Altered white matter integrity in whole brain and segments of corpus callosum, in young social drinkers with binge drinking pattern

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ABSTRACT

Binge drinking is associated with impaired cognitive functioning, but the relationship of cognitive impairments and white matter integrity is less known. We used diffusion tensor imaging (DTI) to investigate the relationships of binge drinking, whole brain white matter integrity and cognitive performance during young adulthood (18 to 25 years), a period of continued brain development in two sessions 1 year apart. Binge drinkers (n = 20) and non-binge drinkers (n = 20) underwent DTI and completed measures of spatial working memory and motor impulsivity. Fractional anisotropy (FA), a measure derived from DTI, was estimated from whole brain and from five segments of the corpus callosum (CC): prefrontal, premotor/supplementary motor, motor, (SMA) sensory and parietal/temporal/occipital (PTO). FA was lower for binge than for non-binge men but not women at Session 1 and 2 for all measurements except for FA in the motor segment, which was significantly increased from Session 1 to Session 2. Lower FA in the prefrontal and PTO CC segments was associated with higher binge score, whereas lower FA in all five segments was associated with greater drug use in men and worse spatial working memory both in men and women. These findings extend the literature by showing that in early adulthood, binge drinking and drug use are linked with degradations in neural white matter and that compromised white matter at this period of brain development is linked with impaired cognitive functioning.

Keywords Addiction, corpus callosum, diffusion tensor imaging.

INTRODUCTION

Binge drinking behaviour is characterised by speed of drinking on a particular occasion, frequency of drunkenness during the most recent 6 month period and the percentage of times getting drunk when drinking (Scaife & Duka 2009; Townshend & Duka 2002). The prevalence of weekly binge drinking among European Union drinkers in 2009 was reported to be 28 percent of the student population and 33 percent among all young people aged 15–24 years (European Union: Directorate General Communication 2010).

At these ages, the brain is still developing. Maturation of dorsolateral prefrontal and orbitofrontal cortices, and several subregions within the temporal cortex, continues until the end of adolescence up to 25 years of age (Gogtay et al. 2004). In particular, it has been reported that gray matter volume decreases, whereas white matter volume and the area of corpus callosum increase, across the ages 7 to 17 years (e.g. De Bellis et al. 2001); these changes were more pronounced in men than in women.

Diffusion tensor imaging (DTI) provides an indirect but sensitive method of assessing white matter structure and integrity by measuring the properties of diffusivity of water molecules in white matter. DTI indices, in particular fractional anisotropy (FA; Pierpaoli & Basser 1996), which measures the degree of diffusion directionality within white matter tracts, have increased our knowledge with regard to changes in white matter during brain development. FA was found to increase across ages 6 to 19 years in many white matter tracts throughout the brain (Barnea-Goraly et al. 2005; Lebel et al. 2008). More recently, Hasan et al.
(2010) found that in participants aged between 6 and 68 years, commissural pathways to prefrontal cortex peak at approximately 22 years, to anterior frontal at 28 years and to posterior parietal at 27 years of age. Generally, increases in FA with age in areas related to corpus callosum have been reported among adolescents and young adults (e.g. Ben Bashat et al. 2005; Fryer et al. 2008; Snook et al. 2005). Furthermore, among age groups (13–21 and 23–42 years), age was found to correlate positively with mean FA across the skeleton of the brain—in particular the body of the corpus callosum (right-sided) and the right superior region of the corona radiata (Giorgio et al. 2008).

Abuse of alcohol and/or drugs, as well as binge drinking, have been reported to affect the microstructure of neural white matter (e.g. De Bellis et al. 2008; McQueeny et al. 2009; Thatcher et al. 2010); however, the direction of these effects is not consistent across studies. For instance, it is not clear whether white matter integrity is further compromised by continuous alcohol abuse with a binge drinking pattern at a time that brain development is still in progress (e.g. Asato et al. 2010); on the other hand, De Bellis et al. (2001) found that abstinence for 1.5 years improved white matter integrity. Importantly, binge drinking in adolescents and young adults is associated with impaired cognitive functioning, especially spatial working memory (SWM; Scaife & Duka 2009; Squeglia et al. 2011; Townshend & Duka 2005; Weissenborn & Duka 2003).

Taken together, these data suggest that binge drinking and/or drug use may be associated with changes in white matter structure. However, it is not clear how these changes may relate to cognitive function in these populations. Thus, the aims of the present study were (1) to use DTI to examine further whether white matter integrity is compromised in young social drinkers with a behavioural pattern of binge drinking, using a classification of binge drinkers and non-binge drinkers as previously described (Scaife & Duka 2009); see also Methods); (2) to examine the role of gender (gender will be entered as a factor in the analysis), as several of the findings in brain structure differ by gender; and (3) to use simple correlations to examine whether changes in white matter integrity, cognitive performance and patterns of drinking are associated.

An additional aim was (4) to examine whether white matter integrity would change across time (after 8–12 months lapse) differently in social drinkers with binge drinking pattern compared with social drinkers who do not binge. Based on the literature, we expected to find differences in FA between the two drinking groups, although the direction of differences and their relationship to gender is difficult to predict. As discussed earlier, many studies in the literature have provided data on white matter tracts within the corpus callosum. The present study will look at whole brain analysis with a particular focus in the corpus callosum. Behavioural measures of motor impulsivity and SWM functions usually reported to be compromised in binge drinkers (e.g. Townshend & Duka 2005) were also taken, in order to explore the possibility of a relationship between cognitive impairment among the binge-drinking group and white matter alterations. Participants performed the tasks outside the scanner within a week before the DTI. The tasks were the well-established CANTAB Stop Signal (CANTAB SST) and SWM tasks, previously shown to be compromised in binge drinkers (Weissenborn & Duka 2003; Townshend & Duka 2005).

**MATERIALS AND METHODS**

**Participants**

Seventy-nine (40 male and 39 female) healthy moderate-to-heavy social drinkers between the ages of 18 and 25 years (mean 20.48, SD 1.77) were recruited, by means of an advertisement for social drinkers willing to take part in a study of the relationship between social drinking, mood and performance on cognitive tasks. All recruitment was limited to students at two local universities. From that pool of 79 participants, 40 were identified to take part in a follow-up neuroimaging study. These 40 people were chosen on the basis that their binge scores were in the non-binge range [binge score greater than 4 and less than 16 (see succeeding discussion regarding how the score was obtained)] or in the binge range (binge score higher than 30), they had no past or present medical, neurological or psychiatric illness, they were free of any medication (except the contraceptive pill) and they conformed to standard health and safety regulations regarding the use of magnetic resonance imaging (MRI). Women were advised not to take part if there was any possibility that they might be pregnant. For the current study, 40 participants (non-binge drinkers: 10 male, 10 female; binge drinkers: 10 male, 10 female) completed the behavioural measures and the first session of brain scanning. Thirty-seven of these people (non-binge drinkers: nine male, nine female; binge drinkers: 10 male, nine female) also completed the second session of brain scanning, 8 to 12 months later. Participants had been instructed to abstain from use of recreational/illicit drugs for at least 5 days and to abstain from alcohol for at least 12 hours prior to the study. The study was approved by the University of Sussex Ethical Committee and the Brighton and Sussex Medical School Ethical Committee; all participants gave informed consent and were paid for their time at a rate of approximately £6 per hour.

**Questionnaires (Session 1)**

**Alcohol Use Questionnaire and binge drinking score**

A quantity-frequency, beverage-specific (wine, beer/cider, spirits and alcopops) index of alcohol consumption for the
previous 6 months was obtained using a revised version of the Alcohol Use Questionnaire (Mehrabian & Russell 1978). The ‘binge drinking’ score was calculated as previously (Townshend & Duka 2002) for all participants on the basis of the information ‘average drinks per hour’, ‘number of times being drunk in the previous 6 months’ and ‘percentage of times getting drunk when drinking (average)’. Non-binge drinkers had a ‘binge score’ of <16 (minimum score > 4) and binge drinkers of >30. Subjects with scores between these ranges were considered not classifiable. Binge score was not adjusted for gender: binge score takes into account the sensitivity to drunkenness, and this way, women, who may get drunk more often, will get a higher binge score.

**Drug Use Questionnaire**

This questionnaire (Scaife & Duka 2009) asks for duration of use, time since last use, how often used and dose per session for all the main drug categories (cannabinoids, stimulants, hallucinogens, opiates, barbiturates/benzodiazepines and inhalants). For the purposes of this study, ‘the number of types of recreational drugs ever used’ was used. This index may represent a measure of novelty seeking, but it reflects the patterns of persistent recreational drug use in our student population.

**Demographic information, anxiety and depression questionnaires**

Information concerning age of starting drinking and number of cigarettes smoked per day was obtained via a structured interview. Trait anxiety was assessed with the Spielberger State-Trait Anxiety Inventory (Spielberger et al. 1970). Depression scores were obtained by use of the Beck Depression Inventory-II questionnaire (Beck et al. 1996).

For more details on questionnaires see also Supplemental Methods.

**Cognitive measures (Session 1)**

*The National Adult Reading Test* (NART; Nelson 1982)

The NART was administered to obtain scores for full-scale and verbal intelligence.

*Stop Signal Task (CANTAB SST; CANTAB, Cambridge Cognition Limited, 2006)*

The CANTAB SST is a task measuring the ability to inhibit a pre-potent motor response. The stop signal reaction time, which represents the participant’s mean stop signal delay at which he or she was successful in stopping the pre-potent response, was the dependent variable. For more details see Supplemental Methods.

*Spatial Working Memory (CANTAB, Cambridge Cognition Limited, 2006)*

The CANTAB SWM requires retention and manipulation of visuospatial information. This self-ordered task has notable executive function demands, and measures strategy use as well as errors. Errors in 8-boxes arrays and strategy score were the dependent variables (see Supplemental Methods for additional details).

**MRI Protocol**

All images were collected on a 1.5-Tesla Siemens Avanto magnetic resonance scanner (Siemens, Erlangen, Germany). High-resolution anatomical images were acquired using a three-dimensional T1-weighted magnetisation-prepared rapid acquisition gradient echo sequence [repetition time (TR) = 1160 ms; echo time (TE) = 4.44 ms; inversion recovery time = 600 ms; field of view (FOV), 230 × 230 mm²; matrix size, 256 × 256; flip angle θ = 15°; voxel dimensions, 0.9 × 0.9 × 0.9 mm³; acquisition time = 5 min]. Diffusion-weighted images were acquired using whole brain echo planar imaging (TR = 12400 ms; TE = 111 ms; echo spacing = 0.83 s; FOV = 240 × 240 mm²; matrix size = 96 × 96; slices = 68 (contiguous); slice thickness = 2.5 mm; acquisition time = 7 mins). Diffusion gradients were applied in 30 non-collinear directions with a b-value of 1000 s/mm². One non-diffusion-weighted (b = 0) image was also acquired. To ensure the reproducibility and stability of the MRI scanner in multisession studies, daily quality assurance tests were performed, and the data were studied by the MR physics team in our department to identify any problems.

**MR image analysis (Sessions 1 and 2)**

**Brain volume**

The high-resolution anatomical images were used to calculate intracranial volume and the volume of white matter, grey matter and cerebrospinal fluid (CSF) for all participants (see Supporting Information for details).

**Pre-processing of DTI data**

DTI images were preprocessed as described in Smith et al. 2006, using the Diffusion Toolbox (FDT; Smith et al. 2004), part of the FMRIB (Oxford University Centre for Functional MRI of the Brain) Software Library (FSL). (For more details see Supplemental Methods).

**Tract-based spatial statistics**

FA maps from each participant were then submitted to tract-based spatial statistics (Smith et al. 2006), following the steps as described in Smith et al. (2006); see details in...
Supplemental Methods. The FA values of each participant were then projected onto the skeleton, and the resulting data were fed into voxelwise cross-subject statistical analysis.

**DTI data analysis procedure**

A statistical analysis of drinking group (binge-drinkers and non-binge-drinkers) × gender, with current age as a covariate, was conducted across the skeletonised FA map; for this, a Monte-Carlo permutation-based approach (1000 permutations per contrast) was chosen, using the ‘randomise’ FSL (Analysis Group, FMRIB, Oxford, UK) function; multiple comparisons were controlled for by means of threshold-free cluster enhancement (Smith & Nichols 2009).

Following whole brain analysis, we performed regions of interest (ROIs) tractography of the corpus callosum based on Hofer & Frahm (2006), who had classified five segments of the human corpus callosum on the basis of cortical projections of each region. The five ROIs were manually outlined onto the mid-sagittal slice of the across-group mean FA map as follows: region I: prefrontal; region II: premotor and supplementary motor (SMA); region III: motor; region IV: sensory; and region V: parietal, temporal and occipital (Fig. 1). The regions were then warped into each subject’s native space, by inverting the transformation computed during tract-based spatial statistics. Using these five sections as seed regions, the five segments of the corpus callosum were reconstructed for each participant, using probabilistic tractography and a model of diffusion that includes crossing fibres (Behrens et al. 2007). A univariate analysis of variance (ANOVA) was conducted for each ROI separately with drinking group and gender as the between-subject factors, and age was covaried out. Repeated measures MANOVA was not conducted as the FAs of the five segments were correlated.

**DTI comparisons between Sessions 1 and 2**

The FA skeletonised images from the second session were subtracted from the corresponding images from the first session (as recommended for ‘randomise’ analysis, which was used for the skeletonised difference map), for the 37 participants who attended both sessions. These differences were then entered into a univariate ANOVA with drinking group (binge-drinkers and non-binge-drinkers) and gender as between-subject factors and with current age as a covariate across the skeletonised difference map; for this, a Monte-Carlo permutation-based approach (1000 permutations per contrast) was chosen, using the ‘randomise’ FSL (Analysis Group, FMRIB, Oxford, UK) function; multiple comparisons were controlled for by means of threshold-free cluster enhancement (Smith & Nichols 2009). Further to the analysis earlier, FAs of the five corpus callosum ROIs were analysed by ANOVA, with Sessions 1 and 2 as the within-subjects factor and drinking group (binge-drinkers and non-binge-drinkers) and gender as the between-subject factors; age at first time point was covaried out.

**CORRELATIONS**

To examine the relationship between FA and alcohol drinking as well as drug-taking habits, correlations were performed between FA in the segments of corpus callosum and binge score, units per week of alcohol consumption and drug use estimates. Relationships between FA and cognitive performance in the two tasks were also examined using correlational analyses. Correlations were only performed in the data from Session 1, when cognitive tasks were performed. Pearson or Spearman correlations were performed depending on the data distribution.

**RESULTS**

**Group demographics (Sessions 1 and 2)**

Table 1 shows the demographic data for the drinking pattern groups and for men and women within the groups. As expected, binge scores were significantly higher in the binge than the non-binge group in both Session 1 and 2. Weekly consumption differed significantly between the groups in each of the two sessions; binge drinkers compared with non-binge drinkers consumed more alcohol per week [(session 1: t_{30.3} = -2.89, P = 0.007; session 2: t_{22.25} = -3.012, P = 0.006)]. There was also a significant difference between bingers and non-bingers with respect to the number of recreational drugs ever used, but
only in Session 1 ($t_{38} = -2.755, P = 0.009$). There was a significant difference in the number of cigarettes smoked daily between bingers and non-bingers, at Session 1 (Mann–Whitney U-test, $P = 0.005$) and at Session 2 (Mann–Whitney U-test, $P = 0.005$). There were no differences between men and women in any of the demographic characteristics with the exception of Beck Depression Inventory-II questionnaire (Beck et al. 1996) score; women had higher ratings than men ($t_{31.92} = 2.595, P = 0.014$), but only in Session 1. Binge scores did not change from Session 1 to Session 2 (no gender × bingeg group × time interaction; $F_{s} < 2.28$).

Cognitive tasks (Session 1)

Stop-Signal Task (SST; CANTAB, Cambridge Cognition Limited, 2006)

Mean stop signal reaction time did not differ significantly, either by group or by gender.

Spatial Working Memory (SWM; Cambridge Cognition Limited, 2006)

Strategy (a measure of how systematic the search of boxes is) was marginally worse among women (mean 30.2, SD 6.48) than among men (mean 24.5, SD 5.23; $F_{1, 35} = 49.577, P = 0.09$, partial eta$^2 = 0.980$). No other differences were found.

Imaging data (Sessions 1 and 2)

Brain volume

A main gender effect was found for intracranial volume in Session 1 and Session 2 ($F_{1, 36} = 18.9, P < 0.001$ and $F_{1, 31} = 13.707, P = 0.001$, respectively) indicating intracranial volume (ml) to be significantly greater in men than in women.

In Session 1, adjusting for intracranial volume, a gender effect was also found ($F_{1, 35} = 7.445, P = 0.01$) with regard to white matter volume indicating white matter volume (ml) to be greater in women than in men. See Table S1 and Results section in the Supporting Information for further details.

DTI whole-brain analysis results

Analysis of the skeletonised FA maps showed that in Session 1 ($n = 40$) and Session 2 ($n = 37$), in several areas of the brain (forceps minor/major, inferior fronto-occipital fasciculus, left corticospinal tract, and body and splenium of CC), the group × gender interaction was significant (Fig. 2). FA was lower for Binge compared with non-binge

Table 1 Demographics of study population at Session 1 and Session 2.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-BD</th>
<th>BD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male (n = 10)</td>
<td>Female (n = 10)</td>
</tr>
<tr>
<td>Binge scores$^a$</td>
<td>11.9 (2.08)</td>
<td>10.5 (3.49)</td>
</tr>
<tr>
<td>Weekly consumption (grams)$^a$</td>
<td>170.4 (90.49)</td>
<td>100.3 (95.79)</td>
</tr>
<tr>
<td>Age started drinking</td>
<td>15.7 (2.26)</td>
<td>15.3 (1.83)</td>
</tr>
<tr>
<td>Age</td>
<td>20.5 (2.46)</td>
<td>20.8 (2.15)</td>
</tr>
<tr>
<td>BDI$^b$</td>
<td>3.1 (4.20)</td>
<td>6.0 (4.57)</td>
</tr>
<tr>
<td>No of types of recreational drugs ever used$^a$</td>
<td>0.70 (0.82)</td>
<td>2.6 (3.41)</td>
</tr>
<tr>
<td>Smokers (yes/no)</td>
<td>1/9</td>
<td>2/8</td>
</tr>
<tr>
<td>Number of cigarettes smoked per day$^b$</td>
<td>0.10 (0.32)</td>
<td>0.40 (0.70)</td>
</tr>
<tr>
<td>STAI-TRAIT</td>
<td>34.5 (8.38)</td>
<td>38.5 (8.99)</td>
</tr>
<tr>
<td>NART IQ full scale</td>
<td>114.1 (4.43)</td>
<td>112.2 (3.93)</td>
</tr>
<tr>
<td>NART IQ verbal</td>
<td>112.1 (4.01)</td>
<td>110.4 (3.47)</td>
</tr>
<tr>
<td>Binge scores$^a$</td>
<td>14.3 (10.81)</td>
<td>12.8 (6.61)</td>
</tr>
<tr>
<td>Weekly consumption (grams; n = 36)$^a$</td>
<td>123.3 (55.16)</td>
<td>76.0 (48.22)</td>
</tr>
<tr>
<td>Number of types of recreational drugs ever used</td>
<td>1.1 (0.93)</td>
<td>3.1 (4.43)</td>
</tr>
<tr>
<td>Number of cigarettes smoked per day$^b$</td>
<td>0.11 (0.33)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>BDI</td>
<td>7.4 (6.89)</td>
<td>6.9 (4.25)</td>
</tr>
<tr>
<td>Rescan_Elapsed_#_Days</td>
<td>324 (25)</td>
<td>317 (31)</td>
</tr>
</tbody>
</table>

Data are presented as Mean (SD). $^a$Significant difference between bingeg and non-binge group. $^b$Significant difference between men and women. BDI, Beck Depression Inventory; STAI-TRAIT, Spielberger State-Trait Anxiety Questionnaire (trait only); NART IQ, National Adult Reading Test.
men, but higher for Binge compared with non-binge women (see Table S2 in the Supporting Information for details).

**Tractographic reconstruction of callosal segments (ROI analysis)**

**Session 1** \((n = 40)\). The mean FAs of each participant in Session 1 \((n = 40)\), for each of the five corpus callosum segments, were extracted from the tractography analysis. The group × gender interaction was significant for each ROI except for motor and premotor/SMA in which there was a tendency for an interaction of group and gender (Table 2). There were no significant main effects of group or of gender in any of the five ROIs. The pattern of mean FAs in each of the five ROIs was that male binge drinkers had lower mean FA than did male non-binge drinkers, whereas female binge drinkers had higher mean FA than did female non-binge drinkers (Fig. 3). Table 2 shows the results of the statistical analysis for each ROI, plus the mean FA \((SE)\) for each of the four subgroups for each ROI. The number of cigarettes smoked per day, which was higher in binge drinkers, was entered as a covariate; significant interactions remained \(F_{1, 34} ≥ 3.855, P ≤ 0.058\).

**Session 2** \((n = 37)\). Mean FA in the five ROIs showed to a great extent similar interaction patterns among group and gender as in Session 1; the exception was for the prefrontal segment of corpus callosum, which was not significant, and for motor and premotor/SMA, which showed only a tendency (Table 2). Once again, the

**Table 2  Tractography of the corpus callosum.**

<table>
<thead>
<tr>
<th>ROI</th>
<th>Group × gender interaction</th>
<th>NB Male</th>
<th>NB Female</th>
<th>B Female</th>
<th>B Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Session 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prefrontal</td>
<td>( F_{1, 35} = 6.019, P = 0.019 ) ((partial \eta^2 = 0.147))</td>
<td>0.545 (0.005)</td>
<td>0.522 (0.005)</td>
<td>0.531 (0.005)</td>
<td>0.528 (0.005)</td>
</tr>
<tr>
<td>Premotor/SMA</td>
<td>( F_{1, 35} = 3.973, P = 0.054 ) ((partial \eta^2 = 0.102))</td>
<td>0.541 (0.007)</td>
<td>0.521 (0.007)</td>
<td>0.530 (0.007)</td>
<td>0.523 (0.007)</td>
</tr>
<tr>
<td>Motor</td>
<td>( F_{1, 35} = 3.512, P = 0.069 ) ((partial \eta^2 = 0.092))</td>
<td>0.530 (0.006)</td>
<td>0.512 (0.006)</td>
<td>0.517 (0.006)</td>
<td>0.514 (0.006)</td>
</tr>
<tr>
<td>Sensory</td>
<td>( F_{1, 35} = 4.249, P = 0.047 ) ((partial \eta^2 = 0.108))</td>
<td>0.517 (0.006)</td>
<td>0.499 (0.006)</td>
<td>0.507 (0.006)</td>
<td>0.499 (0.006)</td>
</tr>
<tr>
<td>Par/temp/occ</td>
<td>( F_{1, 35} = 6.667, P = 0.014 ) ((partial \eta^2 = 0.160))</td>
<td>0.567 (0.005)</td>
<td>0.539 (0.005)</td>
<td>0.550 (0.005)</td>
<td>0.551 (0.005)</td>
</tr>
<tr>
<td>Session 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prefrontal</td>
<td>n.s.</td>
<td>0.522 (0.006)</td>
<td>0.505 (0.006)</td>
<td>0.507 (0.006)</td>
<td>0.511 (0.006)</td>
</tr>
<tr>
<td>Premotor/SMA</td>
<td>( F_{1, 32} = 3.081, P = 0.089 ) ((partial \eta^2 = 0.088))</td>
<td>0.550 (0.006)</td>
<td>0.533 (0.007)</td>
<td>0.533 (0.007)</td>
<td>0.540 (0.007)</td>
</tr>
<tr>
<td>Motor</td>
<td>( F_{1, 32} = 3.043, P = 0.091 ) ((partial \eta^2 = 0.087))</td>
<td>0.550 (0.006)</td>
<td>0.529 (0.006)</td>
<td>0.537 (0.006)</td>
<td>0.539 (0.006)</td>
</tr>
<tr>
<td>Sensory</td>
<td>( F_{1, 32} = 5.739, P = 0.023 ) ((partial \eta^2 = 0.152))</td>
<td>0.512 (0.006)</td>
<td>0.490 (0.006)</td>
<td>0.492 (0.006)</td>
<td>0.501 (0.006)</td>
</tr>
<tr>
<td>Par/temp/occ</td>
<td>( F_{1, 32} = 6.868, P = 0.013 ) ((partial \eta^2 = 0.177))</td>
<td>0.561 (0.005)</td>
<td>0.536 (0.005)</td>
<td>0.546 (0.005)</td>
<td>0.548 (0.005)</td>
</tr>
</tbody>
</table>

Results of statistical analysis of the mean fractional anisotropy (FA) of projections from corpus callosum to named cortical regions. Age is included as a covariate of no interest in the statistical analysis. B, binge; NB, non-binge; par/temp/occ, parietal/temporal/occipital; ROI, region of interest; SMA, supplementary motor area. n.s=non significant, \(p>0.1\).
pattern of mean FAs in each of the five ROIs was that male binge drinkers had lower mean FA than did male non-binge drinkers, whereas female binge drinkers had higher mean FA than did female non-binge drinkers (Fig. 4). Table 2 shows the results of the statistical analysis for each ROI, plus the mean FA (SE) for each of the four subgroups for each ROI.

**DTI comparisons between Sessions 1 and 2**

Diffusion tensor imaging of the whole brain (n = 37). Analysis of the skeletonised FA map for the differences in mean FA from Session 1 to Session 2 showed that there was neither a significant group × gender interaction nor any significant main effects.

Tractographic reconstruction of callosal segments (n = 37). The ANOVA did not show any significant interactions involving session in any of the callosal segments. A significant main effect of the session was found only for the motor callosal segment: mean FA in Session 2 was significantly higher than in Session 1 ($F_{1, 32} = 14.716$, $P = 0.001$, partial $\eta^2 = 0.315$; Figure S1 in the Supporting Information).

**Correlations (Session 1)**

Partial correlations with age partialed out involving mean FA values of corpus callosum segments, which were significant, are shown in Table 3 and Fig. 5.

**Binge score**

Significant negative correlations were found between mean FA in the prefrontal and the parietal/temporal/occipital segment of the corpus callosum and the binge score in men, but not in women (Table 3 and Fig. 5).

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**Figure 3** Mean fractional anisotropy (FA) values [probability; mean (±SE)] at Session 1 for men and women in the group of bingers and non-bingers for each of the five region of interest segments of corpus callosum. SMA, supplementary motor area

**Figure 4** Mean fractional anisotropy (FA) values [probability; mean (±SE)] at Session 2 for men and women in the group of bingers and non-bingers for each of the five region of interest segments of corpus callosum. SMA, supplementary motor area

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*Addiction Biology*
Drug use

Lower mean FA in the premotor/SMA and motor ROI was associated with a greater number of types of recreational drugs ever used in all participants, and drug use in men was negatively associated with mean FA in all segments of corpus callosum (Table 3).

Spatial working memory and stop signal task (CANTAB)

Lower mean FA in all segments of corpus callosum except in premotor/SMA was associated with worse working memory in both male and female participants (poorer strategy, and higher between-errors during eight-box trials: Table 3 and Fig. 5). No relationships were found for the SST.

DISCUSSION

The present study examined differences between binge drinkers and non-binge drinkers in a population of people in late adolescence and early adulthood (minimum age 18 years, mean age 20.48 years) with regard to white matter integrity and aspects of SWM and motor impulsivity. Differences between binge drinkers and non-binge drinkers were found in white matter integrity in several areas of the brain, in particular in three of the five segments of corpus callosum; these differences however were associated with gender. Male binge drinkers had lower FA compared with non-binge drinkers, whereas females showed the reverse pattern. Differences found in several cortical and subcortical white matter fibre tracts during the first session (i.e. inferior fronto-occipital fasciculus, body of corpus callosum, anterior thalamic radiation, forceps minor and major, and corticospinal tract) between the groups were still present when measurements were repeated 1 year later. These findings are consistent with previous cross-sectional studies, which have implicated alcohol use as an important factor of brain structure alterations in adolescents (e.g. Bava et al. 2013; McQueeny et al. 2009; Medina et al. 2008; Medina et al. 2007). The present study has revealed such effects in social drinkers with binge-drinking pattern who are already in...
early adulthood rather than in adolescence, when developmental processes are less complete (Simmonds et al. 2014).

Importantly, the present study has revealed that white matter structural alteration occurs in segments of corpus callosum serving connections to prefrontal cortical areas, to sensory cortical areas as well as to cortical areas (parietal, temporal and occipital), which support perceptual and attentional processes. The relationships between these changes in white matter integrity and alcohol drinking as measured by incidence of binge drinking, including speed of drinking, frequency of drunkenness and percentage of getting drunk, constitute another important finding in our study: that reduced white matter integrity in prefrontal and in the parietal/temporal/occipital segment of corpus callosum were each negatively correlated with the incidence of binge drinking in men. However, it is not possible to isolate which of the factors contributing to the binge score underlies the effects reported here.

Among all participants as a group, drug use was negatively related to FA in the premotor/SMA and motor segments of corpus callosum, whereas, among men, drug use was found to correlate negatively with FA in all segments of corpus callosum. These data indicate that not only alcohol use but also drug use are important factors involved in compromised white matter integrity in young adults. Such a relationship between alcohol and drug use and compromised white matter integrity has been shown in adolescents previously. For instance, past findings have indicated that the effects on white matter were more related to alcohol abuse than to drug abuse (Jacobus et al. 2009), or to alcohol abuse alone (Jacobus et al. 2013a), or in combination with drug abuse (Jacobus et al. 2013b). However, our findings may be the first to report a correlation not only between recreational drug use and compromised white matter integrity among young adult social drinkers but also between the degree of binge drinking and compromised white matter integrity, albeit in male young adults. However, it should be noted that our findings may not be applicable to a broader sample as our sample was limited to university students.

Previous studies with severely alcohol-dependent patients have also shown a negative correlation between FA in the internal capsule, superior longitudinal fasciculus and other white matter tracts and years of alcohol consumption (Pfefferbaum et al. 2009).

Our examination of the relationships between performance in the SWM tasks and FA revealed a negative correlation between performance deficits seen in both measures of the working memory task (strategy score and errors made) and white matter integrity in the callosal segments except the premotor segment. These findings provide evidence that reduction in FA is associated with impaired cognitive function and highlight the importance of preventing excessive alcohol drinking and/or drug taking in young adults that may lead to reduction of FA. Our data showed that these deficits continued to a great extent when measurements were obtained up to a year later supporting previous studies (Bava et al. 2013).

The changes seen in FA with age are related to gender (e.g. Asato et al. 2010; Bava et al. 2011; Schmithorst et al. 2008; Simmonds et al. 2014). For instance, higher FA with increased age is found in women compared with men, in some cases even after controlling for the effects of age (Kanaan et al. 2012). Recent work (Simmonds et al. 2014) has suggested that whereas women show white matter growth during adolescence, men continue to show white matter growth to early adulthood. Our findings that male binge drinkers are more susceptible to the effects of alcohol drinking compared with women may be because of white matter maturing later in men than in women. Consistent with this assumption, white matter volume was found to be less in men than in women. Some female participants had been taking the contraceptive pill, a sex steroid (record not kept); it is possible that variance in the data precluded detection of binge effects on white matter changes in women (Herting et al. 2012).

Gender differences (note that in our study, 50% of participants were females) were also found in the present study with regard to white matter integrity. Men showed higher FA in temporal and other deep white matter regions (i.e. left superior and inferior longitudinal fasciculus as well as anterior thalamic radiation) in accordance with previous studies (Inano et al. 2011; Kanaan et al. 2012; Menzler et al. 2011). Although the literature has also shown that men may have higher FA in regions surrounding the parietal/temporal/occipital junction as well as SMA (Kang et al. 2011), such gender differences were not seen in the present study, perhaps because of inadequate power or because the corpus callosum projections to these areas were compromised in binge-drinking men. Although certain areas of white matter showed higher FA in men compared with women, alcohol abuse was associated with decreased FA in men and increased FA in women. These effects cannot be attributed to differential developmental stage of white matter integrity between men and women (De Bellis et al. 2001) as they were seen not only in regions of the corpus callosum associated with prefrontal brain areas, which reach maturity last, but also in sensorimotor regions, which reach maturity early (Gogtay et al. 2004; Stiles & Jernigan 2010). In addition, the effects seen with binge drinking remained in the measurement after 1 year, although some changes may have been due to continued development (e.g. the increase seen in FA in the motor segment of corpus callosum in the second year of measurements). Thus, it seems that men are more sensitive to the
deleterious effects of alcohol. Importantly, it was in men only that a significant negative correlation was found between binge score and FA in the segments related to higher cognitive function (prefrontal) and attentional processes (parietal/temporal/occipital).

These data taken together suggest that alcohol use is associated with decreased FA in men and affects particular areas of corpus callosum important for functions associated with higher cognition and attentional processes as well as sensory perception.

The correlations between FA and performance in the cognitive tasks revealed interesting relationships indicating that integrity of white matter (i.e. high FA) is associated with better performance in a SWM task supporting previous reports that have shown such tasks to be sensitive to the deleterious effects of alcohol in adolescents (Squeglia et al. 2011) and young adults (Scaife & Duka 2009; Townshend & Duka 2005; Weissenborn & Duka 2003). Importantly, lower FA in the forward projecting callosal region and in the splenium is associated with impulsivity (Silveri et al. 2006) and impaired executive functioning (e.g. Giedd et al. 2001).

Whether these changes in white matter integrity are the result or the cause of alcohol binge drinking (with or without the recreational drug use) is difficult to derive from the current study. The longitudinal data indicated that 1 additional year of drinking did not contribute further to binge drinking-related impairments. While 1 year may be a short time to see any further impairment, it is worth noting that, on average, participants had started drinking at 15 years of age; thus, participants had already been drinking for a minimum of 3 years when included in the study.

An intrinsic limitation of imaging studies based on DTI is that, while FA is extremely sensitive to white matter changes, it is not very specific to the substrate of such changes. One way to specify whether myelin or axonal damage has contributed mostly to overall changes in FA is to measure the axial and radial diffusivities (Song et al. 2002). We have chosen not to perform this additional analysis as it has been shown that there is limited correspondence between the values obtained in this type of analysis and the underlying structural characteristics (Wheeler-Kingshott & Cercignani 2009).

Another limitation of this study was the absence of a drug-free binge-drinking group; however, the drug use in this cohort has been recreational and was spread around the two (binge and non-binge) groups equally.

In summary, the present data extend findings from the literature in that alcohol drinking is associated with reduced integrity of white matter in young adult social drinkers who engage in binge drinking. Furthermore, the data have indicated the importance of examining FA in segments of the corpus callosum as these segments contribute to different functions. Indeed, it was shown that the alcohol effects were more strongly associated with the areas of CC subserving executive functions and attentional processes. Furthermore, the finding in the present study that FA reduction is only seen in male binge drinkers has highlighted the importance of testing gender effects. Finally, the negative relationship between FA and performance in SWM suggests that binge drinking associated with reductions in FA may add to impairments in performance in such tasks.

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Authors Contribution
T. Duka and KW Smith designed the study. KW Smith acquired the data. KW Smith, T Duka, M Cercignani, F Gierski and NG Dowel contributed to the data analysis. T Duka and K Smith wrote the paper. All authors contributed to the interpretation of the data and reviewed and approved the paper for publication.

References

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SUPPORTING INFORMATION

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**Figure S1** Mean FA values (probability; mean (±SE)) at session 1 and at session 2, for Motor segment of corpus callosum.

**Table S1** MRI Volumetric Measures: Mean (SEM) volume (mL) of Gray matter, White matter, Cerebro-spinal fluid (CSF), and Intra-cranial volume (ICV; mL).

**Table S2** The volume and mean p-value of voxels that show a statistically-significant (p < 0.05) difference in mean FA within selected white matter tracts. Age was included as a covariate of no interest in the statistical analysis.