Lett. 373, 212–217.

Miglioli, M., Buchtel, H.A., Campanini, T., De Risio, C., 1979. Cerebral hemispheric lateralization of cognitive deficits due to alcoholism. J. Nerv. Ment. Dis. 167, 212–217.

Mumenthaler, M.S., Taylor, J.L., O'Hara, R., Yesavage, J.A., 1999. Gender differences in moderate drinking effects. Alcohol Res. Health 23, 55–64.

Neuper, C., Pfurtscheller, G., 2001. Event-related dynamics of cortical rhythms: frequency-specific features and functional correlates. Int. J. Psychophysiol. 43, 41–58.

Parker, E.S., Noble, E.P., 1977. Alcohol consumption and cognitive functioning in social drinkers. J. Stud. Alcohol 38, 1224–1232.

Parsons, O.A., 1994. Neuropsychological measures and event-related potentials in alcoholics: interrelationships, long-term reliabilities, and prediction of resumption of drinking. J. Clin. Psychol. 50, 37–46.

Parsons, O.A., 1998. Neurocognitive deficits in alcoholics and social drinkers: a continuum? Alcohol., Clin. Exp. Res. 22, 954–961.

Parsons, O.A., Nixon, S.J., 1998. Cognitive functioning in sober social drinkers: a review of the research since 1986. J. Stud. Alcohol 59, 180–190.

Pijnenburg, Y.A., Van der Made, Y., Van Capellen Van Walsum, A.M., Knol, D.L., Scheltens, Ph., Stam, C.J., 2004. EEG Synchronization Likelihood in mild cognitive impairment and Alzheimer's disease during a working memory task. Clin. Neurophysiol. 115, 1332–1339.

Porjesz, B., Almasy, L., Edenberg, H.J., Wang, K., Chorlian, D.B., Foroud, T., Goate, A., Rice, J.P., O'Connor, S.J., Rohrbaugh, J., Kuperman, S., Bauer, L.O., Crowe, R.R., Schuckit, M.A., Hesselbrock, V., Conneally, P.M., Tischfield, J.A., Li, T.K., Reich, T., Begleiter, H., 2002. Linkage disequilibrium between the beta frequency of the human EEG and a $GABA_A$ receptor gene locus. Proc. Natl. Acad. Sci. U. S. A. 99, 3729–3733.

Posthuma, D., De Geus, E.J.C., Mulder, E.J.C.M., Smit, D.J.A., Boomsma, D.I., Stam, C.J., in press. Genetic components of functional connectivity in the brain: the heritability of Synchronization Likelihood. Hum. Brain Mapp. (Electronic publication ahead of print May 31, 2005.).

Ramnani, N., Lee, L., Mechelli, A., Phillips, C., Roebroeck, A., Formisano, E., 2002. Exploring brain connectivity: a new frontier in systems neuroscience. Trends Neurosci. 25, 496–497.

Rangaswamy, M., Porjesz, B., Chorlian, D.B., Wang, K., Jones, K.A., Bauer, L.O., Rohrbaugh, J., O'Connor, S.J., Kuperman, S., Reich, T., Begleiter, H., 2002. Beta power in the EEG of alcoholics. Biol. Psychiatry 52, 831.

Rangaswamy, M., Porjesz, B., Chorlian, D.B., Wang, K., Jones, K.A., Kuperman, S., Rohrbaugh, J., O'Connor, S.J., Bauer, L.O., Reich, T., Begleiter, H., 2004. Resting EEG in offspring of male alcoholics: beta frequencies. Int. J. Psychophysiol. 51, 239–251.

Ratti, M.T., Bo, P., Giardini, A., Soragna, D., 2002. Chronic alcoholism and the frontal lobe: which executive functions are impaired? Acta Neurol. Scand. 105, 276–281.

Robins, L.N., Wing, J., Wittchen, H.U., Helzer, J.E., Babor, T.F., Burke, J., Farmer, A., Jablenski, A., Pickens, R., Regier, D.A., 1988. The Composite International Diagnostic Interview: an epidemiologic instrument suitable for use in conjunction with different diagnostic systems and in different cultures. Arch. Gen. Psychiatry 45, 1069–1077.

Romberger, D.J., Grant, K., 2004. Alcohol consumption and smoking status: the role of smoking cessation. Biomed. Pharmacother. 58, 77–83.

Rulkov, N.F., Sushchik, M.M., Tsimring, L.S., Abarbanel, H.D., 1995. Generalized synchronization of chaos in directionally coupled chaotic systems. Phys. Rev., E 51, 980–994.

Salek-Haddadi, A., Friston, K.J., Lemieux, L., Fish, D.R., 2003. Studying spontaneous EEG activity with fMRI. Brain Res. Rev. 43, 110–133.

Saletu-Zyhlarz, G.M., Arnold, O., Anderer, P., Oberndorfer, S., Walter, H., Lesch, O.M., Boning, J., Saletu, B., 2004. Differences in brain function between relapsing and abstaining alcohol-dependent patients, evaluated by EEG mapping. Alcohol Alcohol. 39, 233–240.

Schmand, B., Lindeboom, J., Van Harskamp, F., 2003. NLV: Nederlandse Leestest voor Volwassenen. Zwets & Zeitlinger, Lisse, The Netherlands.

Schuckit, M.A., 1994. Low level of response to alcohol as a predictor of future alcoholism. Am. J. Psychiatr. 151, 184–189.

Schuckit, M.A., 2000. Genetics of the risk for alcoholism. Am. J. Addict. 9, 103–112.

Schuckit, M.A., Smith, T.L., 1996. An 8-year follow-up of 450 sons of alcoholic and control subjects. Arch. Gen. Psychiatry 53, 202–210.

Schuckit, M.A., Smith, T.L., Anderson, K.G., Brown, S.A., 2004. Testing the level of response to alcohol: social information processing model of alcoholism risk: a 20-year prospective study. Alcohol., Clin. Exp. Res. 28, 1881–1889.

Singer, C.A., Rogers, K.L., Strickland, T.M., Dorsa, D.M., 1996. Estrogen protects primary cortical neurons from glutamate toxicity. Neurosci. Lett. 212, 13–16.

Skinner, H.A., Sheu, W.J., 1982. Reliability of alcohol use indices. The lifetime drinking history and the MAST. J. Stud. Alcohol 43, 1157–1170.

Stam, C.J., De Bruin, E.A., 2004. Scale-free dynamics of global functional connectivity in the human brain. Hum. Brain Mapp. 22, 97–109.

Stam, C.J., Van Dijk, B.W., 2002. Synchronisation Likelihood: an unbiased measure of generalized synchronisation in multivariate data sets. Physica, D 163, 236–251.

Stam, C.J., Van Capellen Van Walsum, A.-M., Micheloyannis, S., 2002a. Variability of EEG synchronization during a working memory task in healthy subjects. Int. J. Psychophysiol. 46, 53–66.

Stam, C.J., Van Cappellen Van Walsum, A.M., Pijnenburg, Y.A., Berendse, H.W., De Munck, J.C., Scheltens, P., Van Dijk, B.W., 2002b. Generalized synchronization of MEG recordings in Alzheimer's disease: evidence for involvement of the gamma band. J. Clin. Neurophysiol. 19, 562–574.

Stam, C.J., Breakspear, M., Van Capellen Van Walsum, A.-M., Van Dijk, B.W., 2003. Nonlinear synchronization in EEG and whole-head MEG recordings of healthy subjects. Hum. Brain Mapp. 19, 36–78.

Takens, F., 1981. Detecting strange attractors in turbulence. Lect. Notes Math. 898, 366–381.

Theiler, J., 1986. Spurious dimension from correlation algorithms applied to limited time-series data. Phys. Rev. A 34, 2427–2432.

Tizabi, Y., Al Namaeh, M., Manaye, K.F., Taylor, R.E., 2003. Protective effects of nicotine on ethanol-induced toxicity in cultured cerebellar granule cells. Neurotox. Res. 5, 315–321.

Van Beijsterveldt, C.E.M., Van Baal, G.C.M., 2002. Twin and family studies of the human electroencephalogram: a review and a meta-analysis. Biol. Psychol. 61, 111–138.

Wang, G.J., Volkow, N.D., Fowler, J.S., Franceschi, D., Wong, C.T., Pappas, N.R., Netusil, N., Zhu, W., Felder, C., Ma, Y., 2003. Alcohol intoxication induces greater reductions in brain metabolism in male than in female subjects. Alcohol., Clin. Exp. Res. 27, 909–917.

White, A.M., Swartzwelder, H.S., 2004. Hippocampal function during adolescence: a unique target of ethanol effects. Ann. N.Y. Acad. Sci. 1021, 206–220.

Winterer, G., Enoch, M.A., White, K.V., Saylan, M., Coppola, R., Goldman, D., 2003a. EEG phenotype in alcoholism: increased coherence in the depressive subtype. Acta Psychiatr. Scand. 108, 51–60.

Winterer, G., Mahlberg, R., Smolka, M.N., Samochowiec, J., Ziller, M., Rommelspacher, H.P., Herrmann, W.M., Schmidt, L.G., Sander, T., 2003b. Association analysis of exonic variants of the $GABA_B$-receptor gene and alpha encephalogram voltage in normal subjects and alcohol-dependent patients. Behav. Genet. 33, 7–15.

Winterer, G., Smolka, M., Samochowiec, J., Ziller, M., Mahlberg, R., Gallinat, J., Rommelspacher, H.P., Herrmann, W.M., Sander, T., 2003c. Association of EEG coherence and an exonic $GABA_BR1$ gene polymorphism. Am. J. Med. Genet. 117B, 51–56.