ELSEVIER

NeuroImage

www.elsevier.com/locate/ynimg
NeuroImage 26 (2005) 536 – 545

Focal brain matter differences associated with lifetime alcohol intake and visual attention in male but not in female non-alcohol-dependent drinkers

Eveline A. de Bruin,[a,*] Hilleke E. Hulshoff Pol,[b] Hugo G. Schnack,[b] Joost Janssen,[b] Suzanne Bijl,[a] Alan C. Evans,[d] J. Leon Kenemans,[a,c] René S. Kahn,[b] and Marinus N. Verbaten[a]

[a]*Department of Psychopharmacology, Utrecht Institute of Pharmaceutical Sciences, Utrecht University, Sorbonnelaan 16, NL-3584 CA Utrecht, The Netherlands*
[b]*Department of Psychiatry, Rudolf Magnus Institute, University Medical Center Utrecht, Utrecht, The Netherlands*
[c]*Department of Psychonomics, Helmholtz Institute, Utrecht University, Utrecht, The Netherlands*
[d]*McConnel Brain Imaging Centre, Montreal Neurological Institute, Montreal, QC, Canada*

Received 27 September 2004; revised 11 January 2005; accepted 26 January 2005
Available online 11 March 2005

The purpose of this study was to investigate whether current or lifetime alcohol intake is related to focal gray and white matter in healthy non-alcohol-dependent drinkers, and, if so, whether these densities are related to functional brain activity associated with visual attention. Voxel-based morphometric analyses of gray- and white-matter densities, and event-related potentials in response to a visual-attention task were determined in 47 male drinkers (current alcohol intake 20 drinks per week, lifetime alcohol intake 240 kg) and 44 female drinkers (current alcohol intake 15 drinks per week, lifetime alcohol intake 170 kg). All participants had a negative personal and family history of alcohol dependence to reduce possible confounding by genetic factors related to alcohol dependence. In males, mean lifetime alcohol intake was negatively associated with gray-matter density and positively associated with white-matter density in the right frontal gyrus (BA 6) and the right parietal region (BA 40). Right frontal (but not right parietal) gray and white matter in males correlated with the P3 amplitude of the event-related potentials elicited in a visual-attention task. In females, mean lifetime alcohol intake was not associated with gray- or white-matter density. Current alcohol intake was unrelated to gray or white matter in both males and females. In conclusion, lifetime alcohol intake is associated with focal gray-matter decreases and white-matter increases in the right frontal and right parietal brain regions in non-alcohol-dependent males, but not in females. These alcohol-related differences in focal brain matter in males are associated with differences in brain function related to visual attention. As the confounding effects of genetic factors were reduced, the present results may selectively relate to the effects of alcohol intake on focal brain matter.

Keywords: Lifetime alcohol intake; Current alcohol intake; Voxel-based morphometry; Gray matter; White matter; Event-related potentials; Visual attention; P3

Introduction

Alcohol-dependent individuals have smaller total-brain and gray- and white-matter volumes, and greater cerebrospinal-fluid (CSF) volumes than light drinkers (e.g., Agartz et al., 2003; Hommer et al., 2001; Pfefferbaum et al., 1992). The effects of alcohol dependence on brain volumes are regionally specific and particularly involve frontal-lobe volume decreases (Fein et al., 2002; Jernigan et al., 1991; Lingford-Hughes et al., 1998; Pfefferbaum et al., 1997) and neuronal loss (Harper et al., 2003; Kril et al., 1997). In addition, the effects of alcohol dependence on brain metabolism (Dao-Castellana et al., 1998; Johnson-Greene et al., 1997) and brain metabolite concentrations (Meyerhoff et al., 2004; Parks et al., 2002; Schweinsburg et al., 2001) also vary across brain regions.

There are suggestions that heavy drinkers who are not alcohol-dependent have ventricular and sulcal widening that is similar to, but less prominent than that in alcohol-dependent individuals (Ding et al., 2004; Kubota et al., 2001; Mukamal et al., 2001). It appears that the effects of alcohol on the brain are also regionally differentiated in non-alcohol-dependent drinkers, as suggested by a voxel-based morphometry study on aging in Japanese (Taki et al.,

* Corresponding author. Fax: +31 30 253 7900.
E-mail address: E.A.deBruin@pharm.uu.nl (E.A. de Bruin).
Available online on ScienceDirect (www.sciencedirect.com).

1053-8119/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuroimage.2005.01.036

2004). In this study, habitual alcohol intake was negatively associated with focal gray matter in frontal and parietal cortices, and positively associated with focal white matter in the parietal cortex in males. No significant associations were found in females, but lifetime alcohol intake of the females was only 12% of that of the males.

With regard to gender differences in the effects of excessive alcohol intake brain structure, some studies report that alcohol-dependent females have greater volume losses than alcohol-dependent males despite shorter drinking histories and lower or similar lifetime alcohol intake in the females (Agartz et al., 1999; Hommer et al., 1996; Hommer et al., 2001). On the other hand, other studies found that alcohol-dependent females lacked the brain volume reductions that alcohol-dependent males displayed (e.g., Pfefferbaum et al., 2001b; see Hommer (2003) for a discussion). This discrepancy can possibly be explained by the fact that, in the studies reporting greater effects of alcohol intake in females, the females had a higher lifetime alcohol intake per year of their drinking history than the males. This suggests that alcohol-related effects on the structure of the brain may be more related to lifetime alcohol intake corrected for the duration of the drinking history than to cumulative lifetime alcohol intake or the duration of the drinking history alone (De Bruin et al., in press).

Alcohol-dependent individuals have worse cognitive performance than light drinkers (Lawton-Craddock et al., 2003; Parsons, 1994). Though to a lesser extent, heavy drinkers who are not alcohol-dependent also display cognitive impairment (see Parsons, 1998; Parsons and Nixon, 1998 for a meta-analysis), for instance with regard to visual attention. Although voxel-based morphometry is not designed to characterize dependencies among different brain regions (Friston and Ashburner, 2004), it is tempting to hypothesize that the frontal and parietal differences in focal gray and white matter found by Taki et al. (2004) are possibly related to functional abnormalities in the fronto-parietal network for visual attention (Corbetta and Shulman, 2002). Alcohol-dependent individuals display reduced event-related potential (ERP) amplitudes during attention tasks (see Farren and Tipton (1999) and Porjesz and Begeleiter (1996) for a review). In addition, ERP amplitudes elicited during attention tasks correlate with frontal and parietal gray matter volumes in healthy subjects (Ford et al., 1994). Therefore, it would be interesting to investigate whether focal differences in brain structure related to alcohol intake in non-alcohol-dependent drinkers can be related to functional brain activity during a visual-attention task.

Alcohol dependence has a strong genetic component (Enoch, 2003; Schuckit, 2000). Possibly, people with alcohol dependence or with alcohol-dependent relatives (i.e., with a so-called positive personal or family history of alcohol dependence) have a different sensitivity for the toxic effects of alcohol on the brain. Furthermore, different distributions of genetic polymorphisms that code for enzymes involved in alcohol metabolism result in different brain alcohol and acetaldehyde levels in Asians as compared to non-Asians (Quertemont, 2004). As genetic factors related to both alcohol dependence and enzymatic polymorphisms may have played a role in the above-mentioned studies, it is unclear to what extent these findings can be generalized to drinkers with a negative personal or family history in non-Asian populations.

The purpose of the present study was to examine a possible relation between current or lifetime alcohol intake and focal gray and white matter in a Dutch sample of male and female drinkers with a negative personal and family history of alcohol dependence. In addition, in case of alcohol-related differences in gray and/or white matter, possible functional consequences of these brain matter differences with regard to visual attention were explored. Cerebral gray- and white-matter densities were estimated in 91 healthy male and female drinkers using voxel-based morphometric analyses of high-resolution magnetic resonance images (Ashburner and Friston, 2000, 2001). Functional brain activity related to visual attention was investigated by measuring event-related potentials in reaction to a visual-attention task in the same sample. The relationship between structural and functional differences in the brains of non-alcohol-dependent drinkers was explored by correlating brain matter densities related to alcohol intake with P3 amplitudes of event-related potentials elicited in the visual-attention task.

Methods

Participants

Participants were recruited via newspaper advertisements, and were paid for their participation. After written and oral explanation of the study, they signed the informed consent, and filled in an extensive questionnaire on physical and mental health. Eligible subjects were invited for a 3-h screening consisting of a physical check-up and a structured interview assessing for the presence of psychopathological symptoms (the Composite International Diagnostic Interview (Robins et al., 1988), based on the DSM-IV). From about 1500 applications, 96 healthy Caucasian non-dependent drinkers (50 men, 46 women) drinking from one standard drink (i.e., 100 cc wine, 250 cc beer, or 30 cc spirits, equivalent to 12 g of alcohol per drink) per 2 weeks up to 53 standard drinks per week were selected to participate in the study. Total abstainers were not included as they have worse cognitive performance (Britton et al., 2004; Elias et al., 1999; Kalmijn et al., 2002) and a higher risk for coronary heart disease (Abramson et al., 2001; Corrao et al., 2004) and ischemic stroke (Berger et al., 1999; Djoussé et al., 2002; Sacco et al., 1999; Suter and Vetter, 1999) than light-to-moderate drinkers, which might confound the effects of alcohol intake on the brain.

Each participant was right-handed as determined with the Edinburgh Handedness Inventory, and had a blood pressure and resting heart rate within normal limits. The electrocardiogram, hematology, and blood chemistry were screened for abnormalities by a medical specialist. Education was assessed as the number of years of formal education from primary school onwards. Premorbid IQ was estimated with the Dutch Adult Reading Test (Nederlandse Leestest voor Volwassenen, the Dutch version of the National Adult Reading Test; Schmand et al., 2003). The participants had no (history of) chronic somatic or neurological disease, head trauma or loss of consciousness for more than 10 min, or psychiatric disease at any point in life. Other exclusion criteria were: use of psychoactive medication within the past month, drug use (besides alcohol) for more than three times in life, total alcohol abstinence, and first- or second-degree relatives with neurological or psychiatric deficits. Every effort was made to ensure via the questionnaire and the interview that all participants had a negative family history of alcoholism up to the second degree. The main reasons for exclusion were (a history of) psychiatric symptoms (21%, mostly major depression at some point in life), use of psychoactive medication within the past month (19%), chronic somatic or neurological disease (13%), drug use more than three times in life