Binge drinking differentially affects cortical and subcortical microstructure

Laurel S. Morris1,2, Nicholas G. Dowell3, Mara Cercignani3, Neil A. Harrison3 & Valerie Voon1,4

Behavioural and Clinical Neuroscience Institute, University of Cambridge, Cambridge, UK1, Department of Psychology, University of Cambridge, Cambridge, UK2, Department of Psychiatry, Brighton and Sussex Medical School, Brighton, UK3 and Department of Psychiatry, University of Cambridge, Addenbrooke’s Hospital, Cambridge, UK4

ABSTRACT

Young adult binge drinkers represent a model for endophenotypic risk factors for alcohol misuse and early exposure to repeated binge cycles. Chronic or harmful alcohol use leads to neurochemical, structural and morphological neuroplastic changes, particularly in regions associated with reward processing and motivation. We investigated neural microstructure in 28 binge drinkers compared with 38 matched healthy controls. We used a recently developed diffusion magnetic resonance imaging acquisition and analysis, which uses three-compartment modelling (of intracellular, extracellular and cerebrospinal fluid) to determine brain tissue microstructure features including neurite density and orientation dispersion index (ODI). Binge drinkers had reduced ODI, a proxy of neurite complexity, in frontal cortical grey matter and increased ODI in parietal grey matter. Neurite density was higher in cortical white matter in adjacent regions of lower ODI in binge drinkers. Furthermore, binge drinkers had higher ventral striatal grey matter ODI that was positively correlated with binge score. Healthy volunteers showed no such relationships. We demonstrate disturbed dendritic complexity of higher-order prefrontal and parietal regions, along with higher dendritic complexity of a subcortical region known to mediate reward-related motivation. The findings illustrate novel microstructural abnormalities that may reflect an influence of alcohol bingeing on critical neurodevelopmental processes in an at-risk young adult group.

INTRODUCTION

Binge drinking, the rapid intake of alcohol in short bursts of time, is a serious public health issue in the United Kingdom and United States, costing an estimated £4.9bn/year to British society (Francesconi 2015). This common pattern of alcohol intake has the highest prevalence in young adults (Kuntsche, Rehm & Gmel 2004; Grucza, Norberg & Bierut 2009), during a time of heightened risk-taking, impulsivity, neural (ventral striatal) response to rewards (Hill et al. 2000; Braams et al. 2015), and crucially, ongoing neurodevelopment. Young adults who binge drink but not those who drink without this pattern (Miller et al. 2007) partake in other detrimental behaviours, ultimately linking binge drinking with accidents, violence, suicide and alcohol-induced liver disease (Mathurin & Deltenre 2009; Stolle, Sack & Thomasius 2009; Nutt & Rehm 2014) as well as heightened substance abuse or dependence (Chassin, Pitts & Prost 2002).

While acute alcohol consumption can locally modulate neurotransmission, more chronic use has counter-adaptive effects on neural systems (Vengeliene et al. 2008), which is further perturbed by states of withdrawal (Rolland et al. 2011) (Rossetti & Carboni 1995). Local neuromodulatory changes associated with harmful alcohol use also promote both small and large-scale structural and functional changes in the longer term. Adolescent and young adult binge drinkers feature a range of grey and white matter volume changes that coincide with cognitive impairments. In teenagers who developed regular alcohol use patterns in the previous year, reductions in cortical grey matter volumes have been reported, in particular of the dorsolateral prefrontal cortex (dlpfc) and premotor cortex (Luciana et al. 2013). Reduced cerebellar grey matter volume has also been associated with severity of binge drinking in a large sample of healthy teenagers (Lisdahl et al. 2013). Contrastingly, higher left dlpfc grey matter volume has also been...
reported in this group, associated with past alcohol consumption (Doallo et al. 2014). We have also recently reported larger ventral striatal volumes in binge drinkers (Howell et al. 2013). Binge drinkers also display functional changes in these regions; activity in the dorsal prefrontal cortex during a spatial working memory task is reduced (Squeglia et al. 2011), and resting-state functional connectivity of the ventral striatum is reduced and associated with impulsivity (Morris et al. 2015a, 2015b).

While informative, assessments of grey matter volume provide little indication of morphological or microstructural differences that may be present that are associated with neuroplastic restructuring in response to patterns of alcohol use. We therefore employed a recently developed diffusion MRI technique that provides higher specificity of microstructural characteristics than conventional diffusion tensor imaging to examine the relationship between binge drinking and microstructure. Diffusion of water, which is normally isotropic, is restricted in the brain by tissue boundaries such as axonal membranes and as such, different microstructural environments can be assessed. Previous models of white matter use a diffusion ellipsoid or diffusion tensor to capture the features of white matter fibre bundles that restrict movement of water. The ball-and-stick model (Behrens et al. 2003) represents the intracellular water diffusion component as cylinders with zero radius (stick) and extracellular diffusion as isotropic and unrestricted (ball). These models assume one single orientation of fibres, which limits analysis to coherently organized fibre bundles like the corpus callosum while grey matter displays substantial dispersion of fibre orientations. More model-based methods using geometric models of microstructure to predict the MR signal produced by water diffusion can explicitly represent the dispersion of axon orientation, expected in grey matter. We use neurite orientation dispersion density imaging (NODDI) with microstructural modelling that has a more direct relationship with axonal orientation distribution (Jespersen et al. 2012), neurite density and dendritic architecture (Jespersen et al. 2010).

This approach is based on the ‘hindered and restricted model’ of white matter water diffusion and uses three-compartment modelling (Panagiotaki et al. 2012) for three distinct tissue microstructural environments that each uniquely affect water diffusion. The differentiation of such water forms provides a basis for depiction of microstructural features using diffusion MRI. Firstly, the intracellular fraction ultimately provides a measure of how dispersed fibres are, indicating the complexity of neurite or dendritic branching expected in grey matter [orientation dispersion index (ODI)]. Secondly, the extracellular fraction is equivalent to myelinated fibre bundles expected in white matter (neurite density).

Thirdly, the cerebrospinal fluid (CSF) space is where diffusion of water is isotropic (Zhang et al. 2012). As such, measures of neurite density and complexity can be obtained, which provide a more fine-grained microstructural approach and have good scan–revisit reproducibility (Tariq et al. 2012). With traditional DTI measures, like fractional anisotropy, it remains unclear whether lower fractional anisotropy equates to lower coherence of white matter fibres. However, with the current analysis, the ODI captures sprawling dendritic processes, detailing grey matter complexity (Zhang et al. 2012). ODI is consistent with Golgi staining of dendritic processes (Jespersen et al. 2012) and microscopic grey matter dendritic architecture (Jespersen et al. 2010). Indeed, these microstructural features have previously been associated with the hierarchy of computations performed by increasingly higher-level cortical structures (Jacobs et al. 2001), goal-directed behaviour (Morris et al. 2015a, 2015b), lower age (Nazeri et al. 2015) and resting-state functional network connectivity (Nazeri et al. 2015).

We characterized changes in microstructural features across the brain of young adult binge drinkers and examined alcohol use severity and the specific pattern of binge drinking. As neural microstructural maturation trajectories persist into the early 20s (Lebel et al. 2008), we examined a young adult population. In line with our previous findings of larger ventral striatal grey matter volume in binge drinkers (Howell et al. 2013), we expected that binge drinkers would have higher orientation dispersion in this region, potentially marking neural proliferation associated with excessive alcohol use or motivation for reward.

MATERIALS AND METHODS

Participants

Young adult binge drinkers and healthy volunteers were recruited from community-based advertisements in East Anglia. Binge drinkers inclusion criteria was based on the National Institute on Alcoholism and Alcohol Abuse [(NIAAA) 2004] diagnostics: >8/>6 alcohol units consumption (men/women) within a 2 hour period at least once a week. Subjects had to have been ‘drunk’ at least once per week for the previous 6 months and reported an intention to get drunk. Subjects were carefully questioned on their patterns of alcohol consumption and last alcohol binge consumption prior to testing. There was no upper limit for amount of binges or times ‘being drunk’ over the previous 6 months, but alcohol dependence was exclusionary. Healthy volunteers were made up of drinkers (non-binge) and non-drinkers. Psychiatric disorders
including substance addictions were screened with the Mini International Neuropsychiatric Interview (Sheehan et al. 1998). Subjects were excluded if they had a major psychiatric disorder, substance addiction (including alcohol and excluding nicotine) or medical illness or were on psychotropic medications. Subjects were included if they were 18 years of age or over, were right-handed only and had no history of regular or current use of other substances.

All participants completed the National Adult Reading Test (Nelson 1982) to assess verbal IQ, the Beck Depression Inventory (Beck et al. 1961) for depressive symptoms and the UPPS-P scale for impulsivity (Whiteside & Lynam 2001). The Alcohol Use Disorders Test (AUDIT) (Saunders et al. 1993) was used to assess general alcohol use severity. The Alcohol Use Questionnaire was used to assess the pattern of alcohol use, the last binge, frequency of alcohol use, amount of alcohol intake and speed of drinking (Townshend & Duka 2002). From this, a ‘binge score’ can be calculated, which is less susceptible to self-report estimation distortions (Townshend & Duka 2002). This score incorporates the speed of drinking, the amount of times being ‘drunk’ in the previous 6 months and the percentage of times that an individual drinks to get drunk. This provides a measure of the pattern of drinking as opposed to simply the amount of alcohol consumed. Therefore, one may have relatively low alcohol intake but a high binge score. Participants provided written informed consent and were compensated for their time. The study was approved by the University of Cambridge Research Ethics Committee. Grey matter volumetric data have previously been reported in a subset of this sample, showing a sexually dimorphic pattern of volume change in binge drinkers (Kvamme et al. 2016).

Neurite orientation dispersion and density imaging

The current analysis of diffusion MRI data is based on the hindered and restricted model of white matter water diffusion using three-compartment modelling (Panagiotaki et al. 2012) for three distinct tissue microstructural environments. Firstly, the intracellular fraction shows restricted diffusion with a non-Gaussian pattern of water displacement, in which diffusion is bounded by restricted geometries like axonal membranes. The total signal is thus a composite of diffusion restriction by a cylinder with a given orientation and weighted by all cylinders oriented in that direction. While previous models use a single, parallel orientation parameter, here, we used a Watson distribution (spherical analogue of a Gaussian distribution) to signify axons dispersing about a central orientation, which can range from highly parallel to highly dispersed. This ultimately provides a measure of ODI, or how dispersed fibres are, indicating the complexity of neurite or dendritic branching. Secondly, the extracellular fraction shows hindered diffusion and a Gaussian anisotropic displacement, in which water diffusion is hindered by glial and cell body (soma) membranes. Thirdly, the CSF space is where water diffusion is unhindered and isotropic (Zhang et al. 2012). The differentiation of such water forms provides a basis for depiction of microstructural features using diffusion MRI. ODI captures sprawling dendritic processes, detailing grey matter complexity (Zhang et al. 2012) that is consistent with Golgi staining of dendritic processes (Jespersen et al. 2012) and microscopic grey matter dendritic architecture (Jespersen et al. 2010).

We acquired NODDI data from 38 healthy volunteers and 28 binge drinkers. Data were acquired with a Siemens 3T Tim Trio scanner using a 32-channel head coil at the Wolfson Brain Imaging Centre at the University of Cambridge with the following parameters: TE = 128 milliseconds; TR = 11 300 milliseconds; planar FOV = 192 mm × 192 mm; 96 matrix with 2-mm voxel and 2-mm slice thickness. There were 63 slices (b = 0 volumes and diffusion weighted data in two shells, b-values: 2850 and 700 seconds/mm² with 65 and 33 directions, respectively). A NODDI microstructural model was computed and fitted to the data using the NODDI toolbox for Matlab (Zhang et al. 2012) (http://www.nitrc.org/projects/noddi_toolbox).

Resulting parameter maps were normalized to MNI space with ANTS software (http://stnava.github.io/ANTS/). ODI parameter maps were masked to standard grey matter and neurite density to standard white matter templates. Parameter maps for both measures were entered into independent samples t-test analysis to compare between groups, controlling for age and gender. Whole-brain corrected family-wise error (FWE) p < 0.05 was considered significant for these group comparisons and thresholded at cluster extent of <10 contiguous voxels to remove contributions from small spurious clusters. For correlations between microstructure and drinking severity, these whole brain parameter maps were entered into correlation analysis with AUDIT and binge scores, separately for healthy volunteers and binge drinkers and whole-brain FWE p < 0.05 was considered significant.

To examine whether there were group differences in the ventral striatum specifically based on a priori hypotheses, we computed small volume corrected (SVC) region of interest (ROI) analysis (p < 0.05) for ventral striatum. The ventral striatal anatomical ROI, as used previously in other studies (Murray et al. 2008), was hand drawn using MRicro based on the definition of the ventral striatum by Martinez et al. (2003).
RESULTS

Participant characteristics
We acquired data from 38 healthy volunteers (24 women; current/occasional smokers = 1/3) and 28 binge drinkers (11 women; current/occasional smokers, 5/3; days since last binge, 2.85, 1.89 SD). See Table 1 for demographic data. There were no significant group differences in age (p = 0.697), gender (p = 0.102), verbal IQ (p = 0.321) or years of education (p = 0.438).

Binge drinkers had significantly higher ‘binge score’, AUDIT score and had significantly more days that they were ‘drunk’ and percentage that they would drink to get drunk in the last 12 months (Table 1). Of the healthy volunteers, 17 reported zero times ‘being drunk’ in the past 6 months. Binge drinkers also had higher total UPPS total scores, higher sensation seeking and higher positive urgency (Table 1). There was a significant difference between smoking status (p = 0.033) between the two groups. The two groups did not significantly differ in depressive symptoms (p = 0.208).

Table 1 Demographic data.

|                      | Mean  | SD    | p     |
|----------------------|-------|-------|-------|
| Gender (F/M)         | HV    | 24/14 | 0.102 |
|                      | BD    | 11/17 |       |
| Age                  | HV    | 23.69 | 3.85  | 0.697 |
|                      | BD    | 22.03 | 4.47  |       |
| Verbal IQ            | HV    | 115.54| 7.16  | 0.321 |
|                      | BD    | 117.21| 4.58  |       |
| BDI                  | HV    | 6.973 | 7.407 | 0.208 |
|                      | BD    | 9.636 | 8.37  |       |
| AUDIT                | HV    | 4.333 | 3.119 | <0.001|
|                      | BD    | 16.75 | 4.329 |       |
| Binge score          | HV    | 7.545 | 6.035 | <0.001|
|                      | BD    | 33.376| 15.371|       |
| Percent drunk        | HV    | 0.112 | 0.224 | <0.001|
|                      | BD    | 0.47  | 0.291 |       |
| Amount drunk         | HV    | 1.5   | 3.121 | <0.001|
|                      | BD    | 15.889| 14.175|       |
| UPPS total           | HV    | 127.5 | 16.246| 0.004 |
|                      | BD    | 141.091| 16.622|       |
| Sensation seeking    | HV    | 32.5  | 6.701 | 0.025 |
|                      | BD    | 36.409| 5.17  |       |
| Positive urgency     | HV    | 27.594| 4.785 | 0.036 |
|                      | BD    | 31.682| 7.828 |       |

Data are presented for 38 healthy volunteers and 28 binge drinkers. AUDIT = Alcohol Use Disorders Test; BD = binge drinkers; BDI = Beck Depression Inventory; F/M = female/male; HV = healthy volunteers; p = independent samples t-test p value; UPPS = urgency, premeditation, perseverance, sensation seeking, and positive urgency impulsive behavior scale; SD = standard deviation.

Neurite orientation dispersion and density
Microstructural maps derived from the NODDI acquisition and analysis for example healthy volunteer are depicted in the Supporting Information Fig. 1. Binge drinkers had lower grey matter ODI in several regions, including right dlPFC and higher adjacent white matter neurite density (whole-brain FWE corrected p < 0.05, see Table 2 for further statistics) (Fig. 1). Binge drinkers also had decreased ODI and increased neurite density in regions throughout the parietal cortex (Table 2) (Supporting Information Fig. 2). There were no differences between men and women across both groups in ODI or neurite density (FWE p > 0.05). We specifically examined group differences in ventral striatal microstructure given our previous findings of volumetric changes in ventral striatal in binge drinkers (Howell et al. 2013) using ROI analysis. Binge drinkers had higher bilateral ventral striatal orientation dispersion compared with healthy volunteers (peak coordinate at left ventral striatum, xyz = −6 12 0; ventral striatal SVC FWE p = 0.003; Z = 4.62) (Fig. 1).

As there were widespread ODI and neurite density differences between groups, both higher (parietal cortex) and lower ODI (dlPFC) in binge drinkers, it is important to determine whether relationships between microstructure and behaviour can be established across the whole brain, which will illuminate the specificity and relevance of the microstructural differences. Thus, we examined the relationship between microstructural features and drinking severity using AUDIT and the ‘binge score’ obtained from the Alcohol Use Questionnaire (Townshend & Duka 2002). There were no significant correlations between whole brain ODI and drinking severity (binge score or AUDIT) at whole-brain FWE corrected p < 0.05). However, when restricting the analysis to ventral striatum, we find that binge drinkers show a positive correlation between ventral striatal ODI and binge score (bilateral ventral striatum SVC FWE p = 0.011; Z = 4.32, peak xyz = 12 14–8) (Fig. 1) but not AUDIT (p > 0.05). No significant correlations between ventral striatal ODI and drinking severity were observed in healthy volunteers. To explore the specificity of these findings, we controlled for AUDIT in the binge score correlation, which did not affect the significance of the findings (positive correlation between right ventral striatum ODI and binge score controlling for AUDIT in binge drinkers: SVC FWE p = 0.012).

As measures of impulsivity were significantly different between groups behaviourally (UPPS total, positive urgency and sensation seeking), we conducted correlations between microstructural parameter maps and measures of impulsivity in an exploratory manner across groups. There were no significant correlations between whole
brain ODI or neurite density and impulsivity (all whole-brain FWE corrected \( p < 0.05 \)). As smoking status differed between the two groups, smoking was added as a covariate of no interest to the analyses. Smoking did not affect the whole-brain group difference findings (Supporting Information Table 1) or the SVC findings for ventral striatum (bilateral ventral striatum SVC FWE \( p = 0.004; Z = 4.54 \), peak xyz = \(-14 10 0\)).

**DISCUSSION**

We used a recently developed diffusion MRI acquisition and analysis to determine brain tissue microstructure features in young adult binge drinkers. This is the first study demonstrating reduced ODI, a proxy of neurite complexity, in the frontal cortical grey matter of binge drinkers and increased ODI in parietal cortex. Furthermore, neurite density was higher in cortical white matter in adjacent regions of lower ODI in binge drinkers. While there is a weak relationship between ODI and neurite density (Zhang *et al.* 2012), the current study suggests their joint disturbance in binge drinkers. Cortical microstructural changes were not specifically related to alcohol use severity or binge drinking patterns in the cortex; however, the ventral striatum showed higher ODI that was associated with binge severity in binge drinkers. The link between ventral striatal dendritic complexity and binge drinking score but not general alcohol use severity suggests that the behavioural binge pattern of alcohol intake (rapid and frequent bouts of heavy drinking)

**Table 2** Statistics of group differences for neurite density and orientation dispersion index.

|                          | \( p \text{(FWE-corr)} \) | \( K \) | \( Z \) | \( x \)  | \( y \)  | \( z \)  |
|--------------------------|--------------------------|--------|--------|--------|--------|--------|
| **Orientation Dispersion Index** |                         |        |        |        |        |        |
| HV > BD                  |                          |        |        |        |        |        |
| Right inferior parietal cortex | \(<0.001\)              | 14     | \(>8\) | 50     | \(-64\) | 22     |
| Right superior frontal gyrus (DLPFC) | \(<0.001\)              | 27     | 7.75   | 24     | 40     | 38     |
| Left middle occipital gyrus | \(<0.001\)              | 12     | 7.06   | \(-28\) | 82     | 36     |
|                           |                          |        | 6.44   | \(-32\) | 78     | 30     |
|                           |                          |        | 6.94   | \(-28\) | 74     | 44     |
| Right postcentral gyrus   | \(<0.001\)              | 22     | 7.05   | 34     | \(-34\) | 58     |
| Left superior parietal lobule | \(<0.001\)              | 10     | 6.42   | \(-24\) | \(-58\) | 62     |
| BD > HV                  |                          |        |        |        |        |        |
| Right angular gyrus       | \(<0.001\)              | 26     | 7.84   | 50     | \(-60\) | 26     |
|                           |                          |        | 7.33   | \(-40\) | 76     | 32     |
|                           |                          |        | 6.43   | 42     | \(-58\) | 40     |
|                           |                          |        | 5.74   | \(-42\) | \(-62\) | 20     |
| Left superior parietal lobule | \(<0.001\)              | 22     | 7.19   | \(-22\) | \(-64\) | 52     |
| Right supramarginal gyrus | \(<0.001\)              | 22     | 6.95   | 56     | \(-42\) | 40     |
| Left inferior parietal lobule | \(<0.001\)              | 12     | 6.89   | \(-40\) | \(-40\) | 46     |
|                           |                          |        | 6.06   | 30     | \(-42\) | 56     |
| **Neurite density**       |                          |        |        |        |        |        |
| HV > BD                  |                          |        |        |        |        |        |
| Right angular gyrus       | \(<0.001\)              | 19     | 7.77   | 46     | \(-58\) | 26     |
|                           |                          |        | 6.61   | 54     | \(-48\) | 30     |
| Left middle occipital gyrus | \(<0.001\)              | 16     | 6.59   | \(-38\) | 74     | 32     |
| Right postcentral gyrus   | \(<0.001\)              | 15     | 6.08   | 32     | \(-38\) | 48     |
| BD > HV                  |                          |        |        |        |        |        |
| Inferior parietal cortex  | \(<0.001\)              | 20     | \(>8\) | 48     | \(-64\) | 22     |
|                           |                          |        | 6.82   | 34     | \(-84\) | 22     |
|                           |                          |        | 5.68   | 36     | \(-76\) | 22     |
|                           |                          |        | 6.04   | 44     | \(-76\) | 12     |
| Right superior frontal gyrus (DLPFC) | \(<0.001\)              | 27     | 7.71   | 24     | 38     | 38     |
| Left middle frontal gyrus (DLPFC) | \(<0.001\)              | 21     | 7.44   | \(-28\) | 40     | 26     |
|                           |                          |        | 6.6    | \(-22\) | 30     | 38     |
| Right supramarginal gyrus | \(<0.001\)              | 29     | 7.57   | 54     | \(-44\) | 32     |
| Right middle frontal gyrus | \(<0.001\)              | 19     | 6.33   | 38     | 12     | 48     |
| Right superior frontal gyrus | \(<0.001\)              | 12     | 6.18   | 26     | \(-8\)  | 58     |

BD = binge drinkers; DLPFC = dorsolateral prefrontal cortex; HV = healthy volunteers; \( K \) = cluster size; \( p \text{(FWE-corr)} \) = whole brain \( p < 0.05 \) family-wise error corrected \( p \) value; xyz = peak voxel coordinates; \( Z \) = \( z \)-score.
rather than general alcohol use severity is associated with ventral striatal neurite integrity.

The current measure of dendritic complexity has previously been associated with age (Nazeri et al. 2015) and the hierarchy of neural computations (Jacobs et al. 2001). Hetero-modal cortical regions required for downstream processing of information show more complex dendrite and spine features than primary and uni-modal cortical regions (Jacobs et al. 2001). This complexity is captured by the current method and is consistent with both Golgi staining of dendritic processes (Jespersen et al. 2012) and microscopic detailing of grey matter dendritic architecture (Jespersen et al. 2010). Thus, lower dlpfc ODI in binge drinkers may reflect a reduction in the highly dispersed dendritic tree organization expected in high-level cortical regions. Indeed, this converges with observations that binge drinking in young adults is associated with significant attentional and executive functioning deficits subserved by dlpfc (Sealfi & Duka 2009; Parada et al. 2012; Mota et al. 2013). Furthermore, alcohol craving is associated with dlpfc activity (Olbrich et al. 2006), and modulation of dlpfc with transcranial direct current stimulation reduces craving in individuals with alcohol use disorders (Boggio et al. 2008). The finding of higher ODI in the parietal cortex of binge drinkers was unexpected. The parietal lobe plays a diverse role in cognition, directing attentional control (Shulman et al. 1999; Corbetta et al. 2000), task switching (Sohn et al. 2000) and response inhibition (de Zubicaray et al. 2000). While previous studies have implicated dlpfc (Luciana et al. 2013) and ventral striatal (Howell et al. 2013) volume changes in binge drinkers, changes in parietal cortex have also been suggested in alcohol use disorders. Alcohol-dependent individuals show reduced parietal grey matter volumes associated with lifetime alcohol use (Fein et al. 2002; Rando et al. 2011) and spatial processing (Fein et al. 2009), and alcohol-dependent women show reduced parietal activity during a spatial working memory task (Tapert et al. 2001). Together, while the direction of microstructural change requires further exploration and determination, the current findings suggest a disturbance in fronto-parietal integrity in binge drinkers. It will be important for future studies to define the functional relevance of these microstructural changes by specifically examining attentional and executive processing alongside detailed microstructural analyses.

Previous studies of ventral striatal volume in individuals with AUD have engendered mixed results. There have been reports of lower ventral striatal volume (Sullivan et al. 2005; Makris et al. 2008; Wrase et al. 2008); however, a recent report demonstrated an association between higher incidence of familial AUD and greater left ventral striatal volume (Cservenka et al. 2015). We have also recently shown that binge drinkers have enlarged ventral striatal volume (Howell et al. 2013) influenced by gender (Kvamme et al. 2016). These findings relating to grey matter volume are mixed; however, the current measure is distinct from volume.

Distinct from measures of volume, the current finding of higher ventral striatal ODI may reflect a neuroplastic capacity. For example, chronic psychostimulant use increases dendritic arborization in the ventral striatum of rodents (Robinson & Kolb 2004), and plasticity of nucleus accumbens mediates the reinforcing effects of ethanol (Rassnick, Pulvirenti & Koob 1992). Furthermore, while we do not currently examine grey matter volume, we have previously demonstrated in a subset of the same binge drinkers a sexually dimorphic pattern of volume change wherein binge drinking men show higher and binge drinking women show lower ventral striatum volume relative to their healthy counterparts (Kvamme et al. 2016). In contrast to the current study, the same paper reported no group differences in volumetric data, suggesting a dissociation between these measures. While further longitudinal studies are necessary to elucidate the neuroplastic ventral striatal changes associated with patterns of alcohol use, these findings suggest that cortical microstructural may be broadly associated with harmful alcohol use.

**Figure 1** Lower dorsolateral prefrontal cortex but higher ventral striatal orientation dispersion in binge drinkers. Left: clusters illustrate regions of significantly higher white matter neurite density (red) and lower grey matter orientation dispersion index (ODI, blue) in dlpfc of binge drinkers compared with healthy volunteers (displayed at p < 0.001 uncorrected threshold for visualization purposes). Right: small volume corrected family-wise error p < 0.05 analyses revealed that binge drinkers had reduced ODI in ventral striatum compared with matched controls. Left sided peak ventral striatal ODI (peak co-ordinates, xyz = −6 12 0) positively correlated with binge score in binge drinkers. Images are displayed on a standard MNI152 template; R, right; L, left.
We did not find a relationship between impulsivity and whole brain microstructure or ventral striatal microstructure. Impulsivity has been suggested as an endophenotypic marker for subsequent compulsive substance use or dependence (Everitt & Robbins 2005; Belin et al. 2008; Robbins et al. 2012). As such, relating ventral striatal microstructure to impulsivity might suggest it as a potential endophenotypic marker. However, at least for ventral striatal ODI, the differences may be a result of alcohol use rather than the underlying behavioural factor of impulsivity.

We highlight disturbances in neurite microstructure in binge drinkers in regions implicated in higher-order attentional and executive functioning and reward-related motivation. Whether the current neural findings are a cause or effect of alcohol exposure requires further longitudinal studies. Interestingly, adolescents who initiate alcohol use show a reduction in grey matter in the right middle frontal gyrus, overlapping with dlPFC, compared with those who did not initiate alcohol use (Luciana et al. 2013), suggesting a potential pre-morbid role of dlPFC structural integrity. Alternatively, alcohol or drug use may interfere with critical neurodevelopmental stages that persist into young adulthood. We caution that underlying neurobiological differences cannot be directly inferred by the current technique but that there is some broad indication of microstructural change. ODI has been previously associated with higher-level processing (Jacobs et al. 2001) and because we report ODI changes in cortical regions involved with executive behavioural control: we highlight the potential pathological and functional relevance of this measure. Further studies directly examining the relationships between cortical ODI and flexible behavioural control are certainly warranted.

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Authors Contribution
All authors contributed to the study design and acquisition of the data. LSM, NGD analysed the data. LSM drafted the manuscript. All authors assisted the interpretation of the findings, critically reviewed the content and approved the final version for publication.

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**SUPPORTING INFORMATION**

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site:

**Supplementary Table 1.** Statistics of group differences for neurite density and orientation dispersion index, controlled for smoking status. Abbreviations: p(FWE-corr), whole brain ($P < 0.05$) family-wise error corrected $P$ value; K, cluster size; Z, Z-score; xyz, peak voxel coordinates; BD, binge drinkers; HV, healthy volunteers; DLPFC, dorsolateral prefrontal cortex.

**Supplementary Figure 1.** Example microstructure parameters. Microstructure parameters for a single healthy subject are presented. Abbreviations: ODI, orientation dispersion index; ICVF, intracellular volume fraction, for neurite density; CSF, cerebrospinal fluid.

**Supplementary Figure 2.** Regions of reduced orientation dispersion index in binge drinkers compared to healthy volunteers. Binge drinkers had reduced grey matter orientation dispersion index (ODI) in right dorsolateral prefrontal cortex (dlpfc) and in distinct regions throughout the parietal cortex (whole-brain family-wise error (FWE) corrected $p < 0.05$, see Table 1 for further statistics).