Functional Changes in the Brains of Social Drinkers

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FUNCTIONAL CHANGES IN THE BRAINS OF SOCIAL DRINKERS

FUNCTIONELE VERANDERINGEN IN DE BREINEN VAN SOCIALE DRINKERS

(met een samenvatting in het Nederlands)

Proefschrift

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Chapter 1

General Introduction

INTRODUCTION

In this thesis, the effects of long-term chronic social drinking on the functioning of the brain are investigated. Alcohol consumption in social settings makes people relax and enjoy the situation. However, it is generally known that severe long-term alcohol consumption, as in alcohol dependent people, causes extensive medical (e.g. liver deficits, accidents during acute intoxication) and social damage (e.g. problems with social contacts, unemployment). Although much is known about the chronic effects of severe alcohol consumption where it concerns alcoholics, there is still little insight in the question whether moderate social drinking can also result in brain damage. Social drinking is commonly regarded as non-pathological, i.e. normal, behavior. Vast majorities of people drink on a regular basis; 92% of the Dutch population of twelve years and older have ever consumed alcohol in their life, and 75% the Dutch population of twelve years and older drank in the last month (Abraham 2002). There are indications that also social drinking may have long-term negative effects on the brain. In the present study the question was investigated what the effects are of chronic, long-term 'social' alcohol use on the functioning of the brain.

To address this question we will first give an outline of the acute pharmacological effects of alcohol, how it affects the brain, what is known about the long-term effects in alcohol dependent people, and what is already known about social drinkers. This chapter concludes with an outline of the present thesis, which encompasses an Event Related Potential (ERP)* study of social drinkers.

*) An ERP is the average of a number of time segments of the electrical activity recorded from the brain, usually via electrodes on the scalp, in response to sensory stimuli. ERPs have a very high time resolution and consecutive peaks can be distinguished which are indicated with their positivity (P) or negativity (N) and their timing in milliseconds (e.g. 300); thus P300 indicates a positivity around 300 ms, which is in turn usually abbreviated to P3.

PHARMACOLOGY OF ALCOHOL

METABOLISM AND EXCRETION

Alcohol can have an effect on the brain because it is a lipophillic substance (Figure 1), which crosses the blood-brain-barrier easily. After consumption of alcohol, the maximum concentration of alcohol in the blood is reached within 30 to 90 minutes (Julien 1998). Alcohol is directly absorbed from the stomach and upper intestine. After absorption, alcohol is evenly distributed throughout all body fluids and tissues; also, the blood-brain barrier is freely passed by alcohol. The metabolism of alcohol is primarily done by the enzyme alcohol dehydrogenase. This metabolism of alcohol starts directly after the ingestion of alcohol. Approximately 5% is excreted unchanged, mainly through the lungs. About 10% of alcohol metabolism is carried out by gastric alcohol dehydrogenase, which is located in the lining of the stomach (Caballeria et al 1989; Julien 1998). This gastric metabolism of alcohol can be expected to decrease the blood level of alcohol by about 15%, which obviously attenuates its systemic toxicity (Julien 1998). Women have about 50% less gastric metabolism of alcohol than men, because woman have a lower level of gastric alcohol dehydrogenase enzyme (Frezza et al 1990; Julien 1998). Therefore, it is very difficult to compare the effects of alcohol between men and women. Once alcohol is absorbed and distributed throughout all body fluids and tissues, about 85% is metabolized in the liver, which thus converts the largest amount of alcohol. The enzyme alcohol dehydrogenase converts alcohol to acetaldehyde. Acetaldehyde thereafter is converted to acetic acid by acetaldehyde dehydrogenase. Acetic acid is ultimately broken down into carbon dioxide and water.

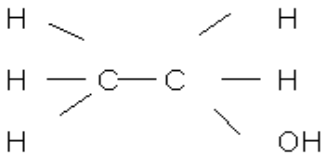

Figure 1. Structure of ethanol (CH_3CH_2OH)

The rate of metabolism of alcohol in the liver is independent of the concentration of alcohol in the blood, but is linear with time, and it increases only marginally by raising the concentration in the blood (a zero order metabolism). In adults approximately 10 milliliters of 100% ethanol is metabolized per hour regardless of the blood alcohol concentration. In other words, it takes 1.5 hour to metabolize a standard drink containing 12 grams of alcohol (15 milliliters of 100% ethanol).

ACUTE EFFECTS OF ALCOHOL ON THE CENTRAL NERVOUS SYSTEM

Alcohol is a central nervous system depressant, which shares many of the effects of other central nervous system depressants, such as sedatives, hypnotics, and anesthetic agents. The acute effects of alcohol ingestion in humans begin with euphoria and disinhibition. As the concen-

tration in the blood rises, motor functions become affected and speech becomes slurred. After ingesting large amounts of alcohol vomiting can occur and persons can fall into a stupor; even higher levels of blood alcohol concentration can lead to coma, respiration failure, or even death. Many of these effects of alcohol are, at least in part, due to interaction with the gamma-aminobutyric acid (GABA) neurotransmitter. GABA affects neurons in a way that reduces their activity; activating or enhancing the function of GABA receptors usually decreases activity in neurons. GABA influences neuronal activity by binding to and activating several classes of GABA receptors (denoted as $GABA_A$, $GABA_B$, and $GABA_C$). The GABA receptor that appears most sensitive to alcohol is $GABA_A$. The $GABA_A$ receptor is a channel forming protein that allows passage of chloride ions into the cell (Mihic and Harris 1997). Acute alcohol administration potentiates GABA-mediated inhibition in the cortex, medial septum, and the substantia nigra pars reticulata (see Grobin et al 1998).

Another neurotransmitter affected by alcohol is glutamate. Glutamate generally acts as an excitatory neurotransmitter that increases the activity of neurons by producing a response that is electrically opposite to that of the inhibitory neurotransmitters. It binds to specific ligand gated ion channels, and depolarizes the post-synaptic neuronal membrane, making it more likely that the neuron will fire. Alcohol is a potent inhibitor of the function of N-methyl-D-aspartate (NMDA) subtype of glutamate receptors. Alcohol appears to exert inhibition of NMDA receptor function by decreasing the frequency of ion channel opening (for calcium and sodium ions) (Gonzales and Jaworski 1997). Excessive stimulation of NMDA receptors by glutamate can kill neurons. This lethal damage to neurons in cases of excessive glutamate receptor activity is usually accompanied by an excessive accumulation of intracellular calcium ions. In addition, chronic alcohol exposure increases sensitivity of neurons to NMDA-stimulated killing (Iorio et al 1993).

As a result of the GABAergic agonist action, the cholinergic (acetylcholine) and the dopaminergic systems are also affected. Alcohol inhibits the release of acetylcholine in the central nervous system (Julien 1998). An intact cholinergic mechanism is necessary for learning and memory; therefore, this anticholinergic effect of alcohol may contribute to the impairment of cognition due to alcohol use. The abuse potential of alcohol seems to be related to the dopaminergic system (Harris et al 1992), particularly the dopaminergic projection from the ventral tegmentum area to the nucleus accumbens and the frontal cortex (an inhibition of inhibitory interneurons mediated via $GABA_A$ receptors; Hartz et al 1997). In addition, neurochemical systems like the serotonergic and opiod peptide system, also likely contribute to the mediation of alcohol's reinforcing actions (Hubbell et al 1991; Fils-Aime et al 1996).

NEUROLOGICAL AND COGNITIVE EFFECTS OF LONG-TERM ALCOHOL INTAKE

ALCOHOL DEPENDENCE

Since alcohol has a strong abuse potential, people who use excessive amounts of alcohol for an extended time could become dependent. According to the DSM-IV criteria, alcohol dependence is a pattern of un-adapted use of alcohol, resulting in significant restraint or suffering

because of craving, tolerance, the lack of control in using alcohol, inability to stop or cut back consumption, time spent on alcohol consumption (either drinking, buying, or visiting health centers), incapability to function in social and professional life, and/or continuing to use excessive amounts of alcohol while knowing it is harmful.

Long-term effects of alcohol dependence

Long-term excessive alcohol ingestion, as is mostly present in alcohol dependent people, appears to cause damage to nerve cells. In some people, alcohol may induce permanent brain damage and even a syndrome with dementia (Korsakoff's syndrome). Structural imaging studies in alcohol dependent participants have shown that the frontal lobes seem most vulnerable to the damaging effect of consuming large amounts of alcohol for an extended period of time (Pfefferbaum et al 1997; Ratti et al 1999; Fadda and Rossetti 1998; Demir et al 2002; Dao-Castellana et al 1998; Kril and Halliday 1999). In addition, also in neurocognitive studies evidence has been found for impairments in functioning of the brain in alcoholics (Parsons 1994; Fox et al 2000). Most evidence for impairment of brain functioning in alcoholics is found using cognitive tasks that rely on the integrity of the frontal brain areas, such as the Wisconsin card-sorting task, verbal fluency tasks, memory tasks, etc. (Ciesielski et al 1995; Ratti et al 1999; Demir et al 2002; Dao-Castellana et al 1998).

Impairments in alcoholics have also been shown in ERP research, which can provide an unique approach to investigate the temporal aspects of cognitive functioning in people. Differences between alcoholics and controls have been found on several ERP components measured with tasks that aim to assess different aspects of attention (see for a review Porjesz and Begleiter 1996). These attention tasks typically include attended and non-attended stimuli, which are relevant or not; participants have to respond to a predefined target stimulus. ERP studies using visual attention tasks in alcoholics showed diminished N1 amplitudes (Cohen et al 2002; Patterson et al 1987; Glenn et al 1996; Porjesz and Begleiter 1996). The visual N1 amplitude reduction in alcoholics indicates an impaired ability to selectively attend to task relevant stimuli imbedded in a series of irrelevant stimuli.

Diminished amplitudes in alcoholics compared to controls have also been found for the N2 component (Porjesz et al 1987; Porjesz and Begleiter 1996), which is typically related to the detection of deviant stimuli in a series of standard stimuli. The reduction in N2 amplitude indicates impairments in evaluating the potential significance of a stimulus. Like the N2, the P3 component is elicited by infrequent stimuli within a repetitive stimulus train of frequent stimuli. The P3 amplitude has also been found to be reduced in alcoholics compared to controls (Patterson et al 1987; Glenn et al 1996; Porjesz and Begleiter 1996; Rodriguez et al 1999; Malone et al 2001; Cohen et al 2002; Polo et al 2003). In studies using auditory tasks, to our knowledge, no deficiencies in alcohol dependent participants were found for the auditory N1 component, which is also related to attentional processes, while diminished amplitudes were found for the other attention related components like the N2 (Realmuto et al 1993) and the P3 (Patterson et al 1987; Realmuto et al 1993; Cohen et al 2002). In other studies, using tasks involving inhibition processes, lower frontal P3 amplitudes in alcoholics compared to controls have been reported (Pfefferbaum et al 1987; Fallgatter et al 1998). These results indicate deficient inhibition processes in alcoholics.

SOCIAL DRINKING

There is no universally adapted definition of social drinking. However, in general, studies on social drinkers exclude participants who meet the DSM-IV criteria for alcohol dependence and/or abuse. Most studies define their drinking groups with respect to amounts per day or per week, where the amounts vary from standard glasses to grams.

Long-term effects of social drinking

In contrast to studies on chronic alcohol use, relatively little research has been done on social drinking. Only one study has been conducted in which possible structural changes of the frontal lobes in the brains of social drinkers were investigated (Kubota et al 2001). In this study it was shown that non-alcoholic heavy drinkers were more vulnerable to shrinkage of the frontal lobes compared to moderate drinkers.

More research with social drinkers has been done using neuropsychological tests. However, the results of these studies provide conflicting evidence. Parsons and Nixon (1998) reviewed 17 studies that used several neuropsychological test batteries, and two studies in which ERPs were used. Only seven of these studies indicated that heavy social drinkers performed significantly worse on one or more cognitive tests compared to light social drinkers. Parsons and Nixon (1998) suggested that these conflicting results are due to different criteria across studies for heavy versus light social drinking. The studies in which no differences were found between light and heavy social drinkers reported significantly lower mean alcohol consumption in the heavy social drinkers group, compared to studies that did find differences (Parsons and Nixon 1998). Parsons and Nixon (1998) concluded that studies in which heavy social drinkers consumed more than 21 standard glasses or units per week (a standard unit contains 12 grams of alcohol), were most likely to find cognitive deficits.

Apart from this, Parsons and Nixon (1998) suggested that changes in the brains of heavy social drinkers who drank less than 21 standard units per week are too subtle to detect with behavioral tests. Some support for the latter conclusion was found in two studies with heavy and light social drinkers in which altered ERP components were found in the heavy social drinking group, despite the fact that the behavioral output was not affected. In both studies, a memory task was used. In the study of Fox et al (1995) ERP differences were found on a memory related N4 component and on a 'late memory effect' (positivity from 700-1100 ms). Nichols and Martin (1996) found smaller amplitudes for the heavy social drinkers for the frontal P3 component elicited by recalled and non-recalled words. Thus ERPs could provide a more sensitive method than behavioral tests for assessing the subtle changes in the brains of social drinkers. Additional evidence for disturbed 'covert' brain processes in heavy social drinkers was reported by Chao et al (2003), who used a classical two-stimuli reaction time paradigm, and found a reduced late CNV component in a heavy social drinkers group, compared to a light social drinkers group. In a visual simulated driving task, Nichols and Martin (1993) found a shorter latency of the P3 peak in light social drinkers compared to heavy social drinkers, but no differences in amplitude. These studies indicate that ERPs could provide an adequate measure to assess possible functional changes in the brains of social drinkers.

THEORIES ON THE LONG-TERM EFFECTS OF ALCOHOL ON THE BRAIN

BRAIN AREAS

Three hypotheses have been formulated in the literature about the locations in the brain where chronic (excessive) alcohol use has its most damaging effect: (1) the 'frontal-lobe' or 'anterior brain deficit' hypothesis; the (2) 'right hemisphere' hypothesis; and (3) the 'diffuse brain deficit' hypothesis.

According to the 'frontal-lobe' or 'anterior brain deficit' hypothesis, cognitive functions related to the frontal lobe are the ones mainly impaired in alcoholics (Ciesielski et al 1995). As stated before, convincing evidence for impairments of frontal brain function and structure in alcoholics has been found using neurocognitive tasks (Ciesielski et al 1995; Dao-Castellana et al 1998; Ratti et al 1999; Demir et al 2002) and structural imaging techniques (Pfefferbaum et al 1997; Dao-Castellana et al 1998; Fadda and Rossetti 1998; Kril and Halliday 1999; Ratti et al 1999; Demir et al 2002).

The 'right hemisphere' hypothesis contends that chronic alcohol consumption results in a more severe impairment of right- compared to left-hemisphere functions (Jones and Parsons 1971; Ellis and Oscar-Berman 1989). This hypothesis has been supported by studies demonstrating that alcoholics were more impaired on tasks measuring visuospatial capacities (right hemisphere) than verbal functions (left hemisphere) (Jones and Parsons 1971; Ellis and Oscar-Berman 1989). Indirect evidence for the 'right-hemisphere' hypothesis has been found in acute alcohol studies of Lewis et al (1960; 1970). These authors used visual evoked potentials revealing a clear right-sided lateralisation for a positive peak around 150 ms and a negative peak around 200 ms. After intake of a moderate dose of alcohol the right-sided lateralisation in response to the visual stimulation disappeared, suggesting a selective depression of right hemisphere activity. More recently, evidence for stronger impairments of right-hemisphere functions in alcoholics was found using ERPs in visual memory and delayed matching to sample tasks (Zhang et al 1997a;b). Major differences in the ERPs between controls and alcoholic patients were found over temporal-occipital and frontal regions, and most prominently over the right hemisphere (Zhang et al 1997a;b).

The so-called 'diffuse brain deficit' hypothesis suggests that alcohol affects both cortical and subcortical structures, and to a similar extent right- and left-hemisphere functions (Ellis and Oscar-Berman 1989; Lishman 1990). Ellis and Oscar-Berman (1989) note that, although evidence exists in favor of the 'right hemisphere' hypothesis, an equally convincing amount of evidence has been found for left or both left and right sided brain damage by alcohol. In general, neuropsychological tasks aiming to measure aspects of the right hemisphere tend to be more difficult for participants to perform correctly than left hemisphere tasks. Perhaps therefore these tasks are more discriminative and sensitive than left hemisphere tasks with respect to chronic alcohol effects.

THE 'CONTINUUM' HYPOTHESIS

Besides theories about which brain areas would be most vulnerable for toxic effects of alcohol, other theories exist, which are more concerned with the manner in which alcohol induces negative effects. The 'continuum' hypothesis has been proposed by Ryback (1971), who reviewed studies concerning memory and alcohol. Ryback (1971) hypothesized that the effects of alcohol on cognitive functions run from very mild effects in social drinkers, through more severe impairments in alcoholic patients to ultimately the neurocognitive deficits apparent in Wernicke-Korsakoff syndrome patients. This hypothesis was based on a review of research on the effects of acute alcohol manipulations, sober alcoholics, and Wernicke-Korsakoff syndrome patients. Evidence for the 'continuum' hypothesis stems from neuropsychological and ERP research in both alcohol dependent participants (Ciesielski et al 1995; Dao-Castellana et al 1998; Ratti et al 1999; Demir et al 2002; Patterson et al 1987; Glenn et al 1996; Porjesz and Begleiter 1996; Rodriguez et al 1999; Malone et al 2001; Cohen et al 2002; Polo et al 2003) and social drinkers (Parker and Noble 1977; Nichols and Martin 1993; Nichols and Martin 1996; Parsons 1998).

The effects of alcohol were more pronounced in the studies assessing alcohol dependent participants than in the studies on social drinking participants. In his review on the neurocognitive deficits in alcoholics and social drinkers Parsons (1998) showed that the studies on heavy drinkers with a high regular alcohol intake (more than 21 standard glasses per week) found more neurocognitive deficits than studies on drinkers with low regular alcohol intake (less than 21 standard glasses per week). The latter findings are in contrast with those reported in the review of Parsons (1986), in which cognitive decline was found in alcoholics but not in social drinkers. These results led Parsons (1986) to accept the step-wise hypothesis: only after passing the 'alcoholic' threshold, cognitive decline would start. The fact that, in his later review in 1998, Parsons also found cognitive deficits in social drinkers, led him to abandon the step-wise hypothesis and switch to the continuum hypothesis.

HYPOTHESIS OF ALCOHOL AND AGING

Some similarities seem to exist between the neurocognitive effects of aging and alcohol use. Therefore, two hypotheses have been formulated to explain a possible relationship between alcohol and aging. First, there is the 'increased vulnerability' hypothesis (Jones and Parsons 1971), which states that with increasing age the brain becomes more vulnerable for the chronic effects of alcohol. Thus, the older brain is more affected by the same amount of regular alcohol consumption than a younger brain. This would result in an interaction as shown in Figure 2. With increasing age the cumulative lifetime alcohol intake also increases, probably one of the factors that may contribute to the pattern of results predicted by the 'increased vulnerability' hypothesis.

The second hypothesis about alcohol and aging is the 'accelerated aging' theory of Ryan and Butters (1984), which states that alcohol adds to the aging process. Thus, due to alcohol intake, the brain of an alcoholic becomes old before its time. This implies that the difference between alcoholics and controls will be equal in young and in older participants, resulting in two parallel lines as shown in Figure 2.

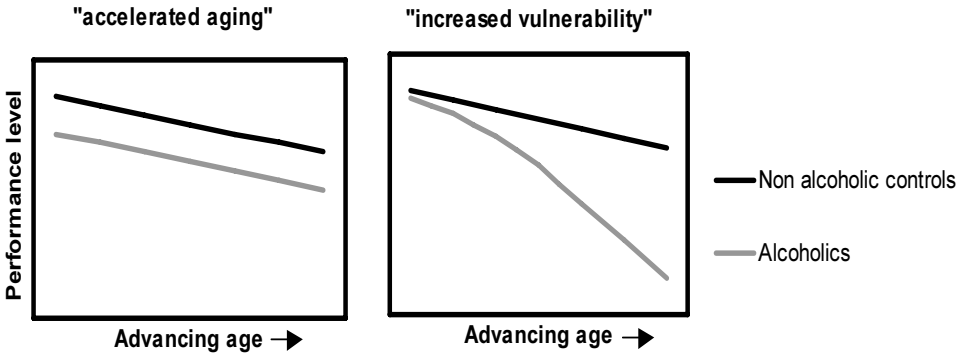

Figure 2. Two models are displayed for the relation between alcoholism and aging. The 'accelerated aging' hypothesis suggests that aging begins earlier in alcoholics than in age-matched controls. The 'increased vulnerability' hypothesis suggests that older alcoholics tend to have more neuropsychological impairments than do younger alcoholics, who may even appear normal on neuropsychological tests (from: Ellis and Oscar-Berman 1989).

The 'increased vulnerability' and 'accelerated aging' hypotheses do not exclude each other, and thus a combination of these two mechanisms is possible. Evidence for the 'increased aging' hypothesis has been described in the extensive review by Ellis and Oscar-Berman (1989), and in the review on alcohol-related evoked potential research by Porjesz and Begleiter (1982). However, Noonberg et al (1985) specifically tested the two hypotheses with a neuropsychological test battery known to be sensitive to alcoholism and to aging, and found clear evidence for the 'increased vulnerability' hypothesis. The 'increased vulnerability' and/or 'accelerated aging' theories have also been addressed by some imaging studies (Pfefferbaum et al 1997; Kubota et al 2001), but no firm conclusion about which theory would be most appropriate could be drawn from these studies, since these studies do not report possible interaction effects between alcohol and age.

GENETIC FACTORS AND ALCOHOL CONSUMPTION

Research has shown conclusively that familial transmission of alcoholism risk is at least in part genetic and not just the result of family environment. Alcoholics are more likely than nonalcoholics to display the Taq I A1 restriction fragment length polymorphism of the D2 dopamine receptor gene, which has been found in 69% of alcoholics, as compared to 20% in non-alcoholics (Smith et al 1992). Another gene polymorphism, a mutant ALDH2*2 allele, can affect the rate of metabolism of alcohol, which is most clearly illustrated by the fact that the mutant ALDH2*2 allele is present in many Asian people (Wall et al 1997), who get intoxicated faster by alcohol and experience more hangover effects than most Caucasian people.

Another approach to investigate the genetics involved in alcoholism is to look at the expressions of these genes. In ERP studies comparisons have been made between individuals with and without familial influences of alcohol related problems. Smaller amplitudes of the parietal P3 component have repeatedly been found in ERP research in alcoholism, which might be comparable to the diminished P3 amplitudes found in participants at high risk for alcoholism (Polich et al 1994; Van Der Stelt et al 1994; Porjesz and Begleiter 1996; Van Der Stelt et al 1998). Pfefferbaum et al (1991) showed that alcoholics with a negative family history of problem

drinking showed normal P3 amplitudes, whereas alcoholics who reported a positive family history showed reduced P3 amplitudes. These authors also demonstrated, with a hierarchical regression analysis, that the smaller P3 amplitudes in family history positive alcoholics were related to their family history positivity, and were independent of their lifetime alcohol consumption. Differences between family history positive and negative non-alcoholic participants have been found for the auditory mis-match negativity (a negative difference wave around 200 ms; Zhang et al 2001). However, these results seem less robust than the diminished P3 amplitudes. For example, in a study by Van Der Stelt et al (1997), no differences in mis-match negativity between children of alcoholics and controls were found. In addition, some genetic influence on the N1 was found in a twin study (O'Connor et al 1994). However, evidence for effects of genetic determinants of alcoholism on the N1 and N2 amplitudes was less clear, which led Porjesz and Begleiter (1996) to the conclusion that the N1 and N2 are probably more state than trait markers of alcoholism, whereas the P3 amplitude clearly reflects genetic determinants of alcoholism.

THE CURRENT STUDY

The aim of this study was to investigate the consequences of chronic non-pathological drinking, i.e., social drinking, on brain functioning. To investigate these effects, socially drinking participants were assessed in a number of ERP tasks.

SOCIAL DRINKING

Since there is no universally adapted definition of social drinking, we have defined social drinkers as people who drink alcohol on a regular basis, but do not meet the DSM-IV criteria for alcohol dependence or abuse. An exception was made for the excessive drinkers who reported to drink more than 60 standard units per week; five of them met the DSM-IV criteria for alcohol dependence. We have chosen to report the consumption of alcohol in terms of standard glasses, containing 12 grams of alcohol per week. The amount of alcohol per week was measured with a drinking diary (Lemmens 1994) and the Lifetime Drinking History (LDH) questionnaire (Skinner and Sheu 1982; as adapted for the Netherlands by Lemmens et al 1997). Lemmens (1994) showed that the self-reported drinks at home contained more than the presumed standard and that this deviation was higher for spirits than for wine. Therefore, we adapted the policy to discuss the drinking diary and LDH questionnaire with the participant, to find out if the alcohol content of each glass reported was indeed 'standard' or if the amount of alcohol varied due to the use of larger/smaller glasses. It obviously made a difference if a participant reported a glass or a bottle of beer; or if a glass of wine was filled halfway, or to the edge. If necessary, the amount of alcohol consumed was recalculated to standard drinks per week. In addition, the exact brand of beverage was asked to correct for possible differences in alcohol content, which was especially variable with different kind of beers.

Participants were divided into four groups based on the two-week drinking diary. The light social drinkers group drank regularly, but not more than 6.25 standard glasses per week, the moderate social drinkers drank more than 6.25, but less than 21 standard glasses per week. The heavy social drinkers drank more than 21, but less than 60 glasses per week and the excessive drinkers group drank more than 60 units per week (see Figure 3).

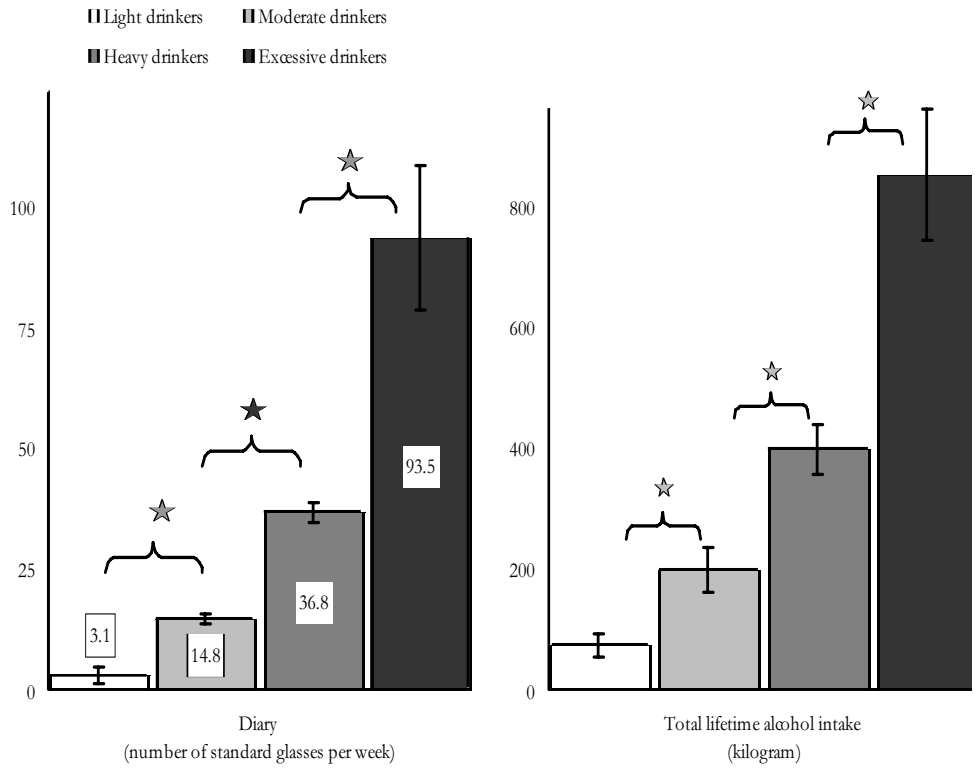

Figure 3. Mean ± SEM for the number of standard glasses a week as reported in the drinking diary and the total lifetime alcohol intake in kilograms for the four groups. Significant differences between groups are marked with stars. Black stars indicate p values <0.001; grey stars indicate p values < 0.05: Post-hoc Dunnet-T3 test was used.

Since men and women differ in their metabolism of alcohol, we will only discuss male participants in this study. In addition, to exclude genetic influences that might be reflected by decreased P3 amplitudes, we only included participants without a family history of alcohol related problems in the first or second degree. Thus, to control for possible sex differences, genetic influences and effects of age in this study, we included similar age groups of male participants without a family history of alcohol disorders.

THE TASKS

Five ERP tasks were used to investigate the effects of social drinking on the brain. The tasks measured a variety of functions. However, the emphasis in all tasks was on cognitive functions for which the integrity of the frontal lobes is thought to be indispensable. The emphasis on frontal tasks was motivated by our hypothesis that alcohol consumption might firstly and perhaps most seriously affect the integrity of the frontal brain areas. However, in order to be able to contrast effects on frontal and those on other brain regions, also parietal and occipital ERP components were investigated; as well as ERP components recorded over the left and right hemispheres. The verb generation task and the computerized version of the Wisconsin card-

sorting tasks were used since those tasks resemble the verbal fluency tasks and Wisconsin card-sorting task used in behavioral neurocognitive studies in which alcoholics have been found to differ from controls (Ciesielski et al 1995; Dao-Castellana et al 1998; Ratti et al 1999; Demir et al 2002). The verb generation is known to activate, among other areas, the left frontal parts of the brain. The functions associated with the specific ERP components in the verb generation task are aspects of attention, response preparation, semantic processing, semantic integration, and word form recognition (Snyder et al 1995; Abdullaev and Posner 1998).

The Wisconsin card-sorting test is a working memory task typically categorized as probing frontal function. The ERP components associated with this task are probably related to orienting of attention, shifts in attention, and the updating of context (Barcelo et al 1997; Barcelo 2003). The continuous performance task was used since it has been found to activate the frontal lobe (Kiefer et al 1998; Falkenstein et al 1999; Bokura et al 2001). In addition, this task is thought to measure inhibitory control and response preparation, which in turn have been associated with substance use disorders such as alcoholism (Vogel-Sprott et al 2001). Furthermore two attention tasks were used, one visual, and the other an auditory task. These attentional tasks have often been used in ERP research, and are thought to activate frontal, parietal and occipital areas (Porjesz and Begleiter 1996). Visual attention and auditory odd-ball tasks have revealed ERP components related to aspects of (selective) attention and template matching, which differed between alcoholics and controls (Porjesz and Begleiter 1996).

HYPOTHESIS

In the present study we investigate the hypothesis that with increasing amounts of regular alcohol intake more differences, in terms of ERP components and tasks, will be found between the groups. Furthermore, we assume that effects of alcohol will be most pronounced in the ERP components thought to be a reflection of activity in the frontal lobes. In the heavy social drinkers group and the excessive drinkers group the effects of alcohol might expand to ERP components measured from e.g. the parietal scalp sites. In addition, behavioral effects are also only expected in the heavy and excessive drinkers.

In the following chapters, the results will be discussed of the verb generation task, the Wisconsin card-sorting task, the continuous performance task, and the attention tasks respectively. In the last chapter, an overview and discussion of the results will be given.

Chapter 2

The Verb Generation Task

ABSTRACT

In alcohol dependent subjects aberrations in electrical brain functioning, as measured with Event Related Potentials (ERPs) have been reported, but few studies have focused on social drinking.

To assess effects of chronic social drinking on the brain, an ERP verb generation task was used, which comprises two conditions (generating verbs describing the use of visually presented nouns; reading nouns aloud).

Study 1 included moderately and heavily social drinking students. Generating evoked more negativity than reading in the heavy group at F6 (right frontal; 700-800 ms). At a longer latency (1250-1500 ms), generating evoked more positivity in the moderate group. Study 2 included older (mean age 50) light, moderate and heavy social drinkers, and excessive drinkers. Light social drinkers, but not the other groups, showed more positivity during generating than during reading at Fz (mid-frontal; 120-220 ms) and F6 (700-800 and 1250-1500 ms). More negativity was found during generating in the excessive than in the heavy group at F4 (right-frontal; 1000-1250 ms).

During a cognitive task, moderate, heavy, and excessive drinkers show abnormal brain potentials over frontal areas.

*)This chapter has been sumitted as: Suzanne Bijl, Eveline A de Bruin, Maria G Veldhuizen, Koen B E Böcker, J Leon Kenemans, Marinus N Verbaten: Effects of chronic social drinking in a verb generation task; an Event Related Potential study

INTRODUCTION

Excessive use of alcohol can lead to changes in the structure of the brain. Structural imaging studies have shown that frontal brain areas seem most vulnerable to damaging effects of consuming large amounts of alcohol over an extended period of time (Pfefferbaum et al 1997; Dao-Castellana et al 1998; Fadda and Rossetti 1998; Kril and Halliday 1999; Ratti et al 1999; Demir et al 2002). In addition, neurocognitive evidence for impairments of brain functioning in alcoholics (Parsons 1994; Fox et al 2000) has been found using cognitive tasks that rely on the integrity of the frontal brain areas (Ciesielski et al 1995; Dao-Castellana et al 1998; Ratti et al 1999; Demir et al 2002). Abnormalities in alcoholics have also been shown in event related potential (ERP) studies using tasks that aim to measure various aspects of attention (see for a review Porjesz and Begleiter 1996).

Few studies have focused on social drinking. The one study examining structural changes revealed that non-alcoholic heavy drinkers were more vulnerable to shrinkage of the brain than moderate drinkers (Kubota et al 2001). Other evidence on the effects of social drinking is available from studies using neuropsychological tests. Parsons and Nixon (1998) reviewed 17 studies, of which only seven found that 'heavy' social drinkers performed significantly worse on one or more cognitive tests compared to the 'moderate' social drinkers. These conflicting results could be due to differences in criteria for heavy and moderate social drinking. All the studies described by Parsons and Nixon (1998), that revealed significant impairments used heavily drinking participants who consumed more than 21 standard units per week. Apart from this, Parsons and Nixon (1998) suggested that the changes in the brains of 'heavy' social drinkers, who drank less than 21 standard units per week, are too subtle to detect with behavioral tests. Three ERP studies that investigated differences between heavy and moderate social drinkers found significantly altered ERP components in the heavily drinking group, in the absence of behavioral differences (Nichols and Martin 1993; Fox et al 1995; Chao et al 2003). This indicates that ERPs can provide a sensitive method for assessing subtle changes in brain functioning in social drinkers, even when the behavioral performance is not affected.

A suitable paradigm to reveal changes in brain functioning is the verb generation task. This task includes an experimental condition, in which participants generate a verb describing the use of a visually presented noun, and a control condition, in which they just read the noun aloud. Positron emission topography (PET; Wise et al 1991; Posner and Raichle 1994; Fiez et al 1996; Poldrack et al 1999), functional magnetic resonance imaging (fMRI; McCarthy et al 1993; Poldrack et al 1999; Cabeza and Nyberg 2000) and ERP (Snyder et al 1995; Abdullaev and Posner 1998) studies have revealed task effects in frontal, parietal, and occipital areas.

Table 1: Comparison of ERP sources and PET data based on Abdullaev and Posner (1998)

Time	ERP	PET
170 ms	Frontal midline	Anterior cingulate cortex
200 ms	Left occipital cortex	Visual word form area
220 ms	Left inferior frontal cortex	Left inferior prefrontal cortex
600 ms	Left parietal-temporal cortex	Wernickes area
800 ms	Right anterior temporal cortex	Right insula

Therefore, the verb generation paradigm should be sensitive to frontal impairments, as well as provide clues to the specificity of these frontal impairments. The findings of Abdullaev et al (1998) with respect to the PET and ERP sources are summarized in Table 1, showing the brain areas that are activated during verb generation relative to reading and their timing.

Abdullaev and Posner (1998) proposed that the initial activation in the anterior cingulate cortex reflects attention. The second activation in the visual cortex would reflect processes contributing to word form recognition. The third activation in the left inferior frontal cortex would reflect semantic processing, the subsequent activation in Wernickes area semantic integration, and the final activation in the right insula response preparation (Snyder et al 1995; Abdullaev and Posner 1998).

The present work included two studies aimed at assessing the effects of chronic alcohol consumption during verb generation, using ERPs.

Study 1 compared young students drinking either moderately or heavily. Study 2 compared four groups of social drinkers with a mean age of approximately fifty years. For study 1 we expected ERP differences between the moderately and heavily social drinking students, especially at frontal scalp locations. These effects might occur in the absence of any behavioral differences between the two groups. Since the cumulative lifetime alcohol intake rises with increasing age, and since it is shown that older brains are more vulnerable for damaging effects of alcohol (Pfefferbaum et al 1997; Kubota et al 2001), we expected even more pronounced ERP abnormalities as a function of drinking history and regular alcohol consumption in study 2, especially over frontal areas. Again, these abnormalities might be revealed in absence of behavioral effects, in particular in the moderate social drinkers.

MATERIALS AND METHODS

PARTICIPANTS

In- and exclusion criteria for study 1 and 2

All participants were treated in accordance with the declaration of Helsinki and all participants provided written informed consent before participating in the studies. In both studies, participants were right-handed (determined with the Edinburgh Handedness Inventory), had good (corrected) sight and hearing, and spoke Dutch as first language. To control for genetic influences participants were excluded if they (ever) had alcoholic relatives in the first or second degree. In addition, participants were excluded if they had a history of epilepsy, cardiovascular deficits, liver deficits, loss of consciousness due to head injury, psychiatric or neurological deficits, relatives with psychiatric or neurological deficits, problems with speech, such as stuttering, or any other medical history, which could influence the experiment. They were also excluded if they were excessively using nicotine (>40 cigarettes a day) and/or caffeine (>10 cups of coffee a day) or were using other psychotropic agents. Before running the experiment, a medical questionnaire was filled out by the participants, to exclude participants with any of the above-mentioned disorders. To obtain estimates of recent and lifetime alcohol consumption participants completed The Lifetime Drinking History (LDH) questionnaire (Skinner and Sheu 1982; as adapted for the Netherlands by Lemmens et al 1997).

Participants study 1

All participants in study 1 were male students at Utrecht University between 22 en 30 years of age. Participants were paid 7 euros per hour; the total duration of the experiment was approximately 2.5 hours. A two-week drinking diary, in which participants filled in the number of alcoholic drinks consumed each day, was used to identify thirteen moderate and thirteen heavy social drinkers. The heavy social drinkers consumed more than 30 standard drinks of alcohol (12 gram) per week and the moderate social drinkers consumed less than 30 standard drinks of alcohol per week.

Participants study 2

Male participants between 30 and 65 years of age were recruited with advertisements in local and national newspapers; excessive drinkers were also recruited at in-patient treatment centers. Participants were paid 70 euros for completing the whole experiment, which included a telephone screening, a medical screening, a task session including ERP recording and a magnetic resonance imaging (MRI) session.

A two-week drinking diary was used to assign the participants to the light (n=14), moderate (n=16) or heavy social drinkers groups (n=19). According to the drinking diary the light drinkers were not total abstainers and consumed at maximum 6.25 standard drinks per week, the moderate social drinkers consumed between 6.50 - 19.75 standard drinks per week, and the heavy social drinkers consumed between 21.00 - 52.70 standard drinks per week. Excessive

drinkers (n=10) drank more than 60 standard drinks per week and five of them scored for alcohol dependence according to the DSM-IV criteria. Participants were screened at the University Medical Center Utrecht. Screening included the composite international diagnostic interview (CIDI; by Robins et al 1988), the Dutch reading test for adults (equivalent of the NART; Schmand et al 1991), an electrocardiogram (ECG), hematology and blood chemistry screening, and sight and hearing tests.

PROCEDURE

Participants were asked to abstain from smoking for at least three hours before the experiment and to refrain from drinking alcohol for 24 hours before the experiment. Blood Alcohol Levels were determined with a breath test device (Alcotest, Dräger Medical, Lübeck, Germany) and urine screening was done for THC, cocaine, barbiturates, benzodiazepines and morphine (Rapid Drug Testing Services, Inc; Key Largo, US). When participants tested positive another appointment was made for the ERP session; participants were excluded when tested positive twice. Participants were instructed not to drink coffee or tea on the day of the experiment. After the electrodes for ERP recording had been attached, participants were escorted to the electrically shielded, soundproof cabin and seated in a chair at a distance of 100 cm from a computer monitor. They were instructed to sit still and to watch a fixation cross on the monitor during tasks. When reading the words aloud, participants had to restrict their chin and head movements. In study 1, the experiment consisted of three tasks: a verb generation task, a visual attention task, and an EEG mental rehearsal task. In study 2, the experiment consisted of six tasks: a verb generation task, a visual attention task, a go/nogo task, a card-sorting task, an auditory odd-ball task, and an EEG mental rehearsal task. Here we report the results of the verb generation task. The order of these tasks was balanced across participants. The word generation task consisted of two blocks (reading and generating), and the order of these blocks was balanced across participants.

VERB GENERATION TASK

In the verb generation task, participants had to verbally generate 100 verbs related to visually presented nouns (e.g., hammer-pound). In the control condition, participants were asked to read the visually presented nouns aloud (100 words). On a rating scale from zero (unknown) to seven (highly imaginable) the nouns had an imaginability score between six and seven (van Loon-Vervoorn 1985). All nouns consisted of one or two syllables and three to six letters, not related to alcohol and did not refer to food, were not derived from a foreign language, and were not multifunctional. Participants were instructed not to produce the verbs by simply adding or subtracting a syllable to the noun (as in bike-biking). All task stimuli were presented with ERTS (Experimental Run Time System, Berisoft). The vertical visual angle of the nouns and the fixation cross was at maximum 1.41°. Three, four, five or six letter words had a maximum horizontal visual angle of respectively 2.68°, 3.68°, 4.28° or 4.89°. The stimuli were white lowercase letters presented on a black background. Word stimuli were presented for 150 ms. The voice response cue consisted of a brightening of the fixation cross, and was presented 2700 ms after word stimulus offset. Participants had to answer within 2700 ms after the voice cue; Figure 1 illustrates the time course of a trial.

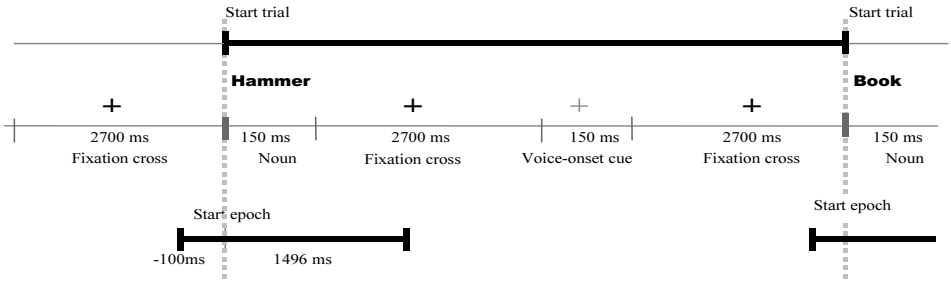

Figure 1. A trial in the verb generation task

Data Recording and Analysis

The voice response cue was presented to avoid vocalization artifacts in the ERPs. Voice onset timing was recorded to discard trials with timing errors (i.e. reading or generating before the voice onset cue), using a microphone and the Exkey logic apparatus (ERTS-Software). All voice responses were also scored offline to detect errors. Before the start of each test condition, the participants generated or read 11 words aloud for practice. Between the first and the second part, the participants rested for about 5 minutes.

EEG was recorded using an electrode cap with 64 tin electrodes (see Figure 2), with the left mastoid as reference. Horizontal electro-oculogram (HEOG) was recorded from the outer canthus of each eye and, vertical electro-oculogram (VEOG) was from electrodes placed infra- and supra- orbitally to the left eye. The ground electrode was placed at AFz. Impedance was kept below 10 kW. All signals were amplified by Synamps amplifiers with online low-pass filters at 50 Hz and high-pass filters at 0.10 Hz. Signals were digitized at 250 Hz.

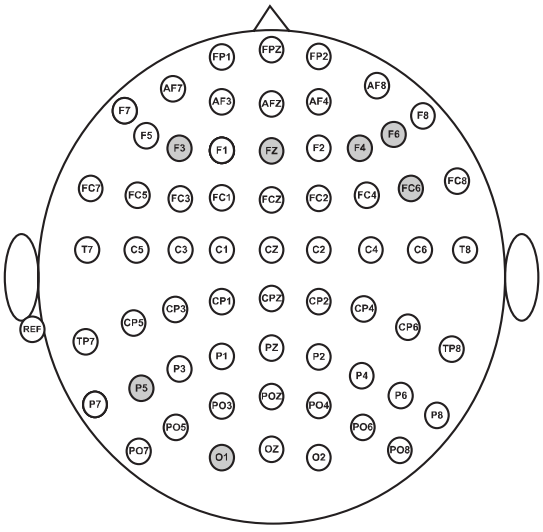

Figure 2. Electrode layout of the 64 lead Quick-cap; the tested replication leads are shown in gray

EEG data were epoched for 1596 ms, starting 100 ms before word stimulus onset. For each trial, the mean amplitude during the 100 ms preceding stimulus onset served as baseline. Off-line, all signals were filtered with a 30 Hz low-pass filter, and all EEG channels were used to calculate an average reference. Trials with amplifier blocking, artifacts, flat lines, or behavioral errors were detected off-line and omitted from further analysis. Ocular artifacts were estimated and subtracted by time-domain regression analysis (Gratton et al 1983). All trials with minimum to maximum amplitude of more than 100 μV after the ocular artifact correction were omitted from further analysis. Trials with incorrect responses were also omitted from analysis. Averages were calculated after sorting trials per condition.

STATISTICAL ANALYSIS

Performance

Statistical analyses were performed using the SPSS software (SPSS 10.0, SPSS Inc., Chicago, IL, USA). Timing errors were defined as the absence of a response in the 2700 ms response window. Retrieval errors were defined as inappropriate verbs or non-verbs (generating condition only). Averages were calculated for timing errors in the reading aloud condition and for timing and retrieval errors in the generating condition. Differences between the groups in these three different error types were tested with ANOVA, using Group as between subjects factor.

ERPs

Preplanned statistical comparisons were performed with respect to the mean amplitudes in selected segments, and selected electrode leads, based on the task effects reported by Snyder et al. (1995), as well as visual inspection of the data. The following segments were tested (see Figure 2): Fz 120 - 220 ms, O1 150 - 250 ms, F3 200 - 300 ms, P5 700 - 800 ms, F6 700 - 800 ms, and F6 1250 - 1500. The comparisons were performed using ANOVA with Group as a between- and Task (Generating versus Reading) as a within-subjects factor. In all tests, a critical α-level of 0.05 was used. Group*Task interactions were delineated by pairwise comparisons and Bonferroni corrections. In study 1 the amount of cigarettes smoked per week was used as a covariate, as the Groups in this study differed on this variable.

RESULTS STUDY 1

DRINKING HISTORY AND DEMOGRAPHIC VARIABLES

A description of age and of alcohol and cigarette consumption for the 13 moderate and 13 heavy drinkers is given in Table 2. Moderate and heavy student drinkers were of similar ages. The two groups did not differ with respect to the number of participants who smoked, but did differ with respect to the average number of cigarettes smoked per week, which was higher in the heavy group. As expected, the daily alcohol intake as well as the lifetime alcohol intake was higher in the heavy group.

Table 2. Mean age, estimation of the number of glasses consumed a week (12 gram of alcohol) and number of cigarettes smoked a week for the light and heavy social drinkers in study 1

	Light drinkers Mean ± SD	Heavy drinkers Mean ± SD	F (1,25)
Age	23.97 ± 1.50	23.92 ± 1.64	0.006
Smoking (Number of cigarettes a week)	0.62 ± 1.56	8.08 ± 8.55	9.59***
Diary (Number of glasses a week)	21.12 ± 6.64	51.48 ± 10.40	78.777****
Total lifetime alcohol intake (Cumulative in kilograms)	64.95 ± 20.45	149.94 ± 113.55	7.055**

** P < 0.02; *** P < 0.01; **** P < 0.001

PERFORMANCE

No significant differences between the two groups were found for timing errors in the reading or in the verb generation condition, or for retrieval errors in the latter condition.

ERPS

Grand average ERPs during generating and reading, collapsed across groups, are shown in Figure 3. Figure 4 depicts difference waves (Generating minus Reading), superimposed for the two groups.

At Fz the mean amplitude in the generating condition between 120 and 220 ms was significantly more positive than that in the reading condition ($F(1,23) = 7.22$; $P < 0.05$). No Task*Group interaction was found at Fz for this segment (see Figure 4). At O1 (150-250 ms), the ERP in the generating condition was significantly more negative than that in the reading condition ($F(1,23) = 8.07$; $P < 0.01$). No Task*Group interaction was found for this segment (see Figure 4). At F3 (200-300 ms), the difference between generating verbs and reading aloud did not reach significance, although there was a trend towards more positivity during generating than during reading ($F(1,23) = 4.07$; $P = 0.056$). No Task*Group interaction was found for this segment (see Figure 4). At P5 (700-800 ms), there was more positivity during generating than during reading ($F(1,23) = 4.88$; $P < 0.05$). No significant Task*Group interaction was found for this segment (see Figure 4).

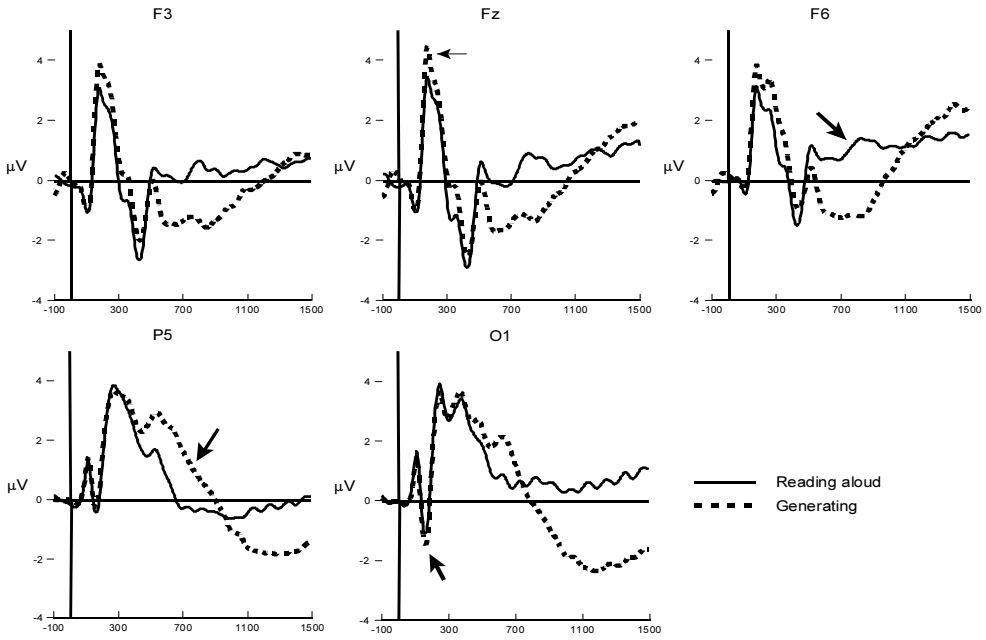

Figure 3. ERPs of the generating verbs condition and the reading aloud condition for the heavy and light social student drinkers of study 1 together (N=26). Areas indicated with an arrow show significant task effects

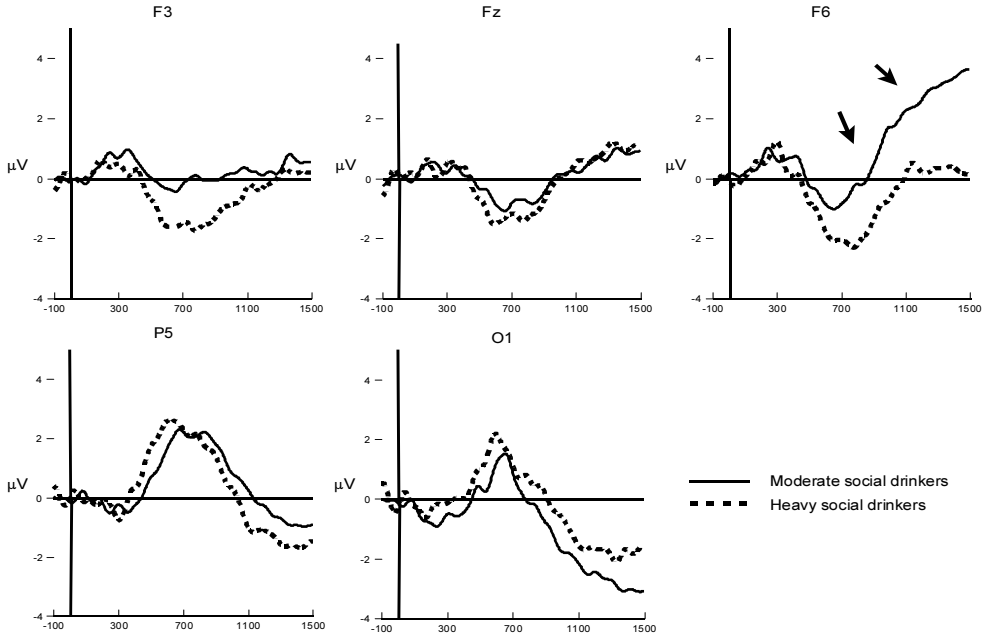

Figure 4. Difference waves (generating minus reading aloud) for the moderate and heavy drinkers of study 1. Areas indicated with an arrow show significant Group*Task interaction effects.

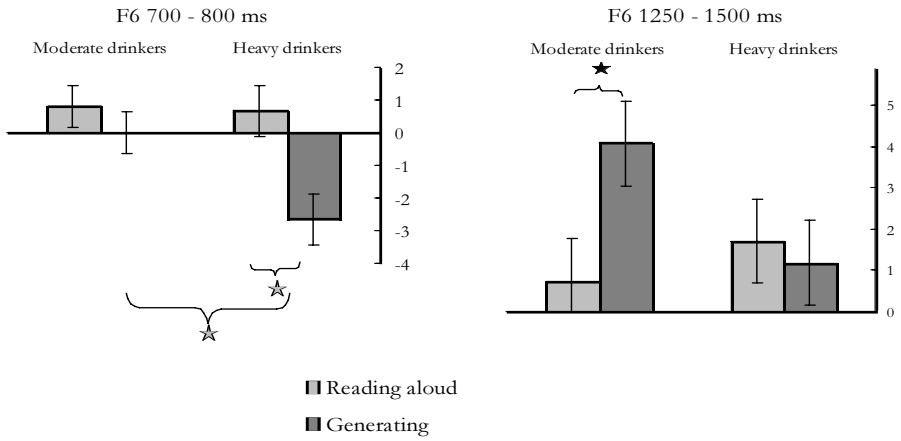

Figure 5. Histogram of the ERP components in study 1, which showed significant Task*Group interactions

At F6 (700-800 ms), there was more negativity during generating than during reading ($F(1,23) = 8.03$; $P < 0.01$). A significant Group*Task interaction was found ($F(1,23) = 4.71$; $P < 0.05$; see Figure 4). Post-hoc tests showed more negativity during generating verbs than during reading aloud for the heavy social drinkers ($F(1,11) = 6.19$; $P < 0.05$). No such task effect was found for the moderate social drinkers. From 1250 - 1500 ms at F6, the difference between generating and reading depended on group (Group*Task interaction; $F(1,23) = 11.39$; $P < 0.01$; no main effects; see Figure 4). Post-hoc tests showed more positivity during generating condition than during reading for the moderate social drinkers ($F(1,11) = 14.00$; $P < 0.01$), but not from the heavy group (see Figure 5).

RESULTS STUDY 2

DRINKING HISTORY AND DEMOGRAPHIC VARIABLES

A description of Age, IQ as measured with the NLV, and smoking for the four Groups is given in Table 3. All groups were of similar ages, had similar NLV scores, and did not significantly differ in the amount of cigarettes smoked a week. As expected, groups differed in the number of glasses a week reported in the drinking-diary ($F(3,53) = 59.82$; $P < 0.001$), and in the total lifetime alcohol-intake ($F(3,55) = 35.98$; $P < 0.001$) (see figure 6). Two participants in the excessive group did not fill in the drinking diary as they had abstained from drinking alcohol two weeks before inclusion in the study but these participants did fill in the LDH questionnaire on which the total lifetime alcohol-intake was based.

Table 3. Mean, Standard Deviation (SD), F-value and P-value for Age, IQ (as measured with the NLV) and number of cigarettes smoked a week for the four drinking Groups in study 2

	Light drinkers Mean ± SD	Moderate drinkers Mean ± SD	Heavy drinkers Mean ± SD	Excessive drinkers Mean ± SD	F (df)	P
Age	47.2 ± 9.7	50.2 ± 8.0	51.9 ± 8.0	49.4 ±8.0	.87 (3,55)	n.s.
NLV IQ	108.0 ±9.0	105.1 ± 7.0	110.3 ± 5.2	103.8 ± 11.2	2.02 (3,55)	n.s.
Smoking (number of cigarettes a week)	3.3 ± 0.9	5.2 ± 1.3	9.7 ± 4.6	9 ± 5.2	1.32 (3,55)	n.s.

(n.s. = not significant)

PERFORMANCE

No significant differences between the four groups were found with respect to Timing errors in the reading aloud or in the verb generation condition. However, a significant Group effect was found on the average number of Retrieval errors ($F(3,55) = 3.39$; $P < 0.05$. Pairwise comparisons revealed a trend towards more retrieval errors for the excessive drinkers compared to the heavy drinkers ($T(1,27) = 2.64$; $P = 0.07$) (see figure 6).

ERPS

ERPs for the generating condition and the reading condition, collapsed over groups, are shown in Figure 7. Figure 8 depicts difference waves (Generating minus Reading), superimposed for the two groups.

At Fz (120-220 ms) generating resulted in a larger positivity than the reading condition ($F(1,55) = 12.970$; $P < 0.01$). Furthermore, a Task*Group interaction was found ($F(3,55) = 2.86$; $P< 0.05$) (See figure 7). Post-hoc tests revealed significant larger positivity for the generating compared to reading condition only in the light social drinkers group ($F(1,13) = 9.63$; $P < 0.01$; see Figure 7). At O1 (150-250 ms), the generating verbs condition resulted in a larger negativity than the reading condition ($F(1,55) = 14.11$; $P < 0.001$). No Task*Group interaction was found for this segment (see Figure 7). At F3 (200-300 ms), the mean amplitude in the generating con-

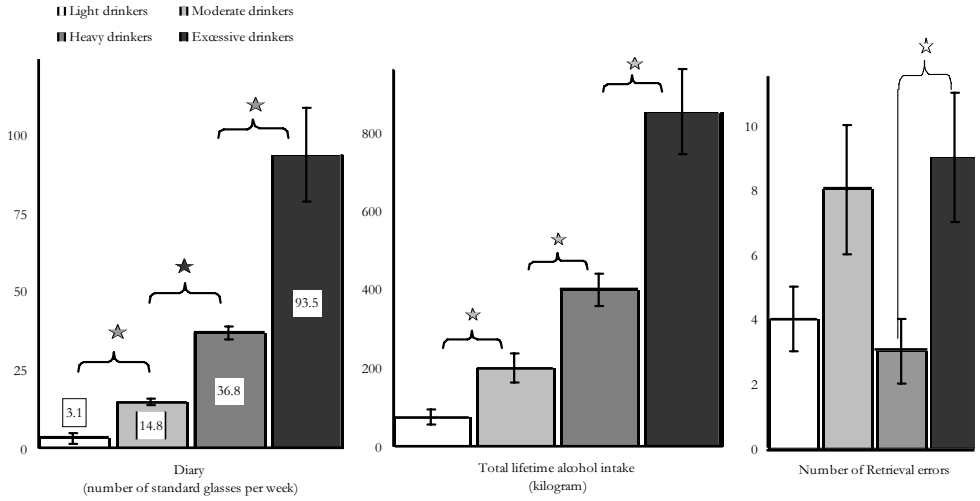

Figure 6. Mean ± SEM for the number of standard glasses a week as reported in the drinking diary and the total lifetime alcohol intake in kilograms for the four groups. Mean number of retrieval errors for the four groups of study 2. Differences between groups are marked with stars. Black stars indicate p values <0.001; Grey stars indicate p values < 0.05; White stars indicate trends. Post-hoc Dunnet-T3 test is used for the alcohol measures

dition was significantly more positive than that in the reading condition ($F(1,55) = 19.84$; $P < 0.001$). No Task*Group interaction was found for this segment (see Figure 7). At P5 (700-800 ms), the mean amplitude was significantly more positive during generating than during reading ($F(1,55) = 53.64$; $P < 0.001$). No Task*Group interaction was found for this segment (see Figure 7). At F6 (700-800 ms), the mean amplitude during generating did not differ from that during reading. However, a Group*Task interaction was found ($F(3,55) = 3.07$; $P < 0.05$) (See figure 7). Post-hoc tests revealed a trend towards larger positive amplitudes during generating than during reading, in the light drinkers group only ($F(1,13) = 4.43$; $P = 0.055$). The mean amplitude in the generating condition between 1250-1500 ms at F6 did not differ from that in the reading condition. However, a Group*Task difference was found ($F(3,55) = 3.39$; $P < 0.05$) (See figure 7). Post-hoc tests revealed significantly larger mean amplitudes for the generating condition, compared to the reading condition, in the light drinkers group only ($F(1,13) = 6.37$; $P < 0.05$).

Non-planned tests

Visual inspection of the difference wave data suggested an additional analysis at F4 from 1000 - 1250 ms (see Figure 8). No Task effect was found for this segment. However, a Task*Group interaction was found ($F(3,55) = 6.37$; $P < 0.01$). Post-hoc tests (Bonferroni corrected) revealed significantly more positivity during generating than during reading in the heavy group ($F(1,18) = 6.26$; $P < 0.05$), and a trend towards more negativity in the generating condition than in the reading condition ($F(1,9) = 4.36$; $P = 0.067$), for the excessive drinkers (See figure 9). No task effects were found for the other groups.

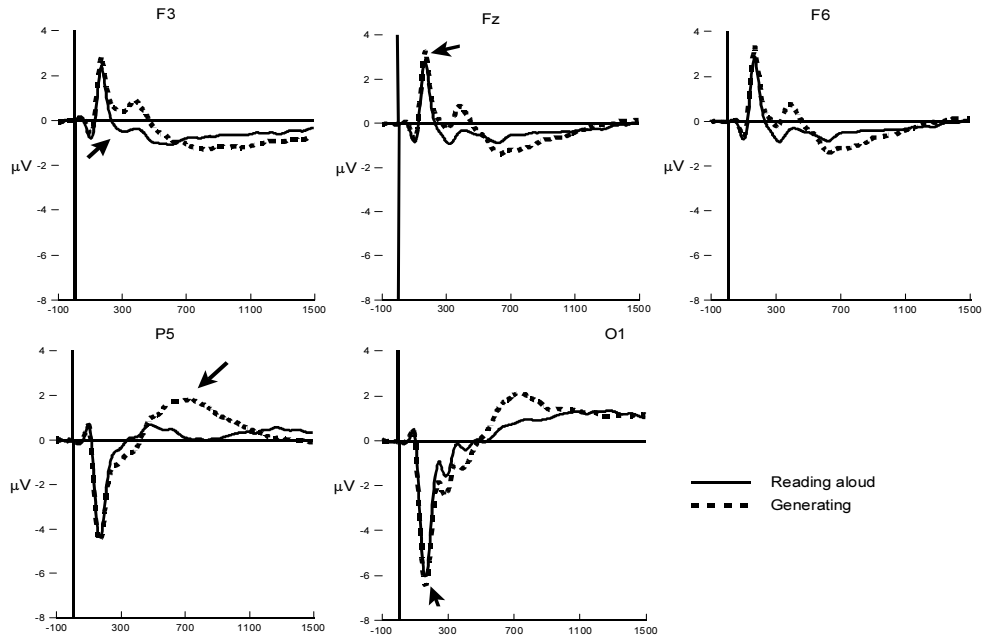

Figure 7. ERPs of the generating verbs condition and the reading aloud condition (N=56). Areas indicated with an arrow show significant task effects

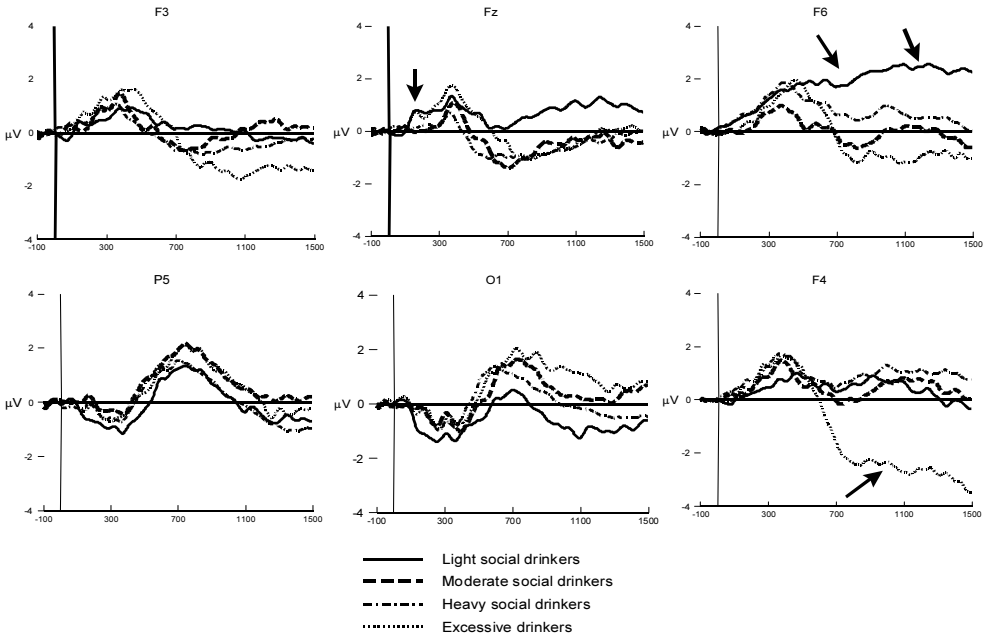

Figure 8. Difference waves (generating minus reading aloud) for the groups of study 2. Areas indicated with an arrow show significant Group*Task interaction effects

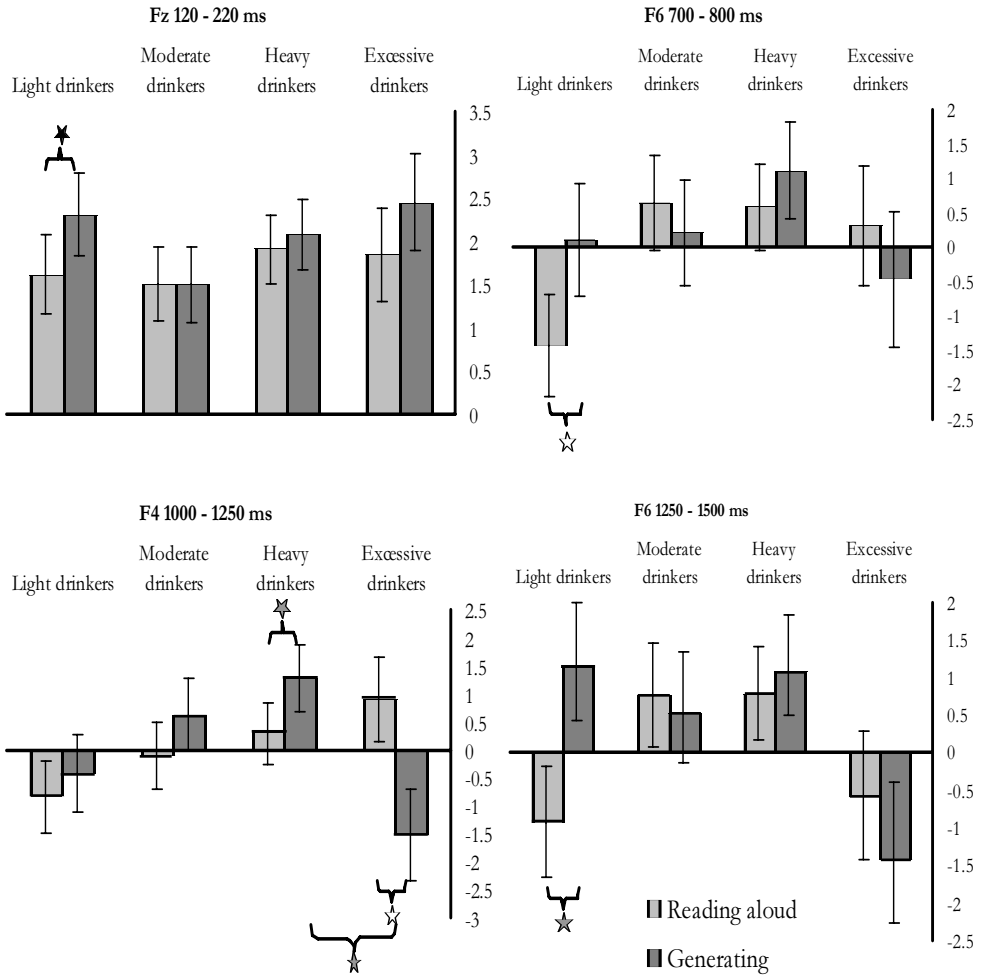

Figure 9. Histogram of the ERP components in study 2, which showed significant Task*Group interactions

DISCUSSION

In this study the verb generation task was used to assess possible differences in brain function between groups that differed in the amount of chronic alcohol consumption, ranging from light, moderate and heavy social drinkers to excessive drinkers. Verb generating, relative to a reading control condition resulted in ERP differences at the expected scalp sites, and in expected latency ranges, replicating earlier research (Snyder et al 1995; Abdullaev and Posner 1998). Differences between groups in these effects were found at the mid- and right frontal scalp locations.

In both studies the ERP results were comparable with the ERP results found in earlier research (Snyder et al 1995; Abdullaev and Posner 1998), although some subtle differences were found with respect to the late components at F6. The significant task effects (i.e., the difference between reading and generating) were found at Fz (120-220 ms), O1 (150 - 250 ms), P5 (700 - 800 ms) and F6 (700 - 800 and 1250 - 1500 ms). At F3 (200 - 300 ms), an expected task effect did not reach significance in study 1 ($p=0.056$), but was highly significant in study 2. The early component at Fz consisted of more positivity for generating than reading, which is probably generated in the anterior cingulate cortex. Posner et al (1998) and Posner and Raichle (1994) argued that this activity reflects higher resource allocation in the generating condition. However, more recent research has linked activation of the anterior cingulate cortex to conflict monitoring (Carter et al 1998; Botvinick et al 2001). In the verb generation condition, conflict could pertain to competing response tendencies, one to read the noun (highly overlearned), and one to generate a verb. The left occipital ERP effect consisted of more negativity for generating verbs, which might be associated with activity in visual cortex contributing to word form processing (Abdullaev and Posner 1998). The more positive ERP during generating at F3 can be related to the identification of word meaning (Posner et al 1988; Posner and Pavese 1998). The more positive amplitude during generating at P5 probably reflects activity in Wernicke's area, related to the integration of word meaning (Posner and Pavese 1998). The overall results in study 1 also showed an exact replication of the bilateral fronto-temporal component at 800-1100 ms latency as reported in earlier research (Snyder et al 1995; Abdullaev and Posner 1998). It consisted of more negativity in generating than reading from 800 ms till 1100 ms, and more positivity from 1100 ms on. Abdullaev and Posner (1998) argue, with reference to Dronkers (1996), that this activity reflects the involvement of the insular/ Sylvian cortex, and that it is related to the planning of articulatory movements. However, Abdullaev and Posner (1998) and the current study, found right hemisphere dominance for this component. In contrast, Dronkers (1996) reported articulatory planning deficits specifically for lesions of the left insular precentral gyrus. Another possibility is that this right frontal component reflects the originality or difficulty of the generated verb.

In study 1, although no significant behavioral differences were found between the moderately and heavily social drinking students, the groups differed significantly with respect to late right-frontally recorded ERP-components (F6). From 700 - 800 ms, there was more task related (generating minus reading aloud) negativity in the heavy group, but not in the moderate group. Here the heavy social drinkers show the same task effect as reported in earlier research (Snyder et al 1995; Abdullaev and Posner 1998), whereas this task effect is absent in the moderate social

drinkers. It might be that the moderate social drinkers generate verbs more quickly than the heavy social drinkers do. However, since this task required a delay of the response no reaction time data could be obtained.

In a later time segment (1250 - 1500 ms) generating verbs results in more positivity than the reading aloud, a shift which was also reported by Snyder et al. (1995). The latter authors reported significantly more positivity during generating than during reading. In the current study 1, this effect was only found in the moderate group but not in the heavy group. The heavy social drinkers showed significantly smaller amplitudes during generating than moderate social drinkers. Snyder et al. (1995) suggested that the late right frontal activity was related to response preparation. We hypothesized that it is more specifically to the originality or difficulty of the generated verb. It might be that the heavy social drinkers generated less original and difficult verbs, and therefore did not show the same task effects as the light social drinkers did.

Study 2 examined the older participants and revealed a significant group effect for retrieval errors; the excessive drinkers group made more retrieval errors than heavy social drinkers did, although this effect was only marginally significant (P=0.07). The other groups did not differ significantly from each other with respect to the behavioral measures. The ERP results at F4 (1000-1250 ms) also showed differences between excessive drinkers and heavy social drinkers, as the former showed more negativity in generating than in reading, whereas the latter showed more positivity in generating than in the reading condition.

A second effect was found at Fz from 120-220 ms. Here, enhanced positivity during generating, relative to reading, appeared only in the light social drinkers group, not in the other groups. This early task effect was also found in the younger participants of study 1, and in other studies using the verb generation task (Snyder et al 1995; Abdullaev and Posner 1998). This activity has been related to the anterior cingulate cortex (Posner et al 1988; Posner and Raichle 1994), and enhanced positivity during generating may reflect intact anterior cingulate activity involved in conflict monitoring (Carter et al 1998; Botvinick et al 2001), which is impaired in the heavier drinking groups.

A similar interaction effect was found at F6 from 700 - 800 ms and from 1250 - 1500 ms. Again the light social drinkers showed more positivity in the generation condition than in the reading condition (albeit at $p < 0.055$ in the 700-800 ms interval), whereas the task effect was absent in the other three groups. Task by Group interactions at F6 were also found in the younger student social drinkers in study 1. The component from 700 - 800 ms showed some inconsistencies between study 1, study 2 and earlier research. The contradictions between the current studies and the studies of Snyder et al. (1995) and Abdullaev and Posner (1998) might be related to the difference between the English and Dutch language. However, since the overall effects of study 1 did resemble their effects and the results of the older participants in study 2 did not, an effect of age might be more likely. Furthermore, when looking at student groups separately the heavy student drinkers showed the same task effect from 700 - 800 ms as found by Snyder et al. (1995) and Abdullaev and Posner (1998).

In study 1, the moderately social drinking students drank less than 30 standard glasses a week, which is intermediate between the amounts for moderate and heavy drinkers among the older participants of study 2. However, moderately social drinking students had a cumulative lifetime

alcohol intake of 65 kilograms, which equals that of the light social drinkers in study 2, with their longer drinking history. Both groups also showed the same task effect at F6, whereas this effect was absent in groups with a higher cumulative alcohol intake. Thus, the absence of this ERP task effect might reflect a toxic effect of cumulative lifetime alcohol intake. As we have hypothesized before, these late task effects at the right frontal site of the brain might be related to a response preparation of originality or difficulty of the generated verb, which could be disturbed with increasing alcohol intake.

In study 1, we expected ERP differences between the moderately and heavily social drinking students especially at frontal scalp locations. These groups did show ERP differences at the right frontal scalp location F6 at relative long latencies. Since the cumulative lifetime alcohol intake rises with increasing age, and since it is shown that older brains are more vulnerable for damaging effects of alcohol (Pfefferbaum et al 1997; Kubota et al 2001), we expected even more pronounced ERP abnormalities as a function of drinking history and regular alcohol consumption in study 2, especially over frontal areas. In the older participants of study 2 additional effects, relative to study 1, were found at the early component at Fz and the right frontal component at F4.

When combining these two studies some additional conclusions can be made. First, the late component at F6 is found in both studies, indicating an effect of chronic alcohol intake on the brain activity independent of age. Second, the early ERP task effect at Fz was present in both groups in study 1, but only in the light group in study 2, whereas the moderate and heavy social drinkers did not show enhanced amplitudes for generating compared to reading. The reduced difference between reading aloud and generating could not be attributed to the effects of alcohol alone, since it was also present in the heavy student social drinkers of study 1, who drank more than the moderate drinkers did in study 2. In addition, this task effect could not be attributed to age alone, since it was present in the older light social drinkers of study 2. Therefore, we conclude that the mid-frontal ERP task effect at Fz is sensitive to both the effects of alcohol and age. Third, for excessive drinkers (more than 60 standard drinks per week), additional abnormalities were found on behavioral measures and with respect to ERPs for the late effect at F4.

In conclusion, during a cognitive task, moderate, heavy, and excessive drinkers show abnormal brain potentials over frontal areas.

Chapter 3

The Wisconsin Card-Sorting Task

ABSTRACT

One of the most widely used neuropsychological tests of frontal lobe function is the Wisconsin Card Sorting Task (WCST). The present study used a computer-adapted version of the WCST to assess the effects of chronic alcohol consumption on the brain. Participants sorted cards according to an initially unknown sorting rule, which referred to either shape, number, or color. The correctness of the chosen sorting rule was indicated by a feedback stimulus. The rule had to be followed for a number of stimuli, and when it changed participants had to find out which rule had to be followed next. A distinction was made between early trials, in which the correct sorting rule had to be figured out, and late trials, in which the known sorting rule was applied. During the task event related potentials (ERPs) were recorded to the target card and to the feedback stimulus in light, moderate and heavy social drinkers and excessive alcohol users.

Behavioral task effects, and also ERP differences between early and late trials were comparable to those from earlier studies that used the WCST. No behavioral differences were found between the four groups. In contrast, a mid-frontal N1 component in reaction to the feedback stimuli did reveal differences between the four groups. In the light and moderate drinkers, on early feedback trials the N1 was larger relative to late feedback trials, but this effect was absent in the heavy social drinkers and excessive drinkers. This reduced N1 effect with increasing alcohol intake could reflect abnormal allocation of attention or impaired conflict monitoring, possibly based on activity in the anterior cingulate cortex.

*)This chapter has been sumitted as: Suzanne Bijl, Eveline A de Bruin, Koen B E Böcker, J Leon Kenemans, Marinus N Verbaten: Effects of chronic social drinking in a Card-Sorting task; an Event Related Potential study

INTRODUCTION

Evidence for impairment of brain functioning in alcoholics has been found using cognitive tasks that rely on the integrity of the frontal brain areas (Ciesielski et al 1995; Ratti et al 1999; Ratti et al 2002; Demir et al 2002). In addition, neuro-imaging studies have found reduced volumes of especially the frontal areas in alcoholics (Pfefferbaum et al 1997; Dao-Castellana et al 1998; Fadda and Rossetti 1998; Kril and Halliday 1999; Ratti et al 1999; Demir et al 2002). The Wisconsin Card sorting Task (WCST) is one of the most widely used neuropsychological tests of frontal lobe function. In the WCST participants have to sort cards according to an initially unknown sorting rule, which could either involve shape, number, or color. Although some debate exists on the exact nature of the frontal functions that would be necessary for adequate performance in the WCST, evidence suggesting at least an important contribution of the frontal brain areas has been found using Positron Emission Tomography (PET) (Berman et al 1995), functional Magnetic Resonance Imaging (fMRI) (Volz et al 1997; Konishi et al 1998; Konishi et al 1999; Monchi et al 2001) and Event Related Potentials (ERPs) (Barcelo et al 1997; Barcelo 1999; Gonzalez-Hernandez et al 2003; Barcelo 2003).

Neuropsychological research has revealed that alcoholics make more errors in the WCST compared to control participants (Joyce and Robbins 1991; Sullivan et al 1993; Ratti et al 2002), although not all studies showed more perseveration errors (Joyce and Robbins 1991; Brokate et al 2003). To our knowledge no attention has been paid to the effects of social drinking on WCST performance. In general, behavioral measures may not be sensitive enough to reveal the more subtle changes in the brain as a result of social drinking. Previous research has shown that ERPs can provide a more sensitive measure of alterations of brain activity in social drinkers, even when the behavioral output is not affected (Fox et al 1995).

In former ERP studies using the WCST, it has been shown that early (correct sorting rule is unknown) and late trials (correct sorting rule is known and applied) in the WCST are marked by distinct patterns of brain activation over frontal (P3a) and parietal (P3b) areas, which could reflect shifts in attention and the updating of context, respectively (Barcelo et al 1997; Barcelo and Rubia 1998; Barcelo 1999; Barcelo et al 2000; Barcelo and Knight 2002; Barcelo et al 2002; Barcelo 2003). Other differences may reflect orrientating of attention (N1) and activation of the frontal eye fields associated with visual scanning (P2) (Barcelo et al 1997). Studies on the electrical activity evoked by the feedback stimulus only investigated the P3a and P3b components (Barcelo et al 2002; Barcelo 2003), although we can also expect the more general processes of orientation of attention, since the feedback stimulus contains information, which has to be used to perform the task correctly. Studies in alcoholic participants using other tasks have shown aberrations in N1, N2, P3a and P3b components (see review of Porjesz and Begleiter 1996). The few studies that have used ERP measures to investigate differences between heavy and light social drinkers found effects on the P3 in an oddball paradigm (Nichols and Martin 1993), on the N4, and on a "late memory wave" (700-1100 ms) in a memory task (Fox et al 1995), at parietal and frontal scalp locations. The present study investigated whether components presumably related to rule shifting and orienting of attention during the WCST (N1, P3a, P3b), are affected in social drinkers, given that similar components are affected in alcoholics. Four groups, each with a mean age of approximately fifty years, were compared. Light social drinkers were no total abstainers and drank not more than 6.25 units (one unit contains 12

grams of alcohol) a week, moderate social drinkers less then 21, heavy social drinkers more than 21, and excessive drinkers more than 60 units a week. Alterations in ERPs associated with alcohol consumption might be found in the absence of behavioral effects (see Fox et al 1995).

MATERIALS AND METHODS

PARTICIPANTS

Male participants between 30 and 65 years of age were recruited with advertisements in local and national newspapers; excessive drinkers were also recruited at in-patient treatment centers. All participants were treated in accordance with the declaration of Helsinki and provided written informed consent before participating in the study. Participants were paid 70 euros for completing the whole experiment, which consisted of a telephone screening, a medical screening, a task session including ERP recording and a magnetic resonance imaging (MRI) session.

A two-week drinking diary, in which participants filled in the number of alcoholic drinks consumed each day, was used to assign the participants to the light (n=14), moderate (n=16) or heavy social drinkers groups (n=19). According to the drinking diary the light drinkers were not total abstainers and consumed at maximum 6.25 standard drinks a week, the moderate social drinkers consumed between 6.50 - 19.75 standard drinks a week, and the heavy social drinkers consumed between 21.00 and 52.70 standard drinks a week. Excessive drinkers (n=10) drank more than 60 standard units a week, five of them scored for alcohol dependence according to the DSM-IV criteria. Participants were right-handed (determined with the Edinburgh Handedness Inventory), had good (corrected) sight and hearing, and spoke Dutch as first language. To control for genetic influences participants were excluded if they (ever) had alcoholic relatives in the first or second degree. In addition, participants were excluded if they had a history of epilepsy, cardiovascular deficits, liver deficits, loss of consciousness due to head injury, psychiatric or neurological deficits, relatives with psychiatric or neurological deficits, problems with speech, such as stuttering, or any other medical history, which could influence the experiment. They were also excluded if they were excessively using nicotine (>40 cigarettes a day) and/or caffeine (>10 cups of coffee a day) or were using other psychotropic agents. Before running the experiment, a medical questionnaire was filled out by the participants, to exclude participants with any of the above-mentioned disorders. To obtain estimates of recent and lifetime quantity and frequency of alcohol consumption participants completed The Lifetime Drinking History (LDH) questionnaire (Skinner and Sheu 1982; as adapted for the Netherlands by Lemmens et al 1997).

PROCEDURE

Participants were asked to abstain from smoking for at least three hours prior to the experiment and to refrain from drinking alcohol for 24 hours prior to the experiment. Blood Alcohol Levels were determined with a breath test device (Alcotest, Dräger Medical, Lübeck, Germany) and urine screening was done for THC, cocaine, barbiturates, benzodiazepines and morphine (Rapid Drug Testing Services, Inc; Key Largo, US). If a participant tested positive another appointment was made for the ERP session and the participant was excluded when tested positive twice. Participants were instructed not to drink coffee or tea on the day of the experiment. After the electrodes for ERP recording had been attached, participants were escorted to the electrically shielded, soundproof cabin and seated in a chair at a distance of 100 cm from a computer monitor. They were instructed to restrict their movements. The experiment consisted of six tasks: a verb generation task, a visual attention task, a go/nogo task, a card-sorting

task, an auditory odd-ball task and, an EEG mental rehearsal task. Here we report the results of the WCST. The order of these tasks was balanced across participants. The WCST consisted of two blocks with a short pause in-between.

WCST

The task was based on the computerized version of the Wisconsin Card Sorting Task (WCST) (Barcelo 2003). Participants had to sort cards with a number of colored geometrical shapes. The sorting rule refered to either shape (triangle, star, cross, or circle), number (one, two, three, or four figures), or color (red, green, purple, or blue). The correctness of the chosen sorting rule was indicated by a feedback stimulus. A given sorting rule was valid for a varying number of stimuli (a series), after which it changed, without warning the participant. After the change, participants had to figure out which rule had to be followed for the subsequent series. The participants were informed that the sorting rule would change several times during the task. They were also instructed to wait for a negative feedback signal before applying a different sorting rule.

The card-sorting task consisted of 432 unambiguous target cards in random order (based on 24 "unambiguous" cards that each results in a different response button for each sorting rule). The 432 cards were split in 54 series that contain randomly 7, 8 or 9 target cards. The 54 series were given a certain sorting rule, balanced on a Latin square model. The targets were presented in the center of a black screen. Four reference cards were displayed simultaneously with the target card just above the center of the screen. Participants were seated at a distance of 100 centimeters from the screen. The target card and the reference cards together measured 14.5 cm x 10 cm, resulting in a visual angle of 8.31° horizontally and 5.73° vertically. The targets

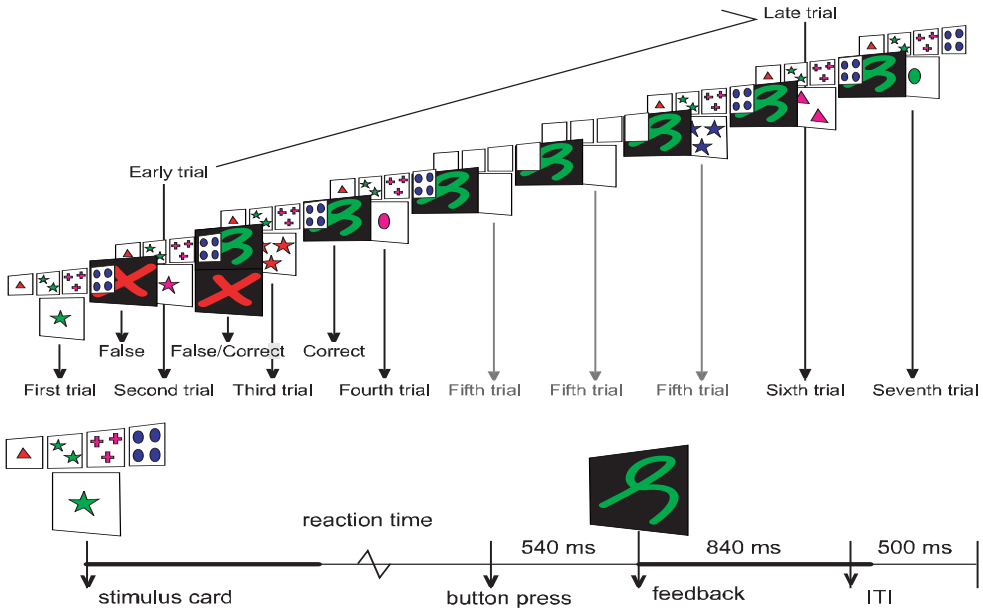

Figure 1. A depiction of a series in the WCST and the time course of a trial

were presented on the screen until the subject responded with a button press on the response panel. The location of the four keys of the response panel corresponded to the reference cards. Five hundred forty ms after the response, a feedback stimulus was presented for 840 ms, consisting of either a green twirl (positive feedback), or of a red cross (negative feedback). The feedback stimulus was of exact the same size as the targets. The Inter Trial Interval (ITI) was 500 ms (See for a depiction of a WCST trial figure 1).

DATA RECORDING AND ANANLYSIS

EEG was recorded using an electrode cap with 64 tin electrodes (see Figure 2), with the left mastoid as reference. Horizontal electro-oculogram (HEOG) was recorded from the outer canthus of each eye and, vertical electro-oculogram (VEOG) was from electrodes placed infra- and supra- orbitally to the left eye. The ground electrode was placed at AFz. Impedance was kept below 10 kW. All signals were amplified by Synamps amplifiers with online low-pass filters at 50 Hz and high-pass filters at 0.10 Hz. Signals were digitized at 250 Hz.

Only 'correct' series were selected for further ERP analyses, with a minimum of 10 correct series for each ERP. In a correct series the response on the first trial should be incorrect, otherwise the participant had been anticipating the upcoming rule. The response on the second trial had a 50% probability of being correct, and from the third trial on all responses had to be correct. The crucial statistical contrast consisted of the second (early) versus the sixth (late) trial. Two epochs were extracted for each second and sixth trial, one locked epoch to the card stimulus and one to the feedback stimulus. Epochs lasted 1000 ms, including 100 ms preceding the stimulus, which served as baseline. Off-line, all signals were filtered with a 30 Hz low-pass filter. All channels, except the EOG channels were used to calculate an average reference. Trials with amplifier blocking, artifacts or flat lines were detected off-line and omitted from further analysis. Ocular artifacts were controlled by time-domain regression analysis (Gratton et al

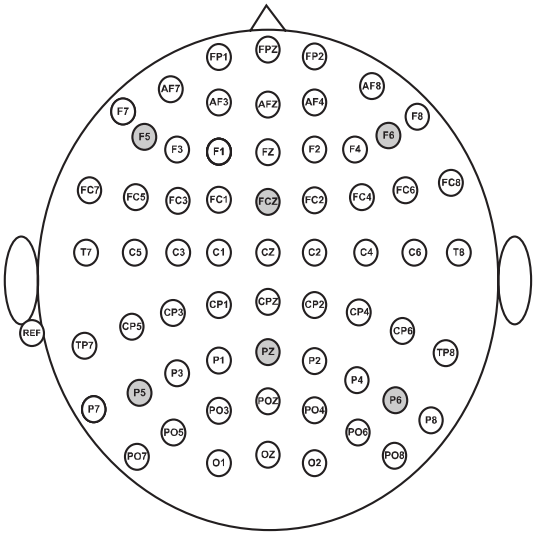

Figure 2: Electrode layout of the 64 lead Quick-cap; the tested leads are shown in gray

1983). All epochs with minimum to maximum amplitude of more than 100 μV after the ocular artifact correction were omitted from further analysis. Averages were calculated separately for card and feedback stimuli, and for early versus late trials. Based on visual inspection, and on earlier studies (Barcelo et al 1997; Barcelo 2003), and studies on alcoholics (see review of Porjesz and Begleiter 1996), specific leads and time ranges were chosen for further analysis.

For the card stimuli, the N1 was quantified as the mean amplitude between 120 and 170 ms and the P3a was quantified as the mean amplitude between 380 and 430 ms post stimulus at FCz, F5 and F6. The P3b in response to the card stimuli was quantified as the mean amplitude between 600 and 650 ms at Pz, P5 and P6. For the feedback stimuli, the N1 was quantified as the mean amplitude between 80 and 130 ms and the P3a was quantified as the mean amplitude between 360 and 400 ms post stimulus at FCz, F5 and F6. The P3b in response to the feedback stimuli was quantified as the mean amplitude between 540 and 640 ms at Pz, P5 and P6.

STATISTICAL ANALYSIS

Performance

Statistical analyses were performed using the SPSS software (SPSS 10.0, SPSS Inc., Chicago, IL, USA). Dependent variables were percentage of correct series, and reaction times. Differences in percentage correct series between the four groups were tested with an ANOVA, with Group as between-subjects factor. Reaction times were analyzed using repeated measurements ANOVA with Trial as within-subjects factor (7 levels), and Group as between-subjects factor (4 levels).

ERPs

Repeated measurements MANOVAs were conducted for the N1, P3a, and P3b components described above, with Group as a between-subjects factor, and Trial (2 levels, early and late) as a within-subjects factor. For all tests a critical α-level of 0.05 was used, however in case of Group*Trial interactions, pairwise comparisons were conducted using Bonferroni corrections. These analyses were performed separately for card and feedback stimuli.

RESULTS

Drinking history and demographic variables

A description of Age, IQ as measured with the NLV, and smoking for the four Groups is given in Table 1. All groups were of similar ages, had similar NLV scores, and did not significantly differ in the amount of cigarettes smoked a week. As expected, groups differed in the number of glasses a week reported in the drinking-diary ($F(3,52) = 59.40$; $P < 0.001$) and in the total lifetime alcohol-intake ($F(3,54) = 35.34$; $P < 0.001$) (see figure 3).

Table 1. Mean age, estimation of the number of glasses consumed a week (12 grams of alcohol) and number of cigarettes smoked per week for the light, moderate,and heavy social drinkers, and the excessive drinkers

	Light drinkers Mean ± SD	Moderate drinkers Mean ± SD	Heavy drinkers Mean ± SD	Excessive drinkers Mean ± SD	F (df)	P
Age	47.2 ± 9.7	49.7 ± 8.0	51.9 ± 8.0	49.4 ±8.0	.87 (3,55)	n.s.
NLV IQ	108.0 ±9.0	105.3 ± 7.2	110.3 ± 5.2	103.8 ± 11.2	2.02 (3,55)	n.s.
Smoking (number of cigarettes per week)	3.3 ± 0.9	5.2 ± 1.3	9.7 ± 4.6	9 ± 5.2	1.32 (3,55)	n.s.

(n.s. = not significant)

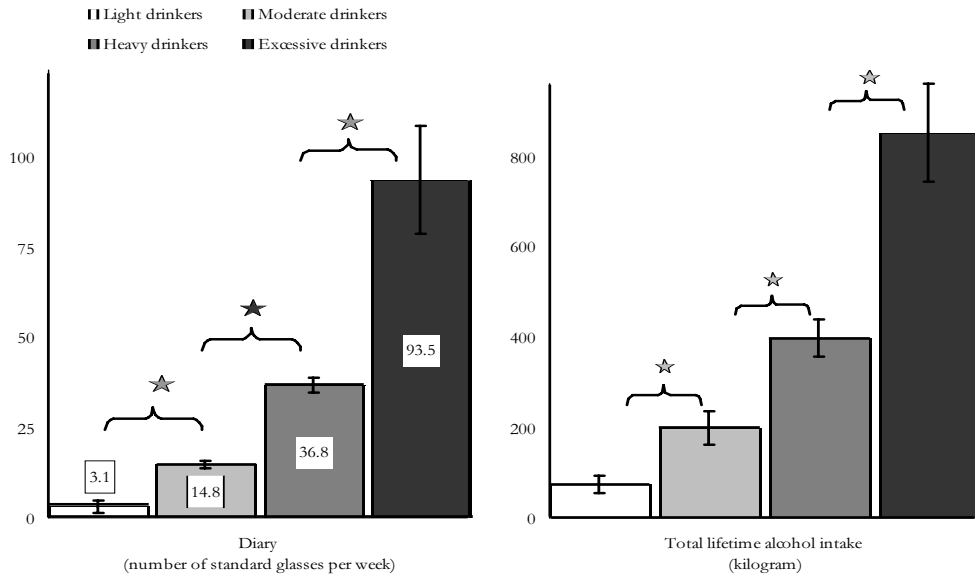

Figure 3. Mean ± SEM for the number of standard glasses a week as reported in the drinking diary and the total lifetime alcohol intake in kilograms for the four groups. Differences between groups are marked with stars. Black stars indicate p values <0.001; Grey stars indicate p values < 0.05; Post-hoc Dunnet-T3 test is used for the alcohol measures

Two participants in the excessive group did not fill in the drinking diary as they had abstained from drinking alcohol two weeks before inclusion in the study, but these participants did fill in the LDH questionnaire on which the total lifetime alcohol-intake was based.

Performance

The seven trials differed with respect to reaction times ($F(6,49) = 19.05$; $P < 0.001$) (See Figure 4). No Group * Trial interaction were found. For comparisons with the analysis of the ERP data, an additional test was done to compare the reaction time on the second trial with that on the sixth. Reaction times were significantly longer for the early than for the late trials ($F(1,54) = 89.53$; $P < 0.001$); again no Group * Trial interaction effects was found. Also, no differences between the four groups were found concerning the percentage of correct series.

ERPs to the card stimuli

Grand average waveforms to card stimuli are shown in Figure 5. Difference waves (Early minus Late) for the four groups are shown in Figure 6

No differences between early and late trials, and no Group * Trial interaction effects were found for the N1 (120 - 170 ms) at Fcz, F6 or F5. No differences between early and late trials, and no Group * Trial interaction effects were found for the P3a (380 - 430 ms) at Fcz, F6 and F5. Significantly more positivity for late relative to early trials was found for the P3b (600 - 650 ms) at Pz ($F(1,54) = 8.92$; $P < 0.01$). No Group * Trial interaction effects were found for the P3b.

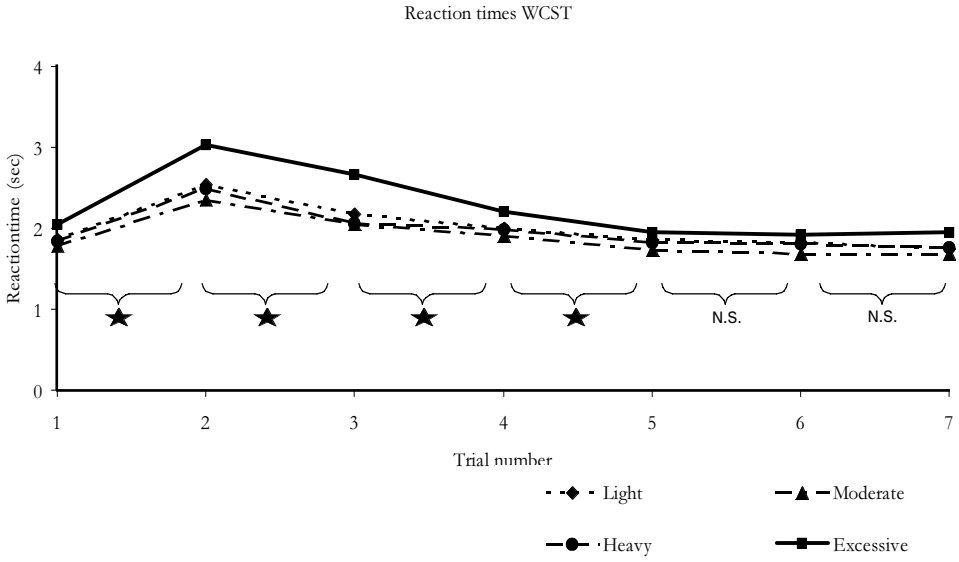

Figure 4. The mean reaction time per trial in a series for the four groups separated and the overall mean for all groups together. Black stars indicate p values < 0.001 in the pairwise comparisons (Bonferroni corrected)

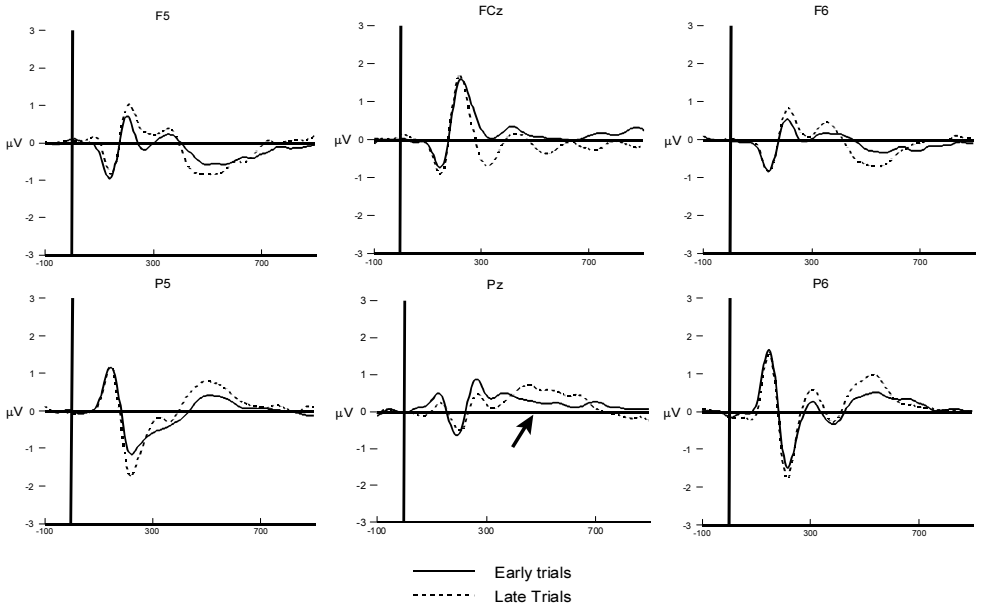

Figure 5. The ERP waveforms for the card-locked early and late trials. Arrows indicate significant differences between the early and late trials

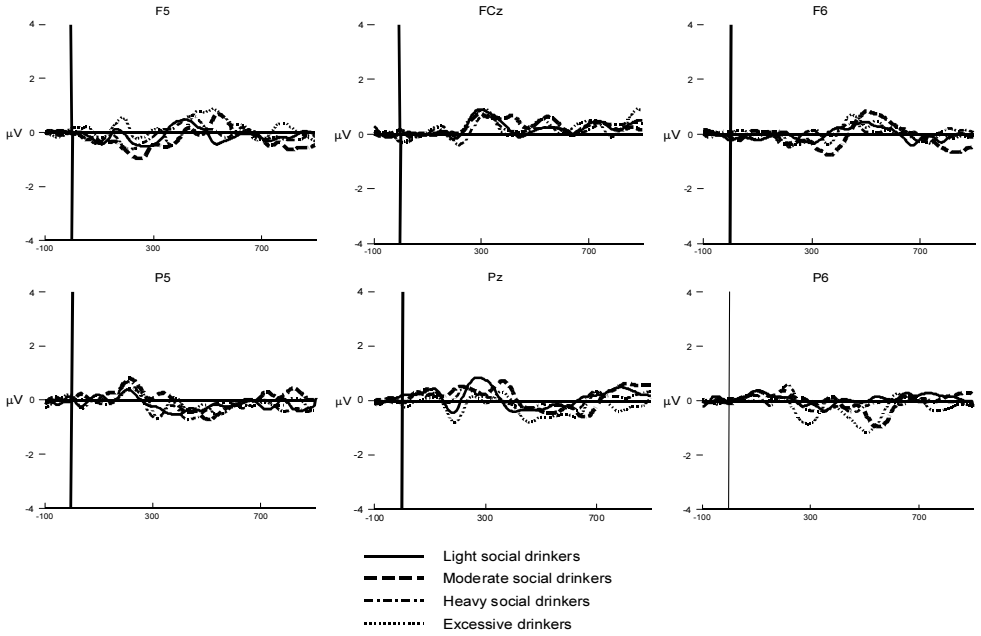

Figure 6. The difference waves (early trials minus late trials) for the four groups for the card-locked epochs

ERPs to feedback stimuli

Grand average waveforms to card stimuli are shown in Figure 7. Difference waves (Early minus Late) for the four groups are shown in Figure 8.

No overall differences between early and late trials were found for the N1 (120 - 170 ms) at Fcz, F6 or F5. However a significant Trial * Group interaction effect was found at FCz ($F(1,54) = 3.37$; $P < 0.05$; see also Figure 9). Post-hoc test at FCz revealed more negativity for early than for late trials, at a marginally significant level in the light group ($F(1,13) = 3.70$; $P = 0.076$), and significantly in the moderate group ($F(1,14) = 17.55$; $P < 0.01$). No significant difference was found for the heavy or excessive drinkers (see Figure 9).

As to the P3a, at FCz between 360 and 400 ms the mean amplitude was more positive for early than for late trials ($F(1,54) = 83.89$; $P < 0.001$). No differences between early and late trial were found at F5 or F6, no Group * Trial interaction effect was found for either lead FCz, F5. For the P3b (540 - 640 ms) a significant Trial effect was found, confirming larger positivity for early than for late trials, at Pz ($F(1,54) = 84.38$; $P < 0.001$), P5 ($F(1,54) = 23.99$; $P < 0.001$) and P6 ($F(1,54) = 34.14$; $P < 0.001$). No Group * Trial interaction effects were found for either lead.

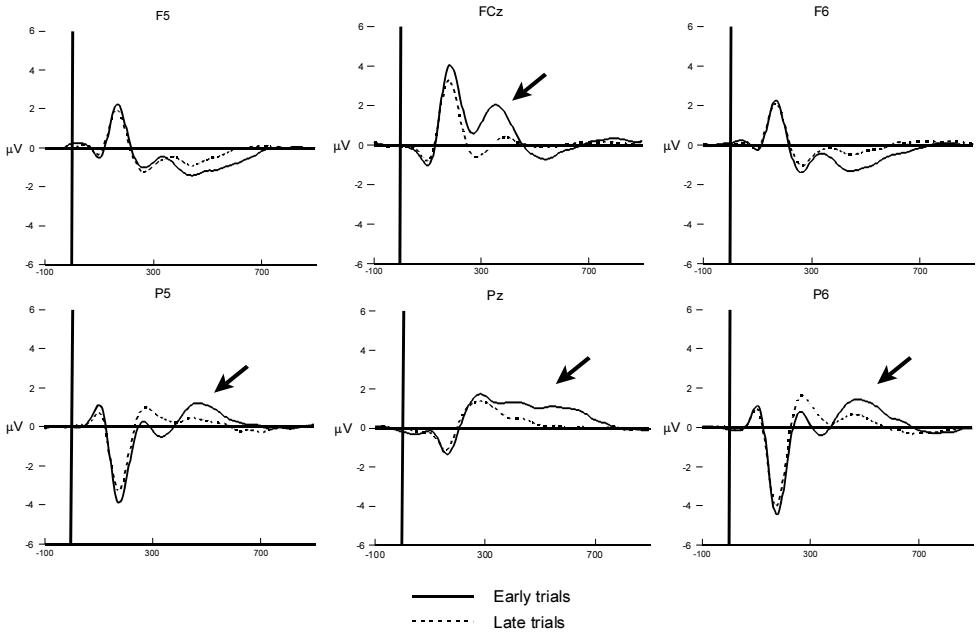

Figure 7. The ERP waveforms for the feedback-locked early and late trials. Arrows indicate significant differences between the early and late trials

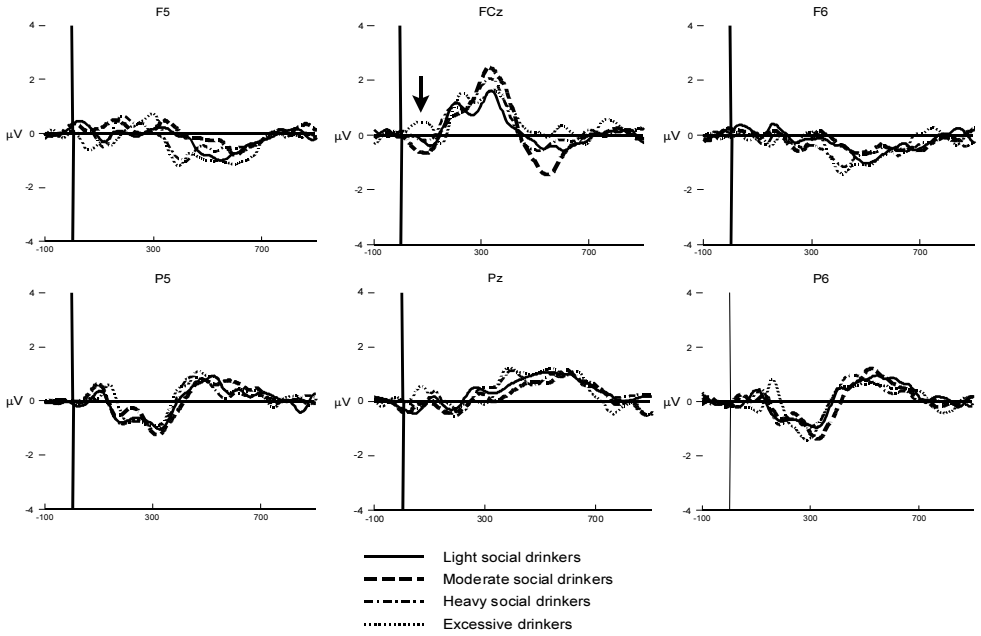

Figure 8. The difference waves (early trials minus late trials) for the four groups for the feedback-locked epochs. Arrows indicate significant differences between the early and late trials

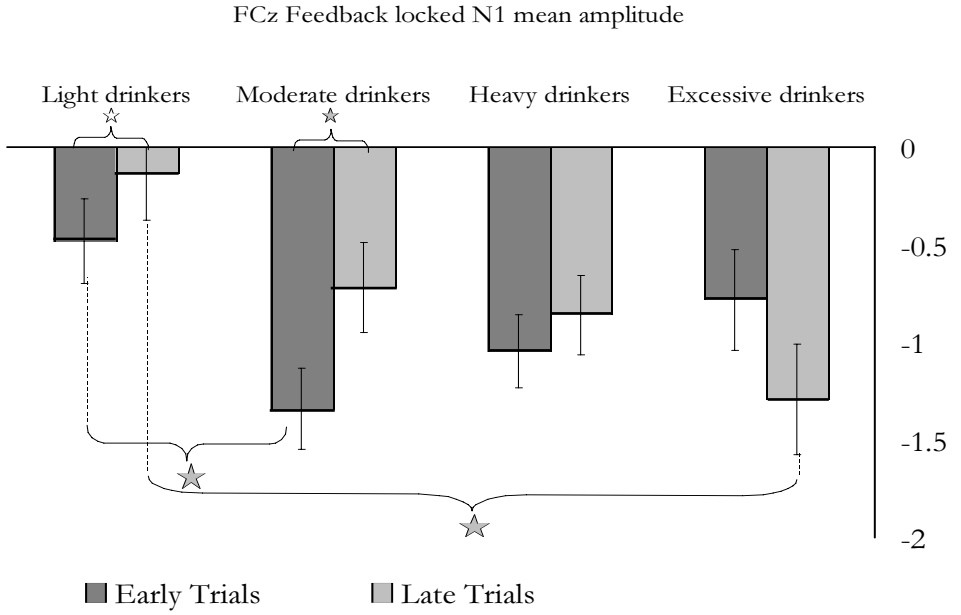

Figure 9. Group * Trial interactions on lead Fcz for the N1. Black stars indicate p values < 0.01, grey stars indicate p values < 0.05, and white stars indicate trends

DISCUSSION

To assess the effects of chronic alcohol consumption on the brain, we investigated behavioral and ERP measures during the WCST in light, moderate, and heavy social drinkers and excessive alcohol users. Previously reported task effects on performance and P3 were largely replicated, allowing for a comparison of these effects across the four drinking groups. Reaction times were longer on early trials than on late trials. As to ERPs for the target cards the P3b at Pz was smaller for early than for late trials. Unlike Barcelo et al (1997), but consistent with Barcelo (2003), no difference between early and late trials with respect to the P3a was found. The present study did not replicate the larger N1 component for early relative to late card trials, across the left frontal area, as reported by Barcelo et al (1997). For the feedback stimuli, the P3a and P3b were significantly larger for early than for late trials, which is again consistent with Barcelo (2003).

Differences in task effects between the present study and those reported by Barcelo (Barcelo et al 1997; Barcelo 2003) may be due to several factors. In the current study, overall absolute ERP amplitudes were relatively low, compared to former studies on the WCST. This may for a large part be due to the average-reference transformation, that was currently applied to enable unbiased comparisons between signals recorded over the left versus right hemisphere. Another factor is age: compared to former studies, the current study included older participants with possible reduced ERP amplitudes, relative to younger participants (Wegesin et al 2002). In addition, reaction times for these older participants were about twice as long compared to the studies of Barcelo, which could concur with more latency variability of various ERP measures.

No significant differences between the four drinking groups were found in error rates or reaction times. The excessive drinkers group was slower on especially the second trial, but not significantly so. Despite the fact that there was no significant differences between groups in performance, their brain activity in reaction to the feedback did differ. The light social drinkers showed a trend towards more early negativity (N1) on early trials than on late trials; this effect was significant for the moderate drinkers, but absent in the heavy and excessive groups.

In the studies of Barcelo no N1 effect in response to the feedback stimuli was reported, so the current study is the first to describe this component. This N1 component in response to the feedback might reflect a more general process of orientating of attention: on early trials the feedback stimulus conveyed information about the correctness of the newly applied sorting rule, whereas on late trials the correct sorting rule was already used correctly. Thus, the feedback contained more relevant information on early than on late trials. Therefore, more attention may have been directed to the early than to the late feedback stimuli. The absence of a difference in N1 between early and late trials in the heavy and excessive drinkers might therefore indicate diminished attentional orienting abilities. One study in abstinent alcoholics (Porjesz and Begleiter 1982) also showed an abnormally reduced N1 component particularly over the right (frontal) hemisphere. In that study, it was also shown that abstinent alcoholics showed the same N1 amplitude regardless of the information value of the stimulus (relevant or not). Porjesz and Begleiter (1982) suggest that alcoholics have difficulty with sensory filtering processes. It could also be that the N1 is related to the anterior cingulate cortex, which has been related to processes of conflict detection (Carter et al 1998; Botvinick et al 2001). This makes sense, since in the early trials there is a 50 % possibility of conflict between the applied

sorting rule and the feedback information. The absence of any differences in the heavy social drinkers and excessive drinkers might indicate that these groups perform the task more on a trial and error base.

In conclusion, using the card-sorting task, differences between drinking groups were found for ERP measures, but not with respect to behavioral measures. In the light and moderate drinkers, the N1 was larger on early relative to late feedback trials, but this effect was absent in the heavy social drinkers and excessive drinkers. This reduced N1 effect with increasing alcohol intake could reflect abnormal allocation of attention or impaired conflict monitoring, possibly based on activity in the anterior cingulate cortex.

Chapter 4

The Continuous Performance Task

ABSTRACT

To assess effects of chronic alcohol consumption on the brain, participants were instructed to press a button when an X followed an A (Go), and to inhibit that response when another letter appeared after the A (Nogo). Behavioral and brain potential (ERP) responses to the letters were recorded.

The study included light, moderate and heavy social drinkers and excessive drinkers (mean age 49.7). ERPs revealed expected task effects at the midline electrodes (Fz, Fcz, Cz and Pz). No differences between the drinking groups were found in behavioral or ERP measures. However, when selecting the alcohol dependent (DSM-IV) subjects from the excessive group, a difference was found: Alcohol dependent subjects showed lower frontal P300 amplitudes in the Go condition than light social drinkers did.

It is hypothesized that the frontally measured Go P3 component is sensitive to possible genetic or addiction-related characteristics in alcohol dependent participants, but not to social drinking.

*)This chapter has been sumitted as: Suzanne Bijl, Eveline A de Bruin, Koen B E Böcker, J Leon Kenemans, Marinus N Verbaten: Effects of chronic social drinking in a Continuous performance task; an Event Related Potential study

INTRODUCTION

The Continuous Performance Task (CPT) is a frequently used neuropsychological task to investigate sustained attention (Rosvold et al 1956). In its cued version (CPT-AX), participants have to respond to a certain combination of stimuli (Go) and to withhold their response to other combinations of stimuli (Nogo). This CPT version contains an execution/inhibition conflict, and is therefore assumed to activate brain mechanisms in the frontal cortex relevant for impulsive vs. controlled behavior. Deficient inhibitory control is associated with a variety of psychiatric disorders, among which substance use disorders such as alcoholism (Vogel-Sprott et al 2001).

To investigate the specific inhibitory correlates of the CPT-AX, electrophysiological measurements are often used. Event Related Potentials (ERPs) in response to Go stimuli differ from those to Nogo stimuli in two ways (Jonkman et al 2003). First, on Nogo trials, with a successful inhibition, a negative wave can be observed with a latency of about 150 - 400 ms after presentation of the stimulus (Kiefer et al 1998; Falkenstein et al 1999; Bokura et al 2001; Bekker et al, in press). This wave is called the Nogo N2 and has its maximum at the frontal scalp sites. Second, following the Nogo N2, most studies also report enhanced fronto-central P3 amplitudes in the latency range of 300 - 500 ms in the Nogo condition, as opposed to a P3 with a parietal maximum in the Go condition (Fallgatter and Strik 1999; Kiefer et al 1998; Falkenstein et al 1999; Bekker et al, in press). Furthermore, the CPT-AX also reveals ERP components related to response preparation, such as the Contingent Negative Variation (CNV).

In previous studies, lower frontal P3 amplitudes in the Go condition were reported in alcoholics compared to controls (Pfefferbaum et al 1987; Fallgatter et al 1998). These studies did not report on the N2 amplitude. To our knowledge no studies have been done with a Go/Nogo paradigm in social drinkers. However, with other paradigms differences between heavy and moderate social drinkers have been found using ERP measures. Chao et al. (2003) used a classical two stimuli reaction time paradigm and did not found any differences between light and heavy social drinkers on the early CNV component, although a reduced late CNV component was found in the heavy social drinkers group. A reduced CNV amplitude has also been reported for alcoholics (Skerchock and Cohen 1984), although other studies did not find any differences in this component across groups with high and low alcohol intake (Olbrich et al 2002; Wagner et al 1996). In another study, a memory task was used to assess differences between social drinkers (Fox et al 1995). In this study, differences were found with respect to the N4 and a "late memory effect" (positivity from 700 to 1100 ms). In an oddball paradigm (Nichols and Martin 1993), heavy social drinkers were found to differ from light social drinkers on the P3 component (Nichols and Martin 1993).

Other evidence on the effects of social drinking is available from studies using neuropsychological tests. Parsons and Nixon (1998) reviewed 17 studies that used several neuropsychological test batteries. Only seven of these studies found that heavy social drinkers performed significantly worse on one or more cognitive tests compared to the light social drinkers. Parsons and Nixon (1998) suggested that the changes in the brains of heavy social drinkers are too subtle to detect with behavioral tests. Both studies, reviewed by Parsons and Nixon (1998) that investigated differences between heavy and light social drinkers using ERP measures found significantly altered ERP components in the heavy social drinking group (Nichols and Martin

1993; Fox et al 1995). Thus, ERPs can provide a sensitive method for assessing subtle changes in brain functioning in social drinkers.

In the present study the CPT-AX was used to assess brain functioning in four groups of participants with a mean age of approximately fifty years. Light social drinkers were no total abstainers and drank not more than 6.25 units (1 unit contains 12 grams of alcohol) a week, moderate social drinkers less then 21, heavy social drinkers more than 21, and excessive drinkers more than 60 units a week. We hypothesized that with higher regular alcohol consumption differences in ERPs would be found in the CPT-AX task (N2, frontal P3, parietal P3b and CNV). These changes in ERP measurements might be found in the absence of behavioral effects (see Fox et al 1995).

MATERIALS AND METHODS

PARTICIPANTS

Male participants between 30 and 65 years of age were recruited with advertisements in local and national newspapers; excessive drinkers were also recruited at in-patient treatment centers. All participants were treated in accordance with the declaration of Helsinki and provided written informed consent before participating in the study. Participants were paid 70 euros for completing the whole experiment, which consisted of a telephone screening, a medical screening, a task session including ERP recording and a magnetic resonance imaging (MRI) session.

A two-week drinking diary, in which participants filled in the number of alcoholic drinks consumed each day, was used to assign the participants to the light (n=14), moderate (n=16) or heavy social drinkers groups (n=19). According to the drinking diary the light drinkers were not total abstainers and consumed at maximum 6.25 standard drinks a week, the moderate social drinkers consumed between 6.50 - 19.75 standard drinks a week, and the heavy social drinkers consumed between 21.00 and 52.70 standard drinks a week. Excessive drinkers (n=10) drank more than 60 standard units a week, five of them scored for alcohol dependence according to the DSM-IV criteria. Participants were right-handed (determined with the Edinburgh Handedness Inventory), had good (corrected) sight and hearing, and spoke Dutch as first language. To control for genetic influences participants were excluded if they (ever) had alcoholic relatives in the first or second degree. In addition, participants were excluded if they had a history of epilepsy, cardiovascular deficits, liver deficits, loss of consciousness due to head injury, psychiatric or neurological deficits, relatives with psychiatric or neurological deficits, problems with speech, such as stuttering, or any other medical history, which could influence the experiment. They were also excluded if they were excessively using nicotine (>40 cigarettes a day) and/or caffeine (>10 cups of coffee a day) or were using other psychotropic agents. Before running the experiment, a medical questionnaire was filled out by the participants, to exclude participants with any of the above-mentioned disorders. To obtain estimates of recent and lifetime quantity and frequency of alcohol consumption participants completed The Lifetime Drinking History (LDH) questionnaire (Skinner and Sheu 1982; as adapted for the Netherlands by Lemmens et al 1997).

PROCEDURE

Participants were asked to abstain from smoking for at least three hours prior to the experiment and to refrain from drinking alcohol for 24 hours prior to the experiment. Blood Alcohol Levels were determined with a breath test device (Alcotest, Dräger Medical, Lübeck, Germany) and urine screening was done for THC, cocaine, barbiturates, benzodiazepines and morphine (Rapid Drug Testing Services, Inc; Key Largo, US). If a participant tested positive another appointment was made for the ERP session and the participant was excluded when tested positive twice. Participants were instructed not to drink coffee or tea on the day of the experiment. After the electrodes for ERP recording had been attached, participants were escorted to the electrically shielded, soundproof cabin and seated in a chair at a distance of 100 cm from a computer monitor. They were instructed to restrict their movements. The experiment consist-

ed of six tasks: a verb generation task, a visual attention task, a go/nogo task, a card-sorting task, an auditory odd-ball task and, an EEG mental rehearsal task. Here we report the results of the CPT-AX. The order of these tasks was balanced across participants.

CPT-AX TASK

The CPT-AX task consisted of a random sequence of 11 different letters (A, B, C, D, E, F, G, H, J, L, and X). The letters were black on a gray background. Two vertical bars, each of 1 cm high (0.05º) and 0.5 mm wide (0.95º), separated from each other by 2 cm (horizontally; 1.9º), were continuously present in the center of the screen, and the letters appeared between them. Subjects were instructed to press a button with the index finger of their dominant hand as quickly as possible in response to the letter X, but only when the X was preceded by the letter A. In all other cases the response had to be withheld.

The Go stimulus was thus defined as the letter X appearing after the letter A. When another letter than X followed an A, this constituted a Nogo stimulus for which the prepared response had to be inhibited. Furthermore, all presentations of the letter A served as cue stimulus. The letters were 1.5 by 1.0 cm (width 1.43º, height 0.95º) and the stimuli remained on the screen for 150 ms, with the inter-stimulus-interval (ISI) varying between 1400 and 1600 ms. The task consisted of 400 stimuli (four blocks of 100 stimuli) and lasted 11 minutes in total. The target letter X and the letter X without the preceding A appeared with a frequency of 10% each. The letters A and H each appeared with a probability of 20%, and the letters B, C, D, E, F, G, J, and L each appeared with a frequency of 5%.

DATA RECORDING AND ANALYSIS

EEG was recorded using an electrode cap with 64 tin electrodes (see Figure 2), with the left mastoid as reference. Horizontal electro-oculogram (HEOG) was recorded from the outer canthus of each eye and, vertical electro-oculogram (VEOG) was from electrodes placed infra- and supra- orbitally to the left eye. The ground electrode was placed at AFz. Impedance was kept below 10 kW. All signals were amplified by Synamps amplifiers with online low-pass filters at 50 Hz and high-pass filters at 0.10 Hz. Signals were digitized at 250 Hz.

Epochs lasted 1000 ms, including 100 ms preceding the stimulus, which served as baseline. Off-line, all signals were filtered with a 30 Hz low-pass filter. All channels, except the EOG channels were used to calculate an average reference. Trials with amplifier blocking, artifacts or flat lines were detected off-line and omitted from further analysis. Ocular artifacts were controlled by time-domain regression analysis (Gratton et al 1983). All epochs with minimum to maximum amplitude of more than 100 μV after the ocular artifact correction were omitted from further analysis. Trials with incorrect responses were also omitted from analysis. Averages were calculated according to stimulus type (Go trials, Nogo trials and Cue trials).

STATISTICAL ANALYSIS

Performance

Statistical analyses were performed using the SPSS software (SPSS 10.0, SPSS Inc., Chicago, IL, USA). Dependent variables were the mean reaction times and the number of correct responses on the Go trials and correct rejections on the Nogo trials. Differences in these behavioral measures between the four groups were tested with an ANOVA, with Group as between-subjects factor.

ERPs

Preplanned statistical comparisons were conducted for the mean amplitude in the Go and Nogo conditions for the N2 (Fz; 230 - 280 ms), P3a (FCz; 330 - 380 ms) and P3b (Pz; 380 - 450 ms) components. These are the specific time intervals and leads at which these components have been reported to be most prominent previously (Kiefer et al 1998; Falkenstein et al 1999; Bokura et al 2001; Fallgatter and Strik 1999; Kiefer et al 1998; Falkenstein et al 1999). ANOVAs were conducted on Group as between-subjects factor and Trial (2 levels, Go and Nogo) as within-subjects factor. For the CNV the ERPs (at Cz, 750 - 900 ms) to the cues were analyzed with ANOVA, with Group as between-subjects factor. For all tests a critical α-level of 0.05 was used, however, in case of Group*Trial interactions, pairwise comparisons were conducted using Bonferroni corrections.

RESULTS

DRINKING HISTORY AND DEMOGRAPHIC VARIABLES

A description of Age, IQ as measured with the NLV, and smoking for the four Groups is given in Table 1. Data of one light social drinker was excluded because of a hardware failure during recording. All groups were of similar ages, had similar NLV scores, and did not significantly differ in the amount of cigarettes smoked a week. As expected, groups differed in the number of glasses a week reported in the drinking-diary ($F(3,52) = 53.66$; $P < 0.001$) and in the total lifetime alcohol-intake ($F(3,54) = 34.46$; $P < 0.001$) (see figure 1).

Two participants in the excessive group did not fill in the drinking diary as they had abstained from drinking alcohol two weeks before inclusion in the study, but these participants did fill in the LDH questionnaire on which the total lifetime alcohol-intake score was based.

PERFORMANCE

No differences between the four groups were found concerning the mean reaction times and the number of correct responses and correct rejections. Mean reaction times and number of correct responses and rejections are shown in Table 2.

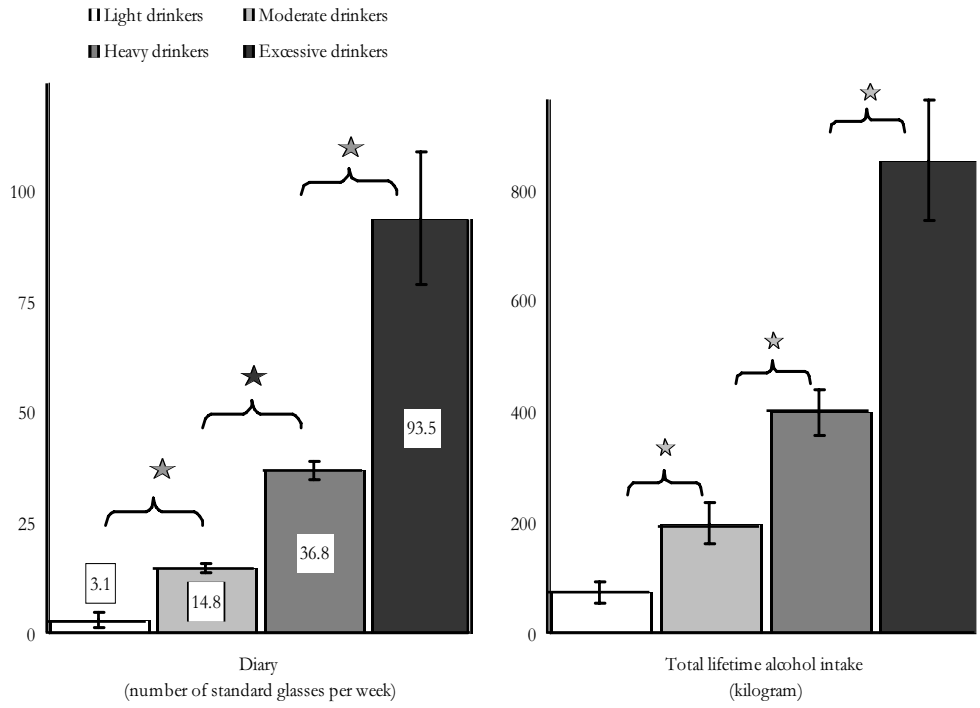

Figure 3. Mean ± SEM for the number of standard glasses a week as reported in the drinking diary and the total lifetime alcohol intake in kilograms for the four groups. Differences between groups are marked with stars. Black stars indicate p values <0.001; Grey stars indicate p values < 0.05; Post-hoc Dunnet-T3 test is used for the alcohol measures

Table 1. Mean age, estimation of the number of standard drinks consumed a week (12 grams of alcohol), number of cigarettes smoked a week, Correct responses, Reaction time on the correct responses and the number of successful inhibitions for the light, moderate and heavy social drinkers and excessive drinkers

	Light drinkers Mean ± SD	Moderate drinkers Mean ± SD	Heavy drinkers Mean ± SD	Excessive drinkers Mean ± SD	F (3.54)	P
Age	47.8 ± 9.8	50.2 ± 8.0	51.9 ± 8.0	49.4 ±8.0	.64	n.s.
NLV IQ	109 ± 8	105 ± 7	110 ± 5	104 ± 11	2.14	n.s.
Smoking (number of cigarettes a week)	3.5 ± 1.0	5.0 ± 1.3	9.7 ± 4.6	9 ± 5.2	1.25	n.s.
Correct responses	39 ± 1	39 ± 1	39 ± 1	40 ± 1	2.02	n.s.
Reaction Time Correct responses	470 ± 74	456 ± 77	481 ± 94	466 ± 77	.27	n.s.
Number of correct rejections	360 ± 0	359 ± 2	360 ± 0	360 ± 1	1.79	n.s.

(n.s. = not significant)

ERPs

Grand average waveforms to Go, Nogo, and Cue trials are shown in figure 2. Difference waves (Nogo minus Go condition) and Cue ERPs for the four groups are shown in Figure 3.

The N2 component at Fz was significantly larger on the Nogo trials than on the Go trials ($F(1,53) = 13.56$; $P < 0.01$; see Figure 2). No Group * Trial interaction effect was found for the for the N2 (See Figure 3). The P3a component at FCz was larger on Nogo trials than on Go trials ($F(1,53) = 58.31$; $P < 0.001$; see Figure 2). No Group * Trial interaction effects were found for the P3a (See Figure 3).

The P3b component at Pz was significantly more positive on Go trials than on Nogo trials ($F(1,53) = 46.82$; $P < 0.001$; see Figure 2). No Group * Trial interaction effects were found for the P3b (See Figure 3). The CNV wave at Cz differed significantly from zero ($F(1,53) = 46.12$; $P < 0.001$; see Figure 2). No Group effects were found for the CNV (See Figure 3).

In this study, no differences between social drinking groups were found. In contrast, previous research using alcohol dependent alcoholics did find differences between alcohol dependent participants and controls (Pfefferbaum et al 1987; Fallgatter et al 1998). Therefore, an additional post-hoc analysis was performed between the light social drinkers and the five alcohol dependent participants in the excessive drinkers group. This revealed a significant interaction between Trial * Group effect on the frontal P3b ($F(1,16) = 6.13$; $P < 0.05$; see Figure 4). This interaction was caused by the fact that the two groups did not differ in the Nogo condition, but the alcohol dependent Group showed a trend towards smaller amplitudes than the light social drinkers in the Go condition of the frontal P3 ($F(1,16) = 3.76$; $P = 0.07$).

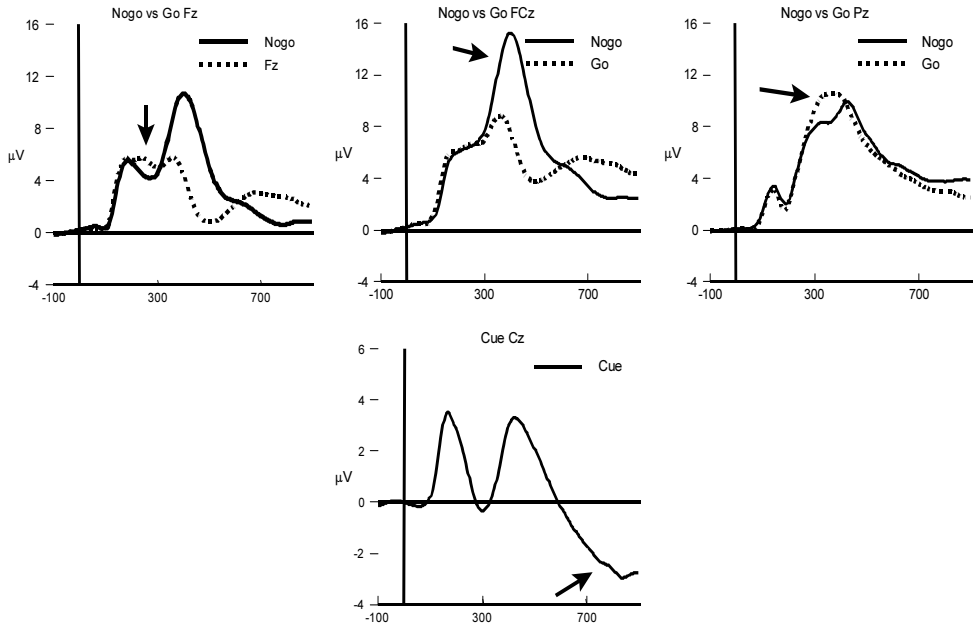

Figure 2. Upper panel, grand mean averaged ERPs for the Go and Nogo condition on the tested Leads Fz, Fcz and Pz. Below, grand mean averaged ERPs for the Cue condition on the Lead Cz

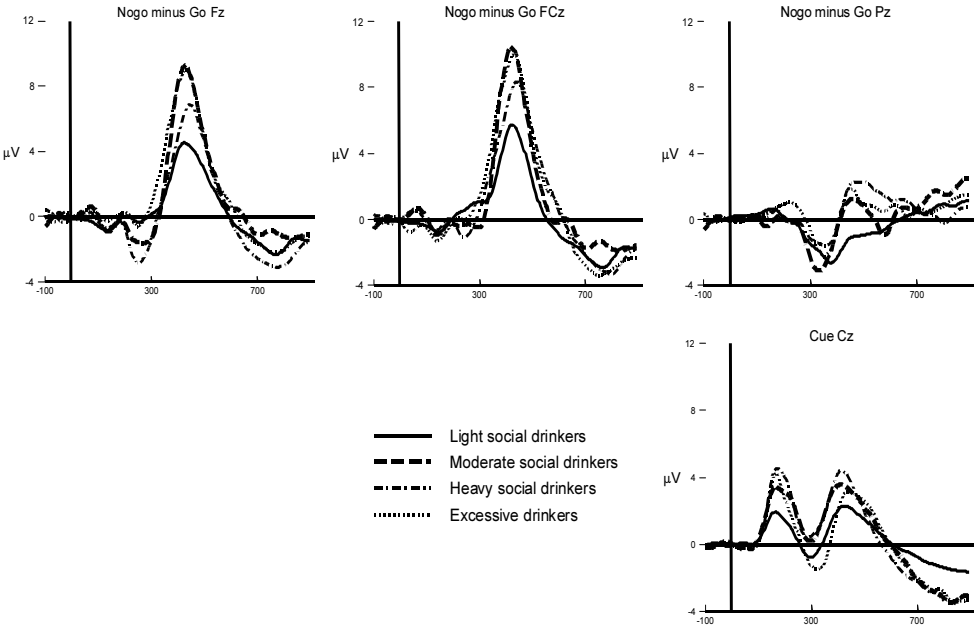

Figure 3. Upper panel, grand mean averaged difference waves on the tested Leads Fz, Fcz and Pz for the Nogo minus Go condition for the four groups. Below, grand mean averaged ERPs for the Cue condition for the four groups

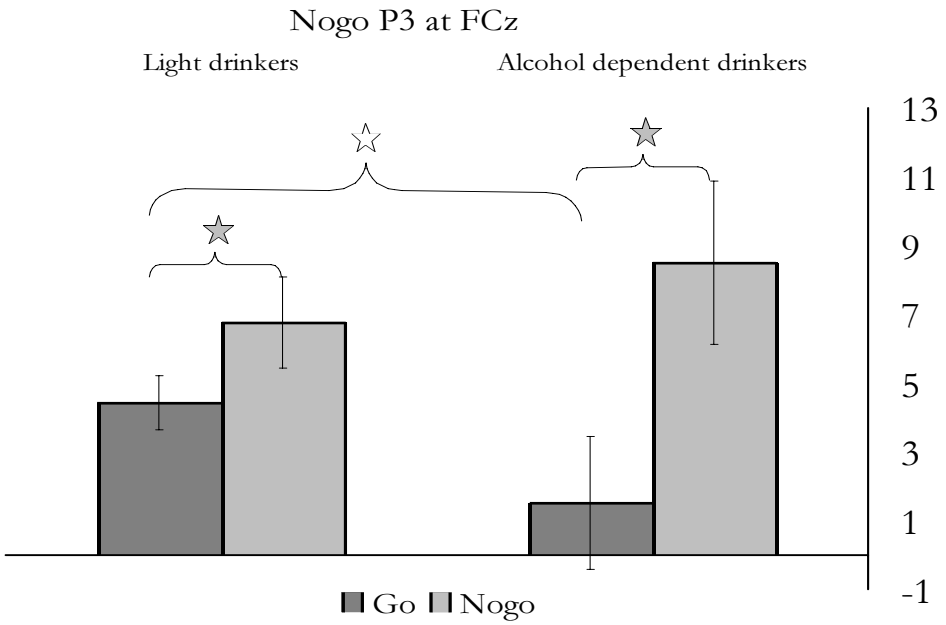

Figure 4. histogram of the mean amplitude of the P3 at FCZ for the alcohol dependent participants and the light social drinkers

DISCUSSION

In this study the CPT-AX task was used to assess the effects of social drinking on the activation of the brain as determined by ERPs. The expected task effects were found across all groups: larger frontal N2b and P3a amplitudes in the Nogo condition, larger parietal P3b amplitude in the go condition, as well as a CNV wave in the cue condition. No differences in these ERP measures were found between the different groups of social drinkers. In addition, no behavioral differences were found between the groups (hits, correct rejections and reaction times).

Fallgatter et al (1998) and Pfefferbaum et al (1987) reported differences between alcoholics and controls with respect to the frontal P3 component in the Go condition. However, these studies concerned subjects with severe alcohol dependence, whereas the excessive drinkers in the current study included only five alcohol dependent subjects. In order to determine whether we could replicate the effects of Fallgatter et al (1988) and Pfefferbaum et al (1987), we contrasted the small group of alcohol dependent participants in this study to the light social drinkers, and also found a significant interaction between Task and Group effects on the frontal P3 component. This interaction was caused by the fact that only in the Go condition the two groups differed; the alcohol dependent group showed a trend ($p=0.07$) towards smaller amplitude than the light social drinkers in the Go condition. Since there was no significant difference in amount of alcohol consumption on drinking diary ($F(1,6) = 1.3$; P = n.s.) or lifetime alcohol intake ($F(1,8) = .012$; P = n.s.), between the alcohol dependent excessive drinkers (mean: 80 glasses a week and 865 kilograms total lifetime alcohol intake) and the non-dependent excessive drinkers (mean: 115 glasses a week and 840 kilograms total lifetime alcohol intake) it is not likely that that the smaller P3 component in alcohol dependent drinkers is related to the toxic effects of regular alcohol use. This frontal P3 component is probably more related to the diagnosis of alcohol dependence according to the DSM-IV criteria. It could be that this alcohol dependence results in an abnormal frontal Go P3 because this subgroup of alcohol dependent participants is more vulnerable to the toxic effects of alcohol. Another possible explanation could be a genetic influence in the alcohol dependent participants. In other tasks it has repeatedly been shown that ERPs, specifically the parietal P3b component, are sensitive to genetic influences (Polich et al 1994; Van Der Stelt et al 1994; Porjesz and Begleiter 1996b; Van Der Stelt et al 1998). Pfefferbaum et al (1991) showed that alcoholics with a positive family history of problem drinking had smaller P3s than did alcoholics who reported a negative family history. These authors also demonstrated that these smaller P3 amplitudes in family history positive alcoholics were independent of their lifetime alcohol consumption. In the present study, we controlled for possible genetic influences by excluding participants who had alcohol dependent relatives in the first or second degree. However, it is possible that participants in our study could not report about alcohol dependent relatives since these relatives had died at young age, or the participants did not know that there was an alcohol-related problem in these relatives. Thus, it is possible that the people who scored for alcohol dependency have a genetic predisposition for alcohol dependency, which might be manifested in the presently observed frontal P3 component to the Go stimuli.

The frontal P3 component in the CPT-AX task is associated with inhibition, a deficit of which is probably an important factor in developing dependence to a substance with abuse potential.

However, one would expect these effects in the Nogo condition, where a response has to be withheld, and not in the Go condition.

The CNV amplitude did not differ between the groups included in the present study. Chao et al (2003) did report a smaller CNV late wave in heavy compared to light drinking participants, but similar early wave amplitudes. Due to the ISI in the present study (1400-1600 ms), the current CNV amplitudes were expected to be a mixture of early and late waves. Therefore, it is difficult to compare the present findings to those of Chao et al (2003).

In the current study, even for rather large amounts of regular alcohol intake, no evidence was found for any toxic effect of chronic social alcohol use on performance or ERPs in the CPT-AX task. However, the small group of alcohol dependent subjects showed abnormal frontal P3s in the Go condition, possibly indicating an effect of a genetic predisposition towards alcohol dependence or addiction-related characteristics.

Chapter 5

The Attention Tasks

ABSTRACT

In alcohol dependent individuals changes in brain functioning, as measured with Event Related Potentials (ERPs) have been reported. In the present study a visual attention and an auditory odd-ball task were used to investigate possible differences between three groups of social drinkers and one group of excessive drinkers. It was hypothesized that with increasing alcohol intake an increasing number of ERP components elicited in the visual attention task and the auditory odd-ball task would show diminished amplitudes. No differences were found between social drinkers. A trend for smaller P3 amplitudes in the visual attention task was found when comparing the alcohol dependent participants with the light social drinkers. It is argued that this effect might be a reflection of possible unknown or undetected family history of alcohol related disturbances.

*)This chapter has been submitted as: Suzanne Bijl, Eveline A de Bruin, Koen B E Böcker, J Leon Kenemans, Marinus N Verbaten: Effects of chronic alcohol consumption in a visual attention task and an auditory oddball task; An Event Related Potential study

INTRODUCTION

In alcohol dependent participants aberrations in brain functioning, as measured with Event Related Potentials (ERPs), have been reported (for reviews, see Porjesz and Begleiter 1985; Porjesz and Begleiter 1996). Numerous ERP studies using visual tasks in alcoholics have shown diminished N1 (Cohen et al 2002; Patterson et al 1987; Glenn et al 1996; Porjesz and Begleiter 1996), N2 (Porjesz et al 1987; Porjesz and Begleiter 1996) and P3 amplitudes (Patterson et al 1987; Glenn et al 1996; Porjesz and Begleiter 1996; Rodriguez et al 1999; Malone et al 2001; Cohen et al 2002; Polo et al 2003).

In studies using auditory tasks, to our knowledge, no deficiencies in alcohol dependent participants were found for the auditory N1 amplitudes, while diminished amplitudes were reported for the N2 (Realmuto et al 1993) and the P3 (Patterson et al 1987; Realmuto et al 1993; Cohen et al 2002). In studies using auditory tasks, the differences between alcoholics and controls vary more than in visual tasks (see for a review Porjesz and Begleiter 1996).

The amplitude of the P3 distinguishes successfully between alcoholics and healthy controls, and is also successfully used to distinguish between participants at high and low risk for alcoholism, findings which seem extremely robust especially in visual tasks (Polich et al 1994; Van Der Stelt et al 1994; Porjesz and Begleiter 1996; Van Der Stelt et al 1998). Pfefferbaum et al (1991) showed that alcoholics with a negative family history of problem drinking had a normal P3, whereas those with a positive family history had reduced P3 amplitudes. These authors also demonstrated, with a hierarchical regression analysis, that these smaller P3 amplitudes in family history positive alcoholics were independent of their lifetime alcohol consumption. In another study no evidence was found for differences between children of alcoholics and controls with respect to the earlier components related to visual selective attention (the frontal selection positivity, selection negativity and N2b; Van Der Stelt et al 1998). In auditory tasks, differences between family history positive and negative non-alcoholic participants were found on the auditory mis-match negativity (Zhang et al 2001). The mis-match negativity is a negative difference wave round 200 ms, revealed by a subtraction of deviant and standard stimuli, and is thought to reflect a process of template matching (Näätänen et al 1993). In a study of Van Der Stelt et al (1997) no differences in mis-match negativity between children of alcoholics and controls were found. Some genetic influence on the auditory N1 was found in a twin study (O'Connor et al 1994). However, evidence for differences in the N1 and N2 between participants with high and low risk for alcoholism is less clear, which led Porjesz and Begleiter (1996) to the conclusion that the N1 and N2 amplitudes did not seem to distinguish between sober participants at high and low risk for alcoholism, and are probably more a state than a trait marker.

In order to examine the effects of chronic alcohol use on the brain, social drinking groups can be investigated. When strictly controlling for family histories of alcohol dependence, possible genetic influences can be controlled to some extent. Then the 'pure' chronic effect of alcohol use on the brain can be described. However, to our knowledge, no ERP studies have been done to that effect with visual or auditory attention and odd-ball tasks in social drinkers. With other paradigms differences between heavy and moderate social drinkers were found using ERP measures. Chao et al (2003) used a classical two stimuli reaction time paradigm and found a reduced late Contingent Negative Variation (CNV) component in a heavy social drinkers group compared to a light social drinkers group. Two studies used a memory task to assess differences

between social drinkers (Fox et al 1995; Nichols and Martin 1996). In the study of Fox et al (1995) differences were found for the N4 and a "late memory wave" (positivity from 700-1100 ms). Nichols and Martin (1996) found smaller amplitudes for the heavy social drinkers of the P3 component elicited by both recalled and non-recalled words. In a simulated driving task Nichols and Martin (1993) found a shorter latency of the P3 peak in light social drinkers compared to heavy social drinkers, but no differences in amplitude.

The present study was designed to detect possible differences between groups of social drinkers and excessive drinkers using a visual and auditory task. It is hypothesized that with increasing alcohol intake an increasing number of ERP components elicited by a visual attention task and an auditory odd-ball task would show diminished amplitudes.

For the visual attention task we hypothesize that with longer drinking history and higher regular alcohol consumption diminished N1, N2b, occipital selection negativity, and frontal selection positivity will be found. Since we controlled for family history of alcohol related disorders, no effect of chronic alcohol consumption is expected on the P3 amplitude.

For the two-channel auditory odd-ball task we hypothesize that with longer drinking history and higher regular alcohol consumption more pronounced ERP effects will be found, in particular a reduced mismatch negativity and a reduced processing negativity (these components are found on comparable latencies as the former discussed N2 amplitudes). No effects of social drinking was expected for the N1, or the P3 (see above). All these alcohol related changes in ERPs might be found in the absence of behavioral effects.

MATERIALS AND METHODS

PARTICIPANTS

Male participants between 30 and 65 years of age were recruited with advertisements in local and national newspapers; excessive drinkers were also recruited at in-patient treatment centers. All participants were treated in accordance with the declaration of Helsinki and provided written informed consent before participating in the study. Participants were paid 70 euros for completing the whole experiment, which consisted of a telephone screening, a medical screening, a task session including ERP recording and a magnetic resonance imaging (MRI) session.

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PROCEDURE

Participants were asked to abstain from smoking for at least three hours prior to the experiment and to refrain from drinking alcohol for 24 hours prior to the experiment. Blood Alcohol Levels were determined with a breath test device (Alcotest, Dräger Medical, Lübeck, Germany) and urine screening was done for THC, cocaine, barbiturates, benzodiazepines and morphine (Rapid Drug Testing Services, Inc; Key Largo, US). If a participant tested positive another appointment was made for the ERP session and the participant was excluded when tested positive twice. Participants were instructed not to drink coffee or tea on the day of the experiment. After the electrodes for ERP recording had been attached, participants were escorted to the electrically shielded, soundproof cabin and seated in a chair at a distance of 100 cm from a computer monitor. They were instructed to restrict their movements. The experiment consist-

ed of six tasks: an auditory odd-ball task, a visual attention task, a go/nogo task, a verb generation task, a card-sorting task, and an EEG mental rehearsal task. Here we report the results of the auditory odd-ball task and the visual attention task. The order of these tasks was balanced across participants.

THE VISUAL ATTENTION TASK

Four different black and white gratings were presented on a gray background. The gratings had high or low spatial frequencies (3.2 and 0.8 cycles per degree) and were presented in a horizontal or vertical orientation. All stimuli had a probability of 0.25 and were randomly mixed in two blocks of 300 stimuli each. Stimuli could be either target, orientation relevant, frequency relevant or irrelevant, depending on the instruction. Each participant had to attend to one spatial frequency in the first, and to the other in the second block, but to the same orientation. Thus, target frequency was balanced within participants and orientation was balanced between participants. Participants were instructed to look at a fixation cross that was presented in the center of the visual field throughout the task. Before each block the participants were instructed to respond to one particular target by pressing a button as fast as possible with the right-hand index finger. Stimulus duration was 50 ms, and the inter stimulus interval (ISI) varied between 750 and 1000 ms. Before the start of the task participants performed a practice block of 30 stimuli.

AUDITORY ODD-BALL TASK

Four different stimuli were used, all consisting of pure sinus waves (tone frequency of 1000 or 1100 herz) of 95 dBa (measured with a Brüel & Kjær audio measuring device type 2226) presented to either the left or the right ear. The tone frequency determined if the stimulus was a standard tone, which appeared in 80% of the cases, or a deviant tone, which appeared in the resulting 20% of the cases. The stimuli were presented evenly to each channel (right and the left ear), which was defined as an attended and an unattended channel; two attended deviants were never presented immediately after each other. The participants were instructed to push a button as fast as possible if the deviant tone occurred in a previously designated ear (attended channel). The task was divided in two blocks of 300 randomly mixed stimuli. Each participant had to attend to a different channel in the first and second block, but to the same tone frequency. Tone frequency was balanced between subjects and channel was balanced within subjects. Participants were instructed to keep their eyes open and to watch a fixation-cross that was presented in the center of the visual field throughout the whole task. Before each block the participants were instructed to respond to one particular target by pressing a button as fast as possible with the right index finger. Stimulus duration was 50 ms, and the ISI varied between 750 and 1000 ms. Before the start of the task participants performed a practice block of 60 stimuli; the practice block was repeated twice if the task was not understood or tone frequencies could not be discriminated. Some participants still failed to discriminate between the high and low tone; they were excluded from further analyses in this task.

DATA RECORDING AND ANALYSIS

EEG was recorded using an electrode cap with 64 tin electrodes, with the left mastoid as ref-

erence. Horizontal electro-oculogram (HEOG) was recorded from the outer canthus of each eye, and vertical electro-oculogram (VEOG) was from electrodes placed infra- and supra-orbitally to the left eye. The ground electrode was placed at AFz. Impedance was kept below 10 kW. All signals were amplified by Synamps amplifiers with online low-pass filters at 50 Hz and high-pass filters at 0.10 Hz. Signals were digitized at 250 Hz.

Epochs lasted 1000 ms, including 100 ms preceding the stimulus, which served as baseline. Off-line, all signals were filtered with a 30 Hz low-pass filter. All channels, except the EOG channels were used to calculate an average reference. Trials with amplifier blocking, artifacts or flat lines were detected off-line and omitted from further analysis. Ocular artifacts were controlled by time-domain regression analysis (Gratton et al 1983). All epochs with minimum to maximum amplitude of more than 100 μV after the ocular artifact correction were omitted from further analysis. Trials with incorrect responses were also omitted from analysis. Averages were calculated according to stimulus type.

In the auditory odd-ball task participants were excluded if they had less than 60 % hits or less than 75% correct rejections. In total, on the basis of this criterion five participants were excluded: 2 light social drinkers, 1 moderate social drinker, 1 heavy social drinker and 1 excessive drinker. These extreme values reflect inability to discriminate between tone frequencies. In the visual attention task no participants were excluded on the basis of performance (no error rates above 10%). All averages were calculated according to stimulus type.

STATISTICAL ANALYSIS

Performance

Statistical analyses were performed using the SPSS software (SPSS 10.0, SPSS Inc., Chicago, IL, USA). Dependent variables were the mean reaction times and the number of correct responses and false alarms. Differences in these behavioral measures between the four groups were tested with an ANOVA, with Group as a between-subjects factor.

ERPs

Preplanned statistical comparisons were conducted with respect to the mean amplitude of selected components. For the visual attention task ANOVAs were conducted for the N1 amplitudes (Fz and Oz; 80 - 100 ms), with Group as between-subjects factor and Frequency and Orientation as within-subjects factors with both two levels. In addition, four difference waves were calculated (Kenemans et al 1995). The frequency relevant minus irrelevant subtraction yielded the frontal selection positivity (Fz; 200 - 250 ms), N2b (Cz; 240 - 290 ms) and the occipital selection negativity (Oz; 220 - 270 ms). Target minus orientation relevant stimuli revealed the P3b (Pz; 390 - 440). All difference wave values were entered in an ANOVA with Group as between-subjects factor.

For the auditory odd-ball task the attended standard minus unattended standard subtraction resulted in the Processing negativity (FCz; 220 - 260 ms), and the unattended deviant minus unattended standard subtraction yielded the Mis-match negativity (FCz; 250 - 300 ms) (Näätänen et al 1993). Both difference wave values were entered in an ANOVA with Group as

between-subjects factor. Separate ANOVAs are conducted for the N1 (FCz; 80 - 120 ms) and P3 (Pz; 400 - 450 ms) amplitudes, with Group as between-subjects factor and Channel and Deviance as within-subjects factors with both two levels. In all tests a critical α-level of 0.05 was used. However, in case of Group differences or Group*Trial interactions, pairwise comparisons for significant differences between Groups were Bonferroni corrected.

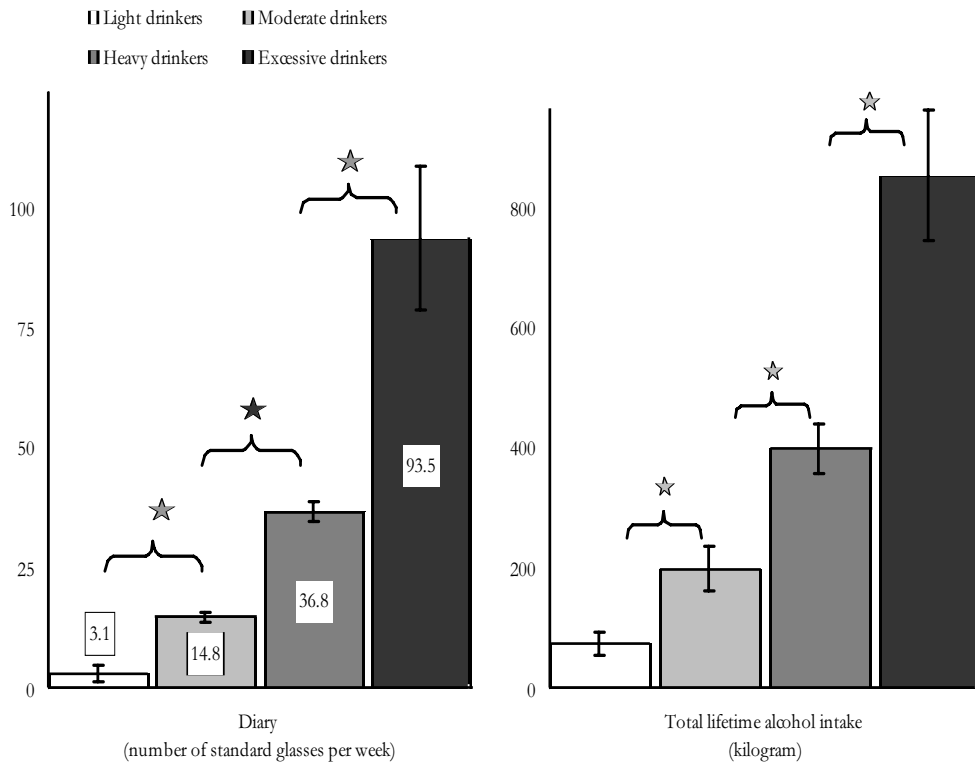

Figure 3. Mean ± SEM for the number of standard glasses a week as reported in the drinking diary and the total lifetime alcohol intake in kilograms for the four groups. Differences between groups are marked with stars. Black stars indicate p values <0.001; Grey stars indicate p values < 0.05; Post-hoc Dunnet-T3 test is used for the alcohol measures

RESULTS

DRINKING HISTORY AND DEMOGRAPHIC VARIABLES

A description of Age, IQ as measured with the NLV, and smoking for the four Groups is given in Table 1 and 2. All groups were of similar ages, had similar NLV scores, and did not significantly differ in the amount of cigarettes smoked a week. As expected, groups differed in the number of glasses a week reported in the drinking-diary (Visual attention Group: $F(3,53) = 59.82$; $P < 0.001$; Auditory odd-ball Group: $F(3,49) = 53.72$; $P < 0.001$), and in the total lifetime alcohol-intake (Visual attention Group: $F(3,55) = 35.98$; $P < 0.001$; Auditory odd-ball Group: $F(3,49) = 39.96$; $P < 0.001$) (see figure 1 for a histogram for the different groups in the visual attention task). Two participants in the excessive group did not fill in the drinking diary as they had abstained from drinking alcohol two weeks before inclusion in the study, but these participants did fill in the LDH questionnaire on which the total lifetime alcohol-intake was based.

Table 1. Mean age, estimation of the number of standard glasses consumed a week (12 grams of alcohol), number of cigarettes smoked a week and mean Reaction time on Hits and False alarms for the four groups in the visual attention task. Since not all subjects made False alarms this test included 56 participants

	Light drinkers Mean ± SD	Moderate drinkers Mean ± SD	Heavy drinkers Mean ± SD	Excessive drinkers Mean ± SD	F (3,55)	P
Age	47.2 ± 9.7	50.2 ± 8.0	51.9 ± 8.0	49.4 ±8.0	.87	n.s.
NLV IQ	108.0 ±9.0	105.1± 7.0	110.3 ± 5.2	103.8 ± 11.2	2.02	n.s.
Smoking (number of cigarettes a week)	3.3 ± 0.9	5.0 ± 1.3	9.7 ± 4.6	9 ± 5.2	1.32	n.s.
Mean Reaction time on Hits	431.9 ± 59.0	432.9 ± 42.6	395.1 ± 52.0	437.42 ± 58.5	2.34	n.s.

(n.s. = not significant)

Table 2. Mean age, estimation of the number of standard glasses consumed a week (12 grams of alcohol) and number of cigarettes smoked a week for the four groups included in the auditory oddball task

	Light drinkers Mean ± SD	Moderate drinkers Mean ± SD	Heavy drinkers Mean ± SD	Excessive drinkers Mean ± SD	F (3.50)	P
Age	48.9 ± 9.5	50.6 ± 8.1	52.5 ± 7.9	51.4 ±5.3	.51	n.s.
NLV IQ	110.6 ±6.1	105.5 ± 7.0	110.1 ± 5.3	106.3 ± 8.3	2.13	n.s.
Smoking (number of cigarettes per week)	3.6 ± 1	5.2 ± 1.3	9.9 ± 4.9	8.9 ± 4.2	.98	n.s.
Mean Reaction time on Hits	413.1 ± 87.3	486.6 ± 56.3	469.72 ± 64.4	457.0 ± 54.2	2.90	< 0.05

(n.s. = not significant)

PERFORMANCE VISUAL ATTENTION TASK

No differences between the four groups were found concerning the percentage of correct reactions or the mean reaction times for Hits. Mean reaction times on Hits and False Alarms are shown in Table 1 and percentage of correct responses is shown in Figure 2.

ERPS VISUAL ATTENTION TASK:

The frequency relevant minus irrelevant subtraction resulted in a frontal selection positivity that differed significantly from zero ($F(1,55) = 11.98$; $P < 0.01$). No differences between the four groups were found on the frontal selection positivity (see Figure 3). The N2b differed significantly from zero ($F(1,55) = 59.59$; $P < 0.001$). No differences between the four groups were found for the N2b amplitude. The Occipital selection negativity, differed significantly from zero ($F(1,55) = 33.49$; $P < 0.001$). No differences between the four groups were found for the Occipital selection negativity (see Figure 3). The target minus orientation relevant subtraction resulted in a significant P3b ($F(1,55) = 102.69$; $P < 0.001$). No differences between the four groups were found for the P3b amplitude. The N1 amplitude at Fz to the frequency relevant stimuli was significantly larger than that to the frequency irrelevant stimuli ($F(1,55) = 6.46$; $P < 0.05$). No effects involving the factor Group were found (see Figure 4). The N1 amplitude at Oz was much more pronounced than that at Fz, but no effects of stimulus type were found. In addition, no differences between the four groups were found for the Occipital N1 (see Figure 4).

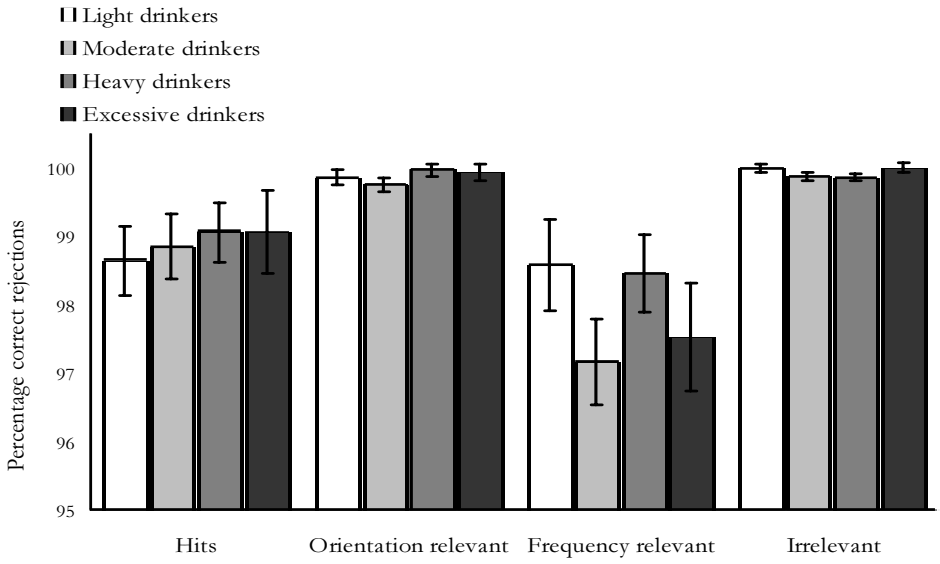

Figure 2. Percentage of correct responses in the visual attention task for the different types of stimuli

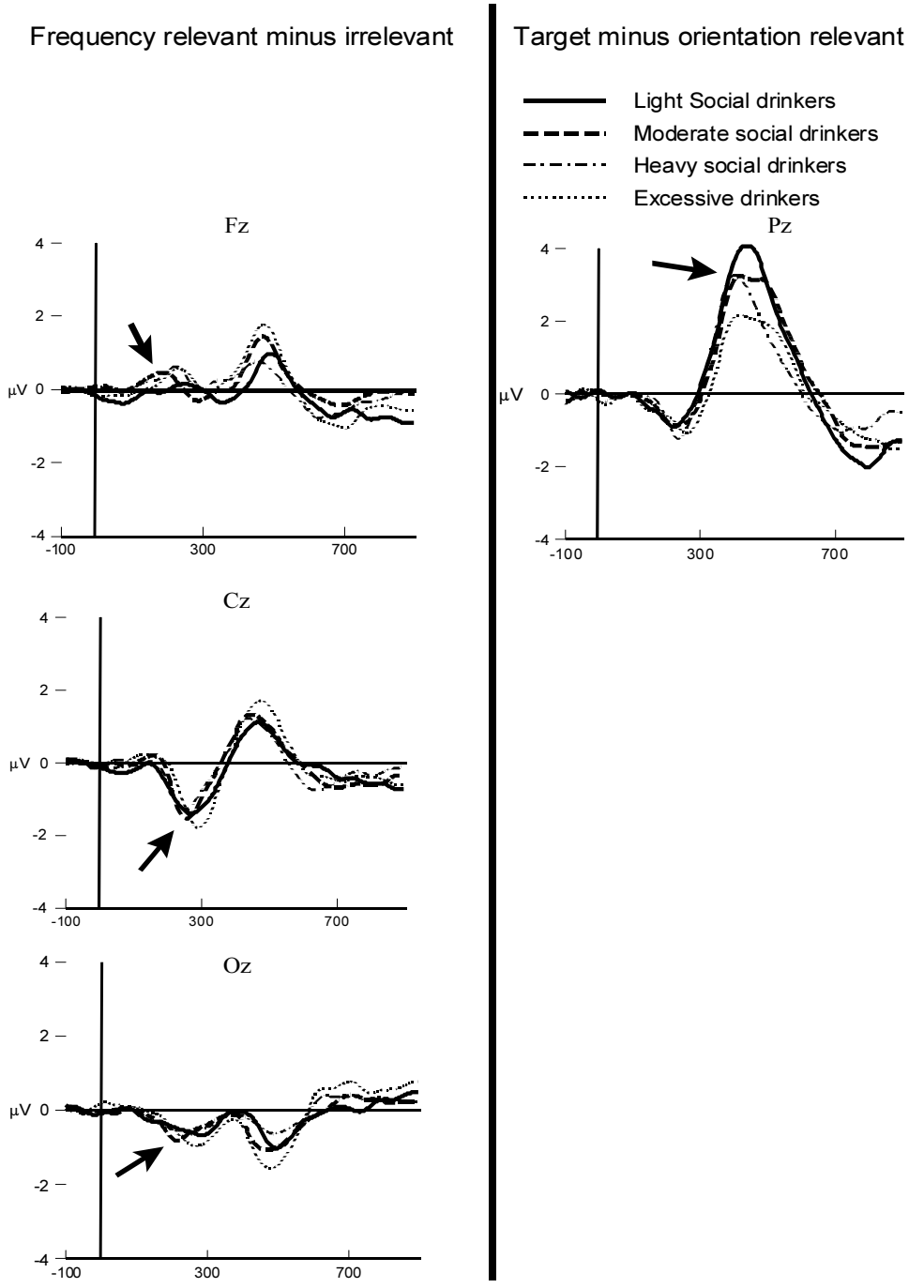

Figure 3. Difference waves for the visual attention task. In the left column the subtraction for frequency relevant minus irrelevant stimuli is displayed for Fz, Cz and Oz. In the right column the subtraction for targets minus orientation relevant stimuli is displayed for Pz. Arrows indicate significant task effects

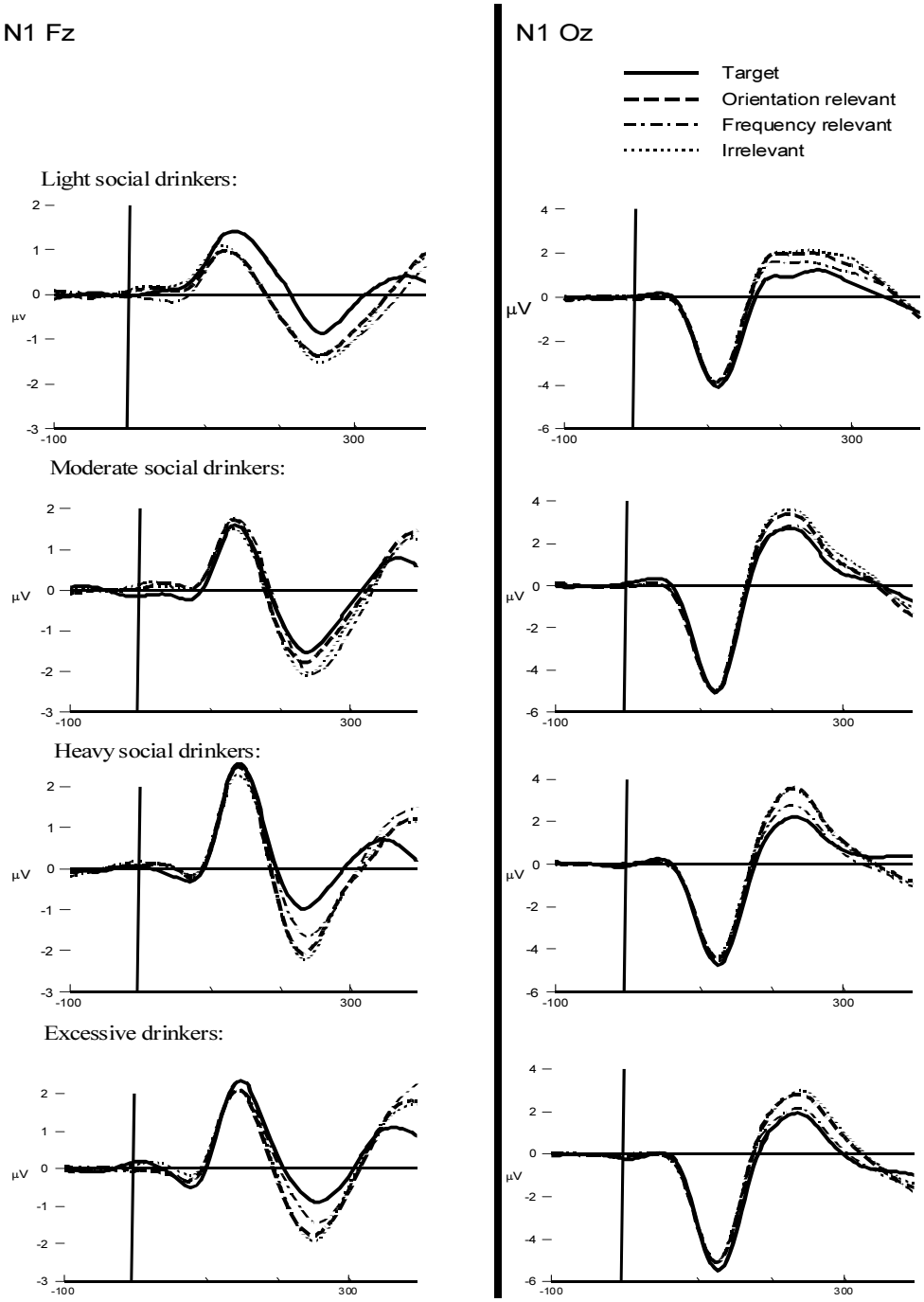

Figure 4. ERPs for the N1 in the visual attention task. In the left column Fz is displayed, and in the right column Oz is displayed. Notice that the scaling is not equal for Fz and Oz

PERFORMANCE AUDITORY ODD-BALL TASK

No differences between the four groups were found concerning the percentage of Hits and Correct rejections. The difference between the groups in mean reaction time was significant ($F(3,50) = 2.90$; $P < 0.05$). Post-hoc tests showed shorter reaction times for the light social drinkers than for the moderate social drinkers ($F(2,25) = 2.84$; $P < 0.05$). Mean reaction times are shown in Table 2.

ERPS AUDITORY ODD-BALL TASK

The processing negativity was significantly different from zero ($F(1,50) = 125.66$; $P < 0.001$). No differences between the four groups were found on the processing negativity (see Figure 5). The mismatch negativity also differed significantly from zero ($F(1,50) = 41.15$; $P < 0.001$). For this difference wave also no effects involving the factor Group were found (see Figure 5). The N1 amplitude at FCz did not show any effects of the stimulus conditions, and no effects involving the factor Group were found (see Figure 6). The P3b for the attended channel was larger than that for the unattended channel ($F(1,50) = 79.93$; $P < 0.001$). Furthermore, P3bs to the deviant stimuli were larger than those to the standard stimuli ($F(1,50) = 94.75$; $P < 0.001$). Channel side and attention did interact with each other ($F(1,50) = 70.70$; $P < 0.001$), reflected in the highest amplitude for the attended deviant stimuli. No effect involving the factor Group was found on the P3b (see Figure 6).

In this study no differences between social drinking groups were found on the visual attention task and the auditory odd-ball task. In contrast, previous research using alcohol dependent alcoholics did find differences between alcohol dependent participants and controls (see for a review Porjesz and Begleiter 1996). Therefore, an additional post-hoc analysis was performed between the light social drinkers and the five alcohol dependent participants in the excessive drinkers group. When contrasting the five alcohol dependent participants with the Light social drinkers group, a trend was found towards higher positive amplitudes for the visual P3b in the light social drinkers than in the alcohol dependent drinkers ($F(1,18) = 3.75$; $P = 0.071$; see Figure 3). No additional effects were found on the other components elicited by the visual attention task or the auditory odd-ball task.

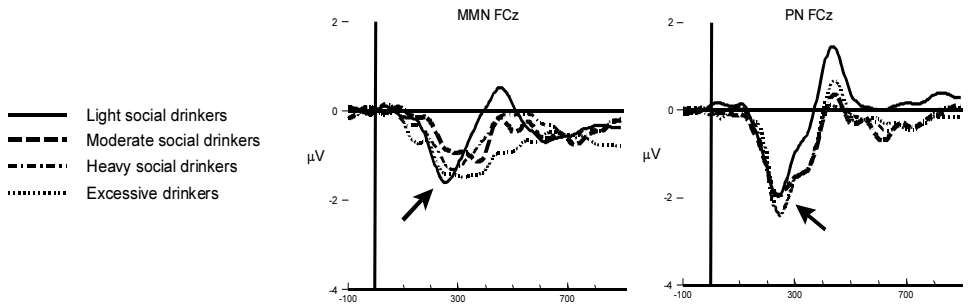

Figure 5. Difference waves for the auditory oddball task. The left column shows the MMN and the right column shows the PN

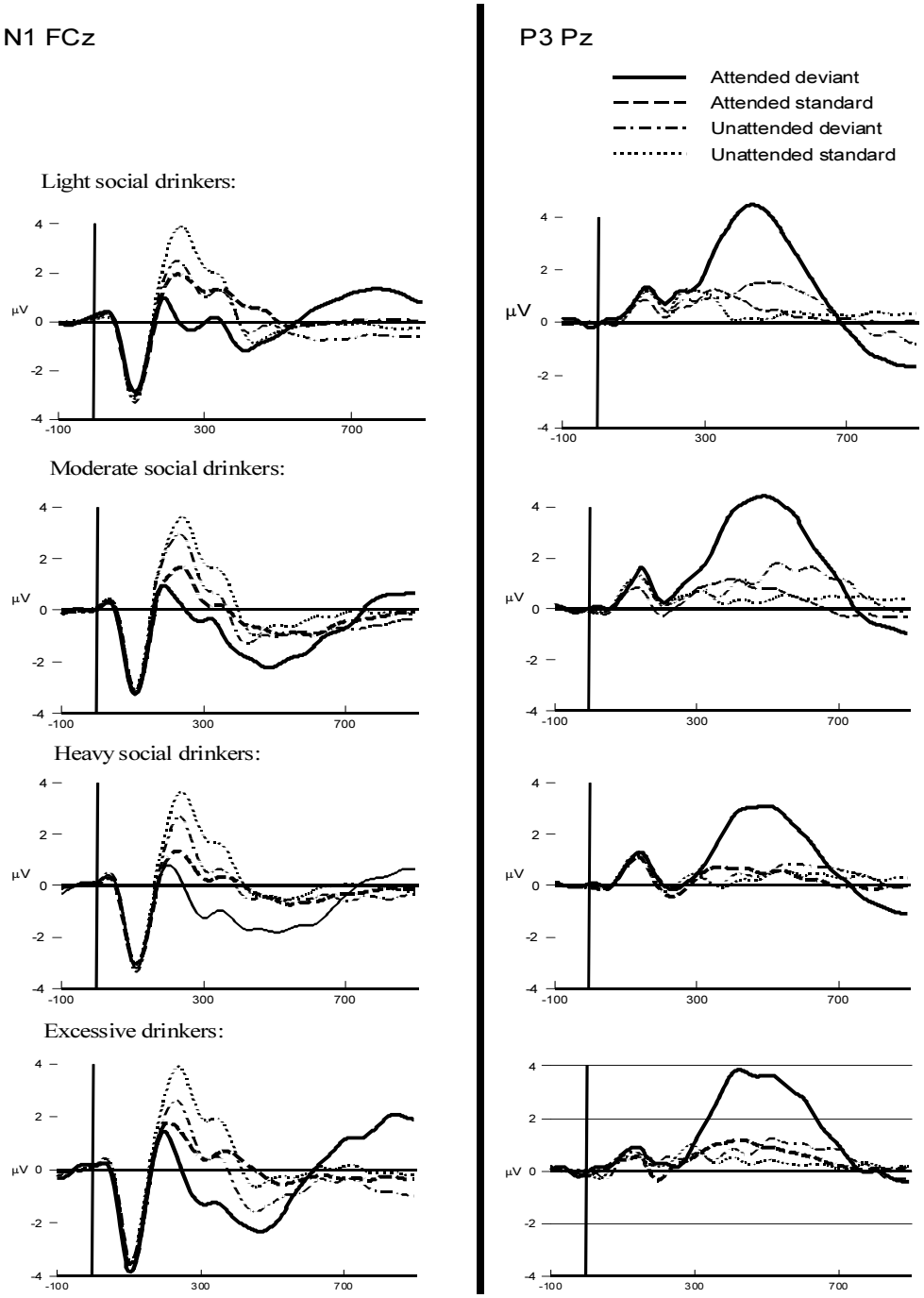

Figure 6. ERPs for the N1 and P3 in the auditory oddball task. In the left column FCz (N1) is displayed, and in the right column Pz (P3) is displayed

DISCUSSION

A visual attention task and an auditory odd-ball task were used to assess the effects of social drinking on the electrical activity of the brain. The expected task effects on ERP were found, but did not differ between the different groups of social drinkers included in this study. With respect to behavioral measures, in the auditory odd-ball task the light social drinkers showed shorter reaction times to hits than the moderate social drinkers did. This is probably a motivational effect, and not an effect of social drinking, since the light group did not differ from the heavy or the excessive drinkers.

In the excessive drinkers group five participants scored for alcohol dependency according to the DSM-IV criteria. When contrasting these alcohol dependent participants with the light drinkers a trend was found towards a larger P3b amplitude in the visual attention task for the light social drinkers; no effects were found on the earlier components of the visual attention task or the auditory odd-ball task. The combination of results in the present study seems consistent with previous studies using alcoholic participants and controls in which effects of alcoholism were most often found using visual attention tasks, and less consistently in auditory tasks.

Since there was no significant difference in amount of alcohol consumption on drinking diary ($F(1,6) = 1.3$; P = n.s.) or lifetime alcohol intake ($F(1,8) = .012$; P = n.s.) between the alcohol dependent excessive drinkers (mean: 80 glasses a week and 865 kilograms total lifetime alcohol intake) and the non-dependent excessive drinkers (mean: 115 glasses a week and 840 kilograms total lifetime alcohol intake), it is not likely that the smaller P3b component in alcohol dependent drinkers is related to the toxic effects of regular alcohol use. This P3b component is probably more related to the diagnosis of alcohol dependence according to the DSM-IV criteria. It could be that this alcohol dependence results in an abnormal P3b because this subgroup of alcohol dependent participants is more vulnerable to the toxic effects of alcohol. Another possible explanation could be a genetic influence in the alcohol dependent participants. In other tasks it has repeatedly been shown that ERPs, specifically the parietal P3b component, are sensitive to genetic influences (Polich et al 1994; Van Der Stelt et al 1994; Porjesz and Begleiter 1996; Van Der Stelt et al 1998). Pfefferbaum et al (1991) showed that alcoholics with a positive family history of problem drinking had smaller P3bs than did alcoholics who reported a negative family history. These authors also demonstrated that these smaller P3b amplitudes in family history positive alcoholics were independent of their lifetime alcohol consumption. In the present study, we controlled for possible genetic influences by excluding participants who had alcohol dependent relatives in the first or second degree. However, it is possible that participants in our study could not report about alcohol dependent relatives since these relatives had died at young age, or the participants did not know that there was an alcohol-related problem in these relatives. Since the current P3b effect is found exclusively in the alcohol dependent participants and not in the social drinking groups, it is concluded that this ERP component is not sensitive to the effects of social drinking. In addition, since no other differences between the social drinkers were found, we conclude that brain structures underlying the visual attention task and auditory odd-ball task used in the current study are not sensitive to the effects of social drinking. However, more research should be done in alcohol dependent participants with and without a positive family history of alcohol disorders, to investigate if these components

of the attention tasks are sensitive either to chronic effects of alcohol abuse or to any genetic dispositions.

When comparing the current study with other studies using visual attention or auditory odd-ball tasks, it seems that we report smaller absolute amplitudes. These lower amplitudes may for a large part be due to the average-reference transformation, that was currently applied to enable unbiased comparisons between signals recorded over the left versus right hemisphere. Another factor is age: compared to former studies, the current study included older participants with possible reduced ERP amplitudes, relative to younger participants (Kenemans et al 1995).

Earlier research in social drinkers using ERP tasks did find differences between heavy and light social drinkers (Nichols and Martin 1993; Fox et al 1995; Nichols and Martin 1996; Chao et al 2003). However, Chao et al (2003), who found a diminished amplitude of the contigent negative variation in heavy social drinkers, did not control for a family history of alcohol disorder in the statistical analysis, although a separate analysis showed a trend for smaller CNV amplitudes in the family history positive participants. The other studies excluded participants with a positive family history of alcohol disorders (Nichols and Martin 1993; Fox et al 1995; Nichols and Martin 1996). In these studies different tasks were used. Two studies used a memory task to assess differences between social drinkers (Fox et al 1995; Nichols and Martin 1996) and Nichols and Martin (1993) used a visual simulated driving task. In contrast to simple visual gratings and pure sounds used for the tasks in the current study, these tasks used complex stimuli (i.e. word and pictures of driving situations). In addition, more complex cognitive actions were demanded, participants had to remember words, or had to select between actions during simulated driving. These tasks probably rely on the integrity of more and/or other brain areas than the simple attention tasks in the current study. It is suggested that heavy social drinkers only differ from light social drinkers in tasks that are more complex and thus rely on the integrity of more brain areas and functions, or that that the brain areas underlying visual and auditory attention are less sensitive for the effects of chronic alcohol consumption than the areas involved in memory or language tasks.

Overall, it is concluded that in the current study, even at rather large amounts of regular alcohol intake, no evidence is found for any toxic effect of chronic social alcohol use neither in a visual attention task nor in an auditory odd-ball task.

CHAPTER 6

Chapter 6

Discussion and Conclusions

ABSTRACT

The aim of this study was to investigate the consequences of chronic non-pathological drinking, i.e., social drinking, on brain functioning. Social drinking participants were assessed on cognitive tasks while ERPs were recorded. The cognitive tasks in the present study were chosen because normal functioning in these tasks allegedly depends on undamaged frontal lobes. Effects of social drinking were only found in tasks using language and working memory functions. In tasks which aimed to measure aspects of attention and inhibition no effects of chronic social drinking were found. With respect to the behavioral data, only the number of retrieval errors made in the verb generation task revealed significant effects of (heavy) social drinking

THE PARTICIPANTS

Only physically and mentally healthy participants were included in this study. The most important exclusion criteria were DSM-IV psychiatric disorders and the exclusion of participants with a family history of alcohol-related disorders. Inclusion of excessive drinkers who met these criteria was problematic, indicating that the use of excessive amounts of alcohol often has co-morbidity with psychiatric disorders, and/or a family history of alcohol related disorders. However, because of these strict criteria, the results described in this thesis can be viewed as fully reflecting the chronic effects of (social) drinking, rather than effects of gender, genetic predisposition, or age related effects. One remark must be made concerning the control for genetic predisposition towards alcohol related disorders. Since we could only control for family histories concerning alcohol related problems by interviewing the participants, it is possible that some cases were not detected. For example, some participants had parents who died at a young age, or with whom they had lost contact. In those cases, the family history was investigated as tho-roughly as possible, but these participants were not excluded. Thus, it could be that some participants had a, to them unknown, family history of alcohol related disorders. This issue will be discussed further later in this chapter. All groups differed from each other with respect to the number of standard glasses (12 grams of alcohol) consumed per week as measured with the two-week drinking diary and the lifetime alcohol intake as measured with the Lifetime Drinking History (LDH) questionnaire (Skinner and Sheu 1982; as adapted for the Netherlands by Lemmens et al 1997).

THE TASKS AND THE EXPECTED TASK EFFECTS ON BEHAVIOR AND ERPS

Five tasks were used in this study: the verb generation task, the Wisconsin card sorting task, the continuous performance task and two attention tasks (visual and auditory). The five tasks were described in detail in chapter two, three, four and five, respectively.

In the verb generation task differences between the generating verbs condition and the control condition, in which participants had to read nouns aloud, were found at the mid-frontal, right-frontal, left-frontal, left-parietal and left-occipital scalp locations. These ERP components most probably reflect aspects of attention, response preparation, semantic processing, semantic integration, and word form recognition, respectively (Snyder et al 1995; Abdullaev and Posner 1998).

For the Wisconsin card-sorting task differences between the early and late trials in response to the card stimuli were found at the mid-parietal scalp location, whereas ERP components to the feedback stimulus revealed significant task effects at the mid-frontal, right-parietal, left parietal, and mid-parietal scalp locations. These task effects probably reflect orienting of attention, shifts of attention, and the updating of context, respectively (Barcelo et al 1997 and Barcelo 2003).

For the continuous performance task, significant task effects were found at mid-frontal, mid-central, and mid-parietal scalp locations, these effects are thought to be related to aspects of inhibition and response preparation (Kiefer et al 1998; Falkenstein et al 1999; Bokura et al 2001).

For the visual attention task significant task effects were found at mid-frontal, mid-central, mid-parietal, and mid-occipital scalp locations. The auditory odd-ball task revealed task effects at

mid-central and mid-parietal scalp locations. These task effects probably reflect aspects of (selective) attention and template matching (Porjesz and Begleiter 1996b). A depiction of the scalp locations at which task effects were found is given in Figure 1.

All tasks revealed the expected task related ERP components. Some differences were noticed between former studies and some of the current studies concerning the absolute amplitudes. This was for a large part due to the average-reference transformation, that was applied to enable unbiased comparisons between signals recorded over the left versus right hemisphere. Another factor that might be related to the smaller observed ERP waves is age: compared to other studies, the current study included older participants with possibly reduced ERP amplitudes, relative to younger participants (Wegesin et al 2002).

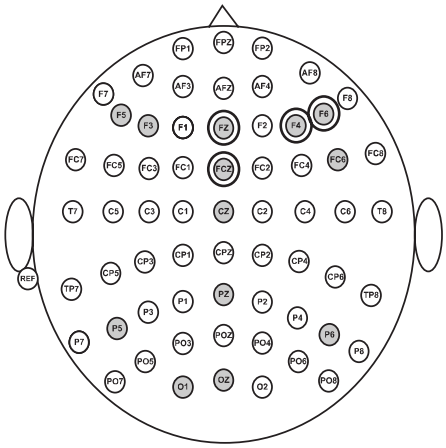

Figure 1. A depiction of the measured scalp locations. Gray circles indicate measured task effects; black circles indicate significant interactions between task and group

We conclude that in the present study most of the expected task effects on behavioral measures and the ERP components were indeed observed, this confirms their suitability for a further analysis on the effects of social drinking on brain function.

THE TASK EFFECTS AND THE EFFECTS OF SOCIAL DRINKING

Verb generation task

Two studies were described. Study 1 involved two groups of students, a moderate social drinkers group and a heavy social drinkers group. Study 2 involved three older groups of social drinkers (light, moderate and, heavy) and an excessive drinkers group (mean age approximately 50 years). Interaction effects between group and verb generation were found at one mid frontal scalp location and at two right frontal scalp locations. An expected task effect, larger amplitudes for generating than for reading at an early latency at Fz, was found in both groups in study 1, but only for the light social drinkers in study 2. The moderate, heavy and excessive drinkers in study 2 did not show this task effect. The absence of the expected task effect at Fz in the heav-

ier drinking groups in study 2 could not be attributed to the effects of alcohol only, since it was also present in the heavy student social drinkers, who drank more or equal amounts of alcohol compared to the moderate and heavy group respectively. In addition, the absence of this task effect can also not result from aging only, since it was present in the light social drinkers, who did not differ in age from the other groups in study 2. Therefore, we conclude that the mid-frontal ERP task effect at Fz is sensitive to both the effects of alcohol and age. The early activation at Fz is probably generated in the anterior cingulate cortex as has been suggested in former PET and ERP research with the verb generation task (Posner et al 1988; Posner and Raichle 1994). The latter authors argued that the early mid-frontal activity reflects a higher attentional resource allocation in the generating condition. However, more recent research has shown activation of the anterior cingulate cortex in tasks involving conflict monitoring (inhibition task, Stroop task, Eriksen flanker task; Carter et al 1998; Botvinick et al 2001). Since there is convincing evidence that the early activation measured at the midfrontal lead Fz is generated in the anterior cingulate cortex (Abdullaev and Posner 1998; Posner and Pavese 1998), this activation may also be related to conflict monitoring. The verb generation task in the present study might be comparable, to some extent, to the Stroop task. While in the Stroop task reading the word must be inhibited in favor of naming the color of the word, in the verb generation condition reading of the word must be inhibited in favor of generating a verb. In addition, the first association with the presented noun must be evaluated to check if this association is indeed a correct verb for the presented noun.

Excessive drinkers also made more retrieval errors than the heavy social drinkers and differed at right frontal (F4) ERP components from the heavy social drinkers. A third interaction effect was found at the right frontal lead F6. Since F6 is located close to F4, and the timing of these effects was comparable, these effects probably reflect the same neuroanatomical process. At F6 higher amplitude was found for generating than for reading for the moderate drinkers of study 1 and the light drinkers of study 2. These two groups had equivalent lifetime alcohol intake scores, which were both lower than the lifetime alcohol intake scores for the heavy student drinkers of study 1, and those for the moderate, heavy and excessive drinkers of study 2, who did not show a task effect at F6. Abdullaev and Posner (1998) argued that this late right frontal ERP component might be related to the planning of articulatory movements, which is discussed in more detail in chapter 2. In addition, we hypothesize that the right frontal activity has a relation with the originality or difficulty of the generated verb.

The pattern of results found in the present study suggests differential effects of social drinking on frontally recorded ERP components in the verb generation task. Thus, alcohol seems to affect different ERP components. Some of these components probably interact with age.

Wisconsin card-sorting task

In the Wisconsin card-sorting task the N1 ERP component in response to the feedback stimuli differed between groups. The light social drinkers showed a trend towards more early negativity (N1) on early trials than on late trials; this effect was significant for the moderate drinkers, but absent in the heavy and excessive groups. It is argued that this frontal N1 component might reflect processes of orienting of attention, since the feedback contained more relevant information on early than on late trials. The absence of this N1 effect in the heavy and excessive

drinkers might indicate diminished attentional orienting abilities in these groups. Diminished N1 effect in alcoholics compared to controls were also reported by Porjesz and Begleiter (1982), they suggested that alcoholics have problems with sensory filtering. It could also be that the N1 reflects activity in the anterior cingulate cortex, which has been contended to be involved in conflict monitoring (Carter et al 1998; Botvinick et al 2001). In the present study, on early trials, there is a 50 % possibility of conflict between the applied sorting rule and the feedback information. This information is probably used more effectively in the light and moderate social drinkers, reducing the conflict perception in the late trials, whereas the heavier groups react comparable on early and late trials. It even might be that the heavier groups are a bit surprised when performing the task correctly, resulting in a greater conflict in the late trials, which had to be performed correctly to enter the ERP analyses.

In conclusion, in the Wisconsin card-sorting task, the difference between early and late trials in N1 amplitude disappeared with increasing alcohol intake, which could reflect impaired allocation of attention or impaired conflict monitoring.

Continuous performance task, Visual attention task and Auditory odd-ball task

In the continuous performance and the visual attention tasks no group differences were found with respect to reaction times, hits, or false alarms. With respect to the behavioral measures of the auditory odd-ball task, the light social drinkers showed faster reactions than the moderate social drinkers. However, this is probably a motivational effect, and not an effect of social drinking, since both the light and moderate groups did not differ from the heavy or excessive drinkers.

In neither the continuous performance task, the visual attention task, nor the auditory odd-ball task, differences between social drinking groups were found on the various ERP components. However, since in studies using alcohol dependent subjects altered ERP components on the continuous performance task (Fallgatter et al 1998; Pfefferbaum et al 1987), the visual attention task (Patterson et al 1987; Glenn et al 1996; Porjesz and Begleiter 1996; Rodriguez et al 1999; Malone et al 2001; Cohen et al 2002; Polo et al 2003), and the auditory odd-ball task (Patterson et al 1987; Realmuto et al 1993; Cohen et al 2002) have been repeatedly found, we decided post-hoc to further investigate the alcohol dependent participants. According to the DSM-IV criteria, a subgroup of five participants in the excessive drinking group scored for alcohol dependence. When contrasting this subgroup of alcohol dependent participants with the light social drinkers a significantly smaller frontal Go P3 was found in the continuous performance task, and a trend towards a smaller parietal P3 to the attended stimuli in the visual attention task was found. No effects were found with respect to the auditory odd-ball task. Since in both the continuous performance and visual attention studies there was no difference in amount of alcohol consumption between the alcohol dependent excessive drinkers and the non-dependent excessive drinkers, it seems not likely that the smaller P3 components in alcohol dependent drinkers are related to a toxic effect of regular alcohol use.

As stated before, we tried to control for possible genetic influences by excluding participants who had alcohol dependent relatives. However, since we could only control by the interviews

for family histories concerning alcohol related problems some positive cases might not have been detected. For example, some participants had parents who died at young age, or with whom they had lost contact. Thus it could be that some participants had a, to them unknown, family history of alcohol related disorders. Thus, it is possible that the people who scored for alcohol dependency have a as yet unknown genetic predisposition for alcohol dependency, which might be manifested in a lower P3 component. Pfefferbaum et al (1991) also suggested on basis of a hierarchical regression analysis that a reduction in parietal P3 amplitude might reflect genetic influences, but not current or lifetime alcohol consumption. Since the current reduction in parietal and frontal P3 is found exclusively in the alcohol dependent participants in this study and not in the social drinking groups, it is concluded that this ERP component is not sensitive to the effects of social drinking.

CONCLUSIONS THUS FAR

Although the P3 effects in the continuous performance task and the visual attention task cannot be attributed to the effects of social drinking, the effects found in the verb generation task and on the Wisconsin card sorting task can. The effects of social drinking appear to be subtle. Such effects might be specific in the sense that isolated brain areas (e.g. involved in planning of articulatory movements) are damaged, but it might also be that brain functioning is only affected when participants have to perform a more complex or demanding task. A task can be more complex or demanding in three different ways. First, tasks can vary in difficulty for the participants. In our study, low error rates were found in the continuous performance task and visual attention task compared to the verb generation and Wisconsin card-sorting task. Although groups had higher error rates in the auditory odd-ball task, this was probably more related to a diminished ability to distinguish between high and low pitches than to higher cognitive demands. For the verb generation task and the Wisconsin card-sorting task much higher error rates were found than in the visual attention, continuous performance, and auditory odd-ball task, indicating that the verb generation task and the card-sorting task were more difficult. Second, a task can be more complex, activating more brain areas, like for example in the verb generation task, which revealed a variety of components. Activation in multiple areas during complex tasks was also shown in an imaging study by Jansma et al (2001). These authors also showed that this activation decreased once the task becomes fully practiced. Third, tasks can require the integrity and communication of more brain areas or networks, thus not measuring isolated functions but more a combination of these functions, probably also reflected in the verb generation task and the Wisconsin card-sorting task. This view implies that more difficult tasks also activate more brain areas and require the integrity and communication of more brain areas or networks. Therefore, we suggest that a combination of these three possible explanations is applicable to the Wisconsin card-sorting task and the verb generation task, both being more complex and demanding. The idea that social drinking only affects more complex and demanding tasks is in accordance with earlier research on social drinking, because differences between groups of social drinkers have only been found in studies using relatively complicated tasks (Fox et al 1995; Nichols and Martin 1996; Nichols and Martin 1993). Thus, we can conclude that the amount of alcohol consumption, in the social drinking range, only has effects on more complex and demanding task that measure aspects of working memory or language functions.

THEORIES ABOUT THE LONG-TERM EFFECTS OF ALCOHOL ON THE BRAIN

Brain areas

Three hypotheses have been formulated in the literature about the locations in the brain where alcohol has its most damaging effect. Firstly, using cognitive tasks that rely on the integrity of the frontal brain areas, evidence has been found for the 'frontal-lobe' or 'anterior brain deficit' hypothesis in alcoholics (Ciesielski et al 1995; Dao-Castellana et al 1998; Ratti et al 1999; Demir et al 2002). Secondly, several investigators contended that 'right-hemisphere' integrity may be selectively disrupted (reviewed in Ellis and Oscar-Berman 1989). And thirdly, the brain damage found in alcoholics is allegedly non-specific as postulated in the 'diffuse brain deficit' hypothesis (Ellis and Oscar-Berman 1989; Lishman 1990). Could this study provide more insight in these hypotheses?

All significant alcohol effects in the current study were found at frontal scalp locations (see Figure 1). This does not necessarily mean that the sources of the activation were in frontal brain areas. However, when we compare our findings to those gathered in studies using imaging techniques, the possibility that the present frontal lead effects reflect differential frontal lobe activity, and that the present effects of alcohol reflect impaired frontal function, is supported. The early effect at Fz in the verb generation task can be related to studies that combined ERPs and PET (Snyder et al 1995; Abdullaev and Posner 1998). There, it was suggested that the early activation at Fz originated in the anterior cingulate cortex. Also, the later effects at F4 and F6 probably correspond to the effect found with PET in the right frontal cortex by Snyder et al (1995) and Abdullaev and Posner (1998). To our knowledge, no combined studies using ERP and imaging have been done using the Wisconsin card-sorting task. Although some debate exists on the exact nature of the frontal functions needed for adequate performance on the WCST, imaging studies have provided convincing evidence for at least an important contribution of the frontal brain areas (Berman et al 1995; Barcelo et al 1997; Volz et al 1997; Konishi et al 1998; Barcelo 1999; Konishi et al 1999; Monchi et al 2001; Barcelo 2003; Gonzalez-Hernandez et al 2003). Therefore, the alcohol related ERP results in the Wisconsin card-sorting task might be related to alcohol induced damage to the frontal lobes.

In conclusion, all effects of social drinking found in this study are thought to be frontally located, providing evidence for the 'frontal-lobe' or 'anterior brain deficit' hypothesis of alcohol. However, since the student drinkers only showed alcohol effects over the right side of the brain we hypothesize that the damage caused by alcohol begins with a selective disruption of the right side of the brain, which extends to mid-frontal locations in older social drinkers. No effects of social drinking were found over other brain areas, thus no evidence was found in this study for a diffuse damage of the brain due to alcohol.

The 'continuum' hypothesis

The 'continuum' hypothesis of Ryback (1971) proposes that the effects of alcohol on cognitive functions run from very mild effects in social drinkers, through more severe impairments in alcoholic patients to ultimately the neurocognitive deficits manifest in Wernicke-Korsakoff syndrome patients. In this study we expected mild cognitive effects in the social drinkers, for the

participants in this study were physically and mentally healthy persons. Mild effects were found, but only in the Wisconsin card-sorting task and in the verb generation task. In addition, we found trends in the continuous performance task and the visual attention task for additional abnormalities of P3 amplitudes in a subgroup of alcohol dependent participants. When looking at the ERP or behavioral effects per task, no specific pattern of results, which could indicate a dose response relationship between alcohol consumption and cognitive components, can be shown. However, when considering all the effects described in this thesis together, a pattern emerges of increasing brain malfunctioning with increasing alcohol intake being associated with task complexity (Figure 2). Therefore, we conclude that this study provides further evidence for Rybacks' 'continuum' hypothesis.

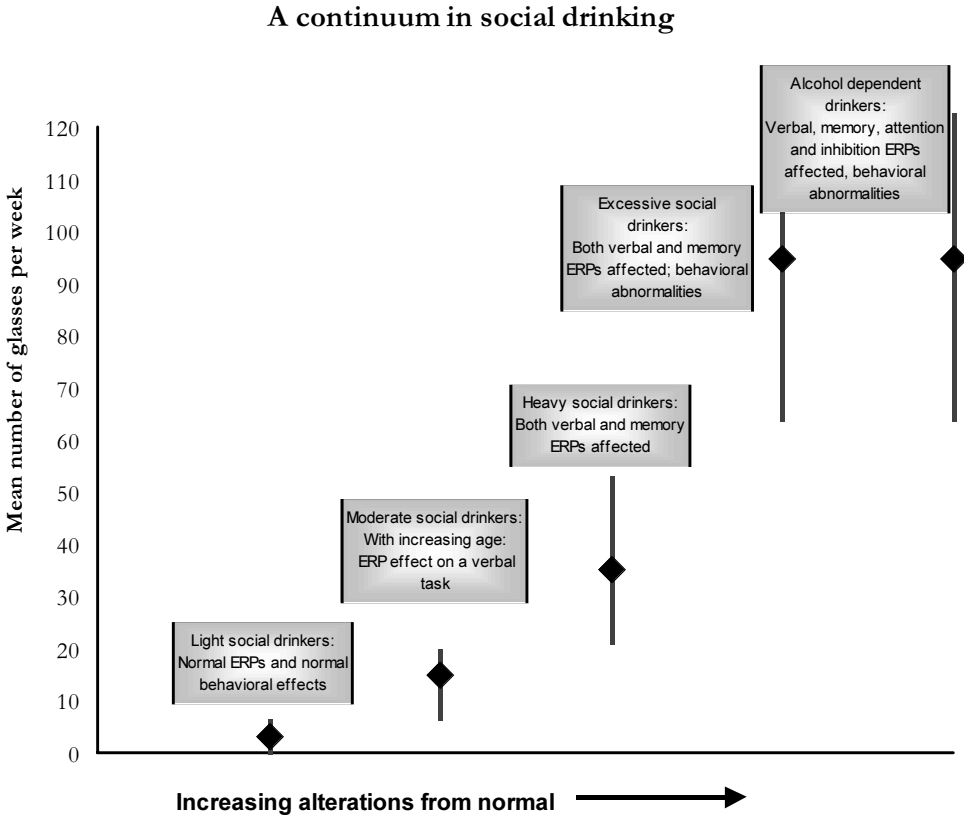

Figure 2. A schematic overview of the effects found in this thesis. The vertical lines indicate the ranges of number of standard glasses consumed in the different groups. Mean number of standard glasses are indicated by the diamond shapes.

HYPOTHESIS OF ALCOHOL AND AGING

Some similarities seem to exist between the neurocognitive effects of aging and alcohol use. Two hypotheses have been formulated to explain a possible relationship between aging and alcohol use. The 'increased vulnerability' hypothesis (Jones and Parsons 1971), states that with increasing age the brain becomes more vulnerable for the effects of alcohol. Thus, the older brain is more affected by the same amount of regular alcohol consumption than a younger brain. The second hypothesis about alcohol and aging is the 'accelerated aging' theory of Ryan and Butters (1984), which states that alcohol adds to the aging process. Thus, due to alcohol intake, the brains of alcoholics becomes old before their time.

In the current study the early effect at the mid frontal lead in the verb generation task provides some evidence for the increased vulnerability theory (Jones and Parsons 1971). The absence of a task effect at Fz in the heavier drinking groups could not be attributed to the effects of alcohol alone, since it was also present in the heavy student social drinkers of study 1, who drank more than the moderate drinkers of study 2. The absence of a task effect in the heavier drinkers in study 2 could also not be a result of age alone, since this task effect was also present in the light social drinkers of study 2, who were of comparable age. Therefore, it was concluded that the early mid-frontal difference between reading aloud and generating was affected by both alcohol and age, interacting in the way predicted by the 'increased vulnerability' hypothesis (see Figure 3).

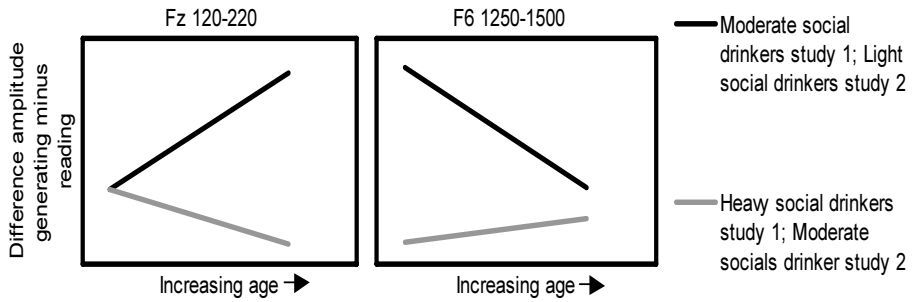

Figure 3. A schematic overview of the effects in study 1 and 2 on the verb generation task. The black line indicates the moderate students vs older light participants, who did not significantly differ on lifetime alcohol intake. The gray line indicates the heavy students versus the older moderate drinkers, who also did not significantly differ on lifetime alcohol intake

The right frontal task effect at F6 was found to be significant in the moderate student drinkers of study 1, and in the light drinkers of study 2. As can be seen in Figure 3, the difference between the younger drinking groups appears to be much larger than in the older groups. The interaction that is shown in Figure 3 indicates an effect of age in the light social drinkers, whereas the heavy student drinkers perform at a comparable level as the older heavier drinkers. This could indicate that in heavy social drinkers no effects of aging can be found at the right

frontal component, since these young heavy drinkers already show very small task effects. These data support neither the 'accelerated aging' hypothesis, nor the 'increased vulnerability' hypothesis. The two interaction patterns shown in Figure 3 clearly indicate that alcohol and age have different effects on different ERP components and brain functions.

MAIN CONCLUSION

This study provides new insights in the effects of long-term alcohol use. We propose that the effects of alcohol use begin with very mild cognitive effects in young social drinkers, which are found at the right frontal cortex; with progressing age and alcohol use the effects become visible on more ERP components that expand to mid-frontal locations. It seems that all these effects in social drinkers are only found when the brain is challenged with more demanding or complex tasks. When participants become dependent on alcohol, also less complex and less demanding attention and inhibition tasks show effects that, in case of the visual attention task, also become more widespread, involving also parietal scalp locations.

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SAMENVATTING

Samenvatting

Samenvatting in het Nederlands

INTRODUCTIE

Het doel van deze studie was te onderzoeken wat lange termijn effecten van sociaal drinken op de hersenen zijn. Het gebruik van alcohol zorgt ervoor dat mensen zich meer ontspannen en dat een situatie vaker als gezellig wordt ervaren. Het is echter ook algemeen bekend dat het gedurende langere tijd overmatig consumeren van alcohol medische en sociale problemen met zich mee kan brengen. Hoewel dit algemeen bekend is wat betreft overmatig alcohol gebruik is er veel minder bekend over de effecten van sociaal drinken. Sociaal drinken wordt gezien als normaal gedrag. Ongeveer 75% van de Nederlandse bevolking van twaalf jaar of ouder heeft de afgelopen maand een alcoholhoudende drank gedronken. Er zijn echter indicaties dat ook sociaal drinken effecten heeft op het functioneren van de hersenen. In de huidige studie hebben we onderzocht wat de effecten van sociaal drinken zijn op het functioneren van de hersenen. Om dit te onderzoeken hebben we gebruik gemaakt van Event Related Potentials (ERPs). Met deze techniek kan de activiteit van hersenen bestudeerd worden die opgewekt wordt tijdens het uitvoeren van bepaalde taken. Ook maakt deze techniek het mogelijk om heel precies activiteit van de hersenen te bestuderen, zonder dat er perse afwijkingen in het gedrag aangetoond worden (het is een zogenaamde maat voor 'coverte' hersenactiviteit.

SOCIAAL DRINKEN

Er is geen algemene definitie voor sociaal drinken. In de meeste studies wordt sociaal drinken gezien als niet pathologisch gedrag, wat in praktijk betekent dat een sociaal drinker geen psychiatrische diagnose voor alcoholafhankelijkheid of alcoholmisbruik heeft. In ons onderzoek hebben we vier groepen bestudeerd. Deze groepen zijn ingedeeld op basis van een alcohol dagboek dat de deelnemers gedurende twee weken voor het onderzoek hebben bijgehouden. De lichtste groep dronk niet meer dan 6.25 standaard glazen (12 gram alcohol) per week; de middelmatige groep dronk maximaal 21 glazen per week, de zware drinkers dronken meer dan 21 glazen per week, en mensen in de excessieve groep dronken minimaal 60 glazen per week. In de excessieve groep kreeg de helft van de deelnemers de diagnose voor alcoholafhankelijkheid, dus dit was geen zuivere sociale drinkers groep. Alcohol wordt op een andere manier afgebroken bij mannen dan bij vrouwen. Daarom hebben we ervoor gekozen om alleen de mannelijke deelnemers te bespreken in dit proefschrift. Daarnaast kunnen ERP amplitudes anders zijn bij mensen met familieleden die lijden aan een alcoholverslaving. Daarom hebben we ervoor gekozen om alleen mensen zonder een familie geschiedenis van alcoholisme deel te laten nemen aan dit onderzoek.

DE TAKEN

Vijf taken zijn gebruikt om de effecten van sociaal drinken op het functioneren van de hersenen te onderzoeken. De nadruk bij alle taken lag op het correct functioneren van de frontale hersengebieden, omdat we veronderstellen dat alcohol consumptie de frontale gebieden als eerste, en wellicht het meest ernstig, aantast. Om een contrast te kunnen aantonen tussen frontale en overige gebieden hebben we ook pariëtale (midden-achter op het hoofd) en occipitale (achter op het hoofd) en linker en rechter hemisfeer ERP componenten onderzocht. De werkwoorden genereertaak en de 'Wisconsin' kaartsorteertaak hebben we gekozen omdat bij vergelijkbare neuropsychologische taken verschillen in het gedrag van alcoholisten ten opzichte van een controlegroep zijn aangetoond. Deze taken hebben, naast componenten aan de rechter en linkerkant van het brein, duidelijke frontale componenten. De continuous performance taak activeert ook de frontale hersengebieden. Verder wordt deze taak geassocieerd met inhibitie (tegenhouden van gedrag) en responspreparatie (voorbereiden van een reactie), welke aangetast zouden kunnen zijn bij mensen met een verslaving aan alcohol. Daarnaast hebben we nog twee aandachtstaken gemeten, een visuele aandachtstaak en een auditieve 'odd-ball' taak. Deze taken maken, naast de frontale gebieden, ook heel duidelijk gebruik van de pariëtale en occipitale hersengebieden. Dit soort aandachtstaken zijn veelvuldig gebruikt in onderzoek van alcoholisten en in deze onderzoeken zijn verschillen gevonden tussen alcoholisten en controle groepen op de frontale en pariëtale ERP componenten.

DE RESULTATEN

Alle taken resulteerden in de verwachte taak effecten wat betreft het gedrag en de ERP componenten. Dit betekent dat de metingen betrouwbaar en geschikt waren om te onderzoeken of de groepen van sociale drinkers verschillen in gedrag of in hersenactiviteit in deze taken.

DE WERKWOORDEN GENEREERTAAK

In de werkwoorden genereertaak moesten deelnemers werkwoorden genereren bij een zelfstandig naamwoord. In de genereertaak hebben we twee onderzoeken beschreven. Studie 1 betrof twee groepen van studenten en studie 2 betrof vier oudere groepen (gemiddelde leeftijd ongeveer 50 jaar). Op Fz, een elektrode die op het midden van het frontale hersengebied ligt, werd meer activiteit verwacht tijdens het generen van een woord dan tijden het lezen van een woord. In studie 2 werd dit verwachte taakeffect niet gevonden in de gemiddelde, zware en excessieve drinkers. Dit taakeffect was wel aanwezig in de lichtste drinkers van studie twee en in beide studenten groepen. Het taakeffect op Fz lijkt dus te verdwijnen naarmate mensen ouder worden en meer drinken. Dit effect heeft waarschijnlijk te maken met verwerking van tegenstrijdigheden ('conflict') of met het richten van aandacht. Tevens werd aangetoond dat de excessieve drinkers uit studie 2 meer fouten maakten tijdens het genereren van werkwoorden en dat zij ook afwijkende activiteit lieten zien aan de rechterkant van de frontale hersengebieden. Dit effect is waarschijnlijk gerelateerd aan de effecten die op de naast gelegen elektrode F6 gevonden zijn. Hier lieten de lichtste groepen van studie 1 en 2 meer activiteit zien tijdens het genereren van werkwoorden dan tijdens het lezen van woorden, terwijl de zwaardere drinkers groepen van beide studies geen verschil lieten zien tussen genereren en lezen. Deze activiteit heeft waarschijnlijk te maken met het prepareren van een antwoord, en we denken dat het met name te maken heeft met het type antwoord wat gegeven wordt, dus de originaliteit of moeilijkheid van het werkwoord dat verzonnen wordt.

DE 'WISCONSIN' KAARTSORTEERTAAK

In de 'Wisconsin' kaartsorteertaak moesten deelnemers kaarten sorteren op kleur, vorm of aantal. Er was een onbekende sorteerregel waar de deelnemers achter konden komen door middel van de 'feedback' (juiste of verkeerde sorteer regel) die na de keuze werd gegeven. ERPs werden gemeten in reactie op de sorteer kaarten en op de 'feedback'. In reactie op de 'feedback' lieten de lichte en gemiddelde drinkers meer negativiteit zien tijdens de vroege trials dan tijdens de late trials, maar dit effect was niet aanwezig bij de zware en excessieve drinkers. Deze activiteit werd frontaal gemeten. Deze frontale activiteit heeft waarschijnlijk te maken met het richten van aandacht, aangezien de 'feedback' in de vroege trials een hogere informatie waarde heeft dan in de late trials. Een andere mogelijkheid is dat deze activiteit te maken heeft met het verwerken van tegenstrijdigheden, aangezien de 'feedback' kan contrasteren met de gevolgde sorteer regel.

'CONTINUOUS PERFORMANCE'-, VISUELE ATTENTIE- EN AUDITIEVE 'ODD-BALL'- TAAK

In de 'continuous performance' taak en de visuele attentietaak zijn geen verschillen tussen de groepen gevonden op gedrag of ERP maten. In de auditieve 'odd-ball' taak zijn ook geen verschillen tussen groepen gevonden op ERP maten, maar er was wel een effect in reactietijd. De lichte sociale drinkers reageerden sneller dan de gemiddelde drinkers. Omdat beide groepen verder niet afweken van de zware en excessieve groep denken we dat dit meer een motivatie effect is dan een alcoholeffect.

In eerdere onderzoeken zijn wel verschillen gevonden tussen alcoholisten en controle groepen op vergelijkbare taken. Daarom hebben we een extra analyse uitgevoerd waarin we alleen de mensen uit de excessieve groep hebben meegenomen die afhankelijk waren van alcohol en deze mensen hebben we vergeleken met de lichte drinkers. Uit deze analyse bleek dat er een verschil was tussen deze groepen op de frontale P3 component in de 'continuous performance' taak en op de pariëtale P3 component in de visuele attentie taak. Het lijkt er dus op dat een kleinere amplitude op deze componenten meer gerelateerd is aan het verslaafd zijn aan alcohol, dan aan het gebruik op zich. Het zou echter ook kunnen zijn dat de afname van deze amplitudes iets te maken heeft met een genetische aanleg voor alcoholisme. Ondanks het feit dat we hebben geprobeerd genetische invloeden uit te sluiten kan het zijn dat deelnemers niet wisten dat familieleden alcoholgerelateerde problemen hadden (geen contact, overlijden etc.).

CONCLUSIES

De werkwoorden genereertaak en de kaartsorteertaak bleken gevoelig te zijn voor de lange termijn effecten van sociaal drinken, terwijl de 'continuous performance' taak, de visuele aandacht taak en de auditieve 'odd-ball' taak dat niet lijken te zijn. De effecten van sociaal drinken blijken dus subtiel en specifiek te zijn. Deze specificiteit kan betekenen dat alleen bepaalde hersengebieden aangetast worden, maar ook dat de effecten van sociaal drinken alleen maar tot uiting komen bij moeilijkere en meer complexe taken. Een taak kan op drie manieren meer complex zijn. Ten eerste kan de taak kan moeilijker zijn voor de deelnemers, hetgeen kan resulteren in meer fouten of langere reactie tijden. Ten tweede kan een taak ook complexer zijn doordat er meer hersengebieden door geactiveerd worden. Ten derde kan het zo zijn dat de hersengebieden die geactiveerd worden meer met elkaar moeten communiceren, dus dat er een complexer netwerk geactiveerd wordt. Wij concluderen dat lange termijn effecten van alcohol in sociale drinkers alleen gedetecteerd kunnen worden tijdens complexe taken, welke ondermeer aspecten van werkgeheugen en taal functies activeren.

Alle lange termijn effecten van alcohol zijn gevonden in de frontale hersengebieden. In de studenten groep werden in de werkwoorden genereertaak alleen effecten gevonden aan de rechterkant van de frontale gebieden. Daarom denken we dat de effecten van alcohol wellicht beginnen met selectieve veranderingen in de rechter frontaal kwab en uitbreiden naar het midden van de frontaal kwab bij de oudere sociale drinkers.

In figuur 2 van hoofdstuk 6 zijn de resultaten van dit proefschrift schematisch weergegeven. In die figuur is te zien dat de oudere gemiddelde drinkers afwijkende ERP amplitudes vertoonden in de werkwoorden genereertaak in vergelijking met de lichtste groep sociale drinkers. Bij de zware drinkers werden naast de effecten op de werkwoorden genereertaak ook effecten gevonden in de ERPs in reactie op de kaartsorteertaak. In de excessieve groep werden naast de ERP effecten in de zware groep nog extra afwijkingen gevonden in ERPs en het gedrag in de woorden genereer taak. Bij de excessieve drinkers die ook verslaafd waren aan alcohol werden effecten aangetoond op de P3 amplitude in de 'continuous performance' taak en de visuele attentietaak. Uit dit overzicht kan de conclusie getrokken worden dat er, naar mate er meer gedronken wordt, meer taken en meer taakeffecten beïnvloed worden. Daarmee geeft dit onderzoek steun aan de zogenaamde continuüm hypothese. Deze hypothese stelt dat de effecten van alcohol steeds uitgebreider worden naar mate men meer drinkt.

HOOFDCONCLUSIES

Deze studie leidt tot nieuwe inzichten met betrekking tot de lange-termijn effecten van alcoholgebruik. Er zijn aanwijzingen gevonden dat de effecten van alcohol beginnen met zeer milde cognitieve effecten in jonge sociale drinkers. Deze effecten worden boven de rechter frontaalcortex gevonden. Met toename van leeftijd en alcohol gebruik breiden de effecten van alcohol op cognitieve processen zich uit tot meer ERP componenten boven het midden van de frontaalcortex. Het lijkt erop dat deze effecten bij sociale drinkers alleen gevonden worden als het brein complexere taken te verwerken krijgt. Bij mensen die afhankelijk zijn van alcohol lijkt het er op dat ook de hersenactiviteit opgewekt door minder complexe taken, zoals inhibitie en attentie taken, afwijkend is. Deze effecten breiden zich dan, in het geval van de visuele attentie taak, ook uit tot de pariëtale hersengebieden.

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Curriculum Vitae

Suzanne Bijl werd geboren op 8 september 1976 te De Bilt. In 1994 behaalde zij het VWO diploma aan het St.Bonifatius college te Utrecht. Na een jaar in de paardensport werkzaam te zijn geweest, begon zij in 1995 aan de studie psychologie aan de Universiteit Utrecht. In 2000 behaalde zij het doctoraal diploma, met als afstudeerrichting Biopsychologie. Aansluitend volgde een aanstelling als AIO bij de disciplinegroep Psychofarmacologie van de Faculteit Farmaceutische Wetenschappen om het onderzoek te verrichten dat in dit proefschrift beschreven is.