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# Substance use and regional gray matter volume in individuals at high risk of psychosis

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**Abstract**

Individuals with an at risk mental state (ARMS) are at greatly increased risk of developing a psychotic illness. Risk of transition to psychosis is associated with regionally reduced cortical gray matter volume. There has been considerable interest in the interaction between psychosis risk and substance use. In this study we investigate the relationship between alcohol, cannabis and nicotine use with gray matter volume in ARMS subjects and healthy volunteers. Twenty seven ARMS subjects and 27 healthy volunteers took part in the study. All subjects underwent volumetric MRI imaging. The relationship between regional gray matter volume and cannabis use, smoking, and alcohol use in controls and ARMS subjects was analysed using voxel-based morphometry. In any region where a significant relationship with drug was present, data were analysed to determine if there was any group difference in this relationship. Alcohol intake was inversely correlated with gray matter volume in cerebellum, cannabis intake was use was inversely correlated with gray matter volume in prefrontal cortex and tobacco intake was inversely correlated with gray matter volume in left temporal cortex. There were no significant interactions by group in any region. There is no evidence to support the hypothesis of increased susceptibility to harmful effects of drugs and alcohol on regional gray matter in ARMS subjects. However, alcohol, tobacco and cannabis at low to moderate intake may be associated with lower gray matter in both ARMS subjects and healthy volunteers—possibly representing low-level cortical damage or change in neural plasticity.


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## 1. Introduction

Individuals with an At Risk Mental State (ARMS) are at increased risk of developing psychosis (Phillips et al., 2000). They have also been shown to have reduced gray matter compared to healthy volunteers (Pantelis et al., 2003; Borgwardt et al., 2007), and, with transition to psychosis, show a further reduction in gray matter volume (Pantelis et al., 2003; Takahashi et al., 2009), findings which have been confirmed by recent meta-analyses (Smieskova et al., 2010; Fusar-Poli et al., 2011). The cause of these changes is not known, but it has been suggested that reductions in gray matter volume might occur, in part, because of increased sensitivity in ARMS subjects to the potentially toxic effects of drugs and alcohol (Welch et al., 2010). Cannabis, tobacco and alcohol have been implicated in brain volume changes in patients with schizophrenia (Sullivan et al., 2000; Nesvag et al., 2007; Szeszko et al., 2007; Tregellas et al., 2007; Bangalore et al., 2008; Rais et al., 2008a; McClernon, 2009; Van Haren et al., 2010), and there is some evidence that moderate levels of intake may be associated with reduced gray matter volume in individuals at genetic risk of schizophrenia, and even in healthy volunteers (McClernon, 2009; Gallinat et al., 2006; Sasaki et al., 2009; Verbaten, 2009; Lorenzetti et al., 2010). Here, using data acquired during an earlier study (Stone et al., 2009), we investigate the hypothesis that the degree of recent cannabis, alcohol and tobacco use is negatively associated with gray matter volume in a dose-dependent manner, and that ARMS subjects show a stronger negative association between substance use and gray matter volume than healthy volunteers due to increased sensitivity to neurotoxic effects.

## 2. Methods

Twenty seven ARMS subjects were recruited from OASIS (Outreach and Support in South London), part of the South London and Maudsley NHS Trust. Twenty seven age- and sex-matched controls were recruited from the same geographical area through advertisements that outlined the study. Subjects with an ARMS were identified using the Comprehensive Assessment of At Risk Mental State (CAARMS) (Yung et al., 2005). All subjects who expressed interest in participation were offered a face-to-face interview, where the full details of the study, including its possible risks and benefits were explained. Controls had no personal history of psychiatric symptoms, psychotropic medication or medical illness, and no family history of schizophrenia. For both groups, exclusion criteria included history of severe head injury (loss of consciousness for over 5 min), drug or alcohol dependence, metallic implants, and pregnancy.

Prior to scanning, all subjects were interviewed about their family and personal psychiatric history, current and past medication use and current and past use of alcohol, tobacco and illicit drugs. Alcohol use was recorded as the average number of units per week taken in the previous month. Tobacco use was recorded as the number of cigarettes taken per day. Cannabis use was recorded as the number of times that cannabis was taken in the previous year. As the cannabis intake for one ARMS subject was 3 times that of the next heaviest user, data on cannabis use were log transformed.

All subjects underwent volumetric MRI scanning. Scanning took place on a General Electric (Milwaukee, USA) 3 Tesla HDx Magnetic Resonance system. After positioning the subject in the scanner with a foam rest under their knees, an initial localizer scan was performed to measure the interhemispheric angle and the AC–PC line (the line passing through the upper part of the anterior commisure and the lower part of the posterior commisure—approximated from the anterior and posterior corpus callosum).

Structural images were acquired using an axial 2D T2-weighted Fast Spin Echo scan and an axial fast FLAIR scan (total scan time 5 min), both prescribed parallel to the AC–PC line. These were followed by a whole brain 3D coronal IR-SPGR (inversion recovery prepared spoiled gradient echo) scan, prescribed from the midline sagittal localizer, giving isotropic 1.1 mm voxel size in a scan time of approximately 6 min (TE = 2.82 ms; TR = 6.96 ms; TI = 450 ms; flip angle = 20°).

Segmentation was performed using Statistical Parametric Mapping software (SPM5, Wellcome Department of Imaging Neurosciences, University College London, UK). Gray matter probability images were then "modulated" (to compensate for the effect of spatial normalisation) by multiplying each voxel value by its relative volume before and after warping. The segmented images were then smoothed with an 8 mm × 8 mm × 8 mm Gaussian kernel to reduce noise, and also allow for the effects of small residual mis-registrations.

In order to reduce multiple comparisons, and to correct for the fact that there was a high degree of overlap between the use of all three substances, correlations of gray matter volume difference with alcohol, cannabis and tobacco intake were analysed in a single model by fitting a GLM at each intracerebral voxel in standard space using the BAMM package. Given that structural brain changes are likely to extend over a number of contiguous voxels, test statistics incorporating spatial information such as 3D cluster mass (the sum of suprathreshold voxel statistics) are generally more powerful than other possible test statistics, which are informed only by data at a single voxel (Bullmore et al., 1999). A relatively lenient p-value ($p = 0.05$) was initially set to detect voxels putatively demonstrating differences between groups; spatial clusters of such voxels were then searched for and the "mass" of each cluster found (the sum of suprathreshold voxel statistics it comprises) was tested for significance. As no parametric distribution is known for cluster mass, permutation based testing, implemented in the BAMM package, was used to assess statistical significance at both the voxel and cluster levels (Bullmore et al., 1999). At the cluster level, rather than set a single a priori p-value below which findings are regarded as significant, the number of clusters which would be expected by chance alone for a range of p-values was calculated. The statistical threshold for cluster significance for each analysis was then set such that the expected number of false positive clusters by chance alone would be less than one (Bullmore et al., 1999). Group differences in the relationship between gray matter volume and substance use were analysed using a separate GLM implemented in R (Ihaka and Gentleman, 1996).

As antipsychotic and antidepressant medication have been reported to affect brain volume (Ho et al., 2011; Navari and Dazzan, 2009; Smieskova et al., 2009; Moore et al., 2009; Warner-Schmidt and Duman, 2006), we reanalysed the group differences in R excluding ARMS subjects who were taking antidepressant or antipsychotic medication at the time of scanning. Lastly, to investigate the possibility that the multivariate analysis may have masked some drug effects shared by two or more of the substances, we then performed separate post-hoc BAMM analyses examining the relationship between gray matter volume and cannabis, alcohol and tobacco intake without covariates.

## 3. Results

Demographic details have been reported in an earlier study (Stone et al., 2009). There were no significant differences in age, sex, ethnicity, social class or IQ (Table 1). Eight ARMS individuals but none of the controls had previously taken psychiatric medication and five of these were still taking medication (four had taken quetiapine, but only one was taking it at the time of the first scan, one was taking aripiprazole, two