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## Externalizing personality traits, empathy, and gray matter volume in healthy young drinkers

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### Abstract

Externalizing psychopathology has been linked to prefrontal abnormalities. While clinically diagnosed subjects show altered frontal gray matter, it is unknown if similar deficits relate to externalizing traits in non-clinical populations. We used voxel-based morphometry (VBM) to retrospectively analyze the cerebral gray matter volume of 176 young adult social to heavy drinkers (mean age= 24.0 ± 2.9, male= 83.5%) from studies of alcoholism risk. We hypothesized that prefrontal gray matter volume and externalizing traits would be correlated. Externalizing personality trait components— Boredom Susceptibility-Impulsivity (BS/IMP) and Empathy/Low Antisocial Behaviors (EMP/LASB)— were tested for correlations with gray matter partial volume estimates (gmPVE). Significantly large clusters ( $p_{FWE} < 0.05$ , family-wise whole-brain corrected) of gmPVE correlated with EMP/LASB in dorsolateral and medial prefrontal regions, and in occipital cortex. BS/IMP did not correlate with gmPVE, but one scale of impulsivity (Eysenck I<sub>7</sub>) correlated positively with bilateral inferior frontal/orbitofrontal, and anterior insula gmPVE. In this large sample of community-dwelling young adults, antisocial behavior/low empathy corresponded with reduced prefrontal and occipital gray matter, while impulsivity correlated with increased inferior frontal and anterior insula cortical volume. These findings add to a literature indicating that externalizing personality features involve altered frontal architecture.

### Keywords

VBM; MRI; alcohol; frontal lobes; personality; impulsivity

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## 1. Introduction

Externalizing psychopathology is marked by the outward expression of maladjustment, causing harm to others. Latent dimensional analysis of common psychiatric diagnoses shows that antisocial personality disorder (ASPD), conduct disorder (CD) and substance use disorders fall into a clear externalizing dimension (Kotov et al., 2011; Krueger, 1999; Krueger and Markon, 2006). The behavioral disinhibition and impulsivity that pervade these disorders (e.g., see Krueger and South, 2009) suggest deficits in prefrontal brain— the region most implicated in behavioral control (Knutson et al., 2015).

For example, magnetic resonance imaging (MRI) suggests that antisocial personality disorder is marked by an 11% reduction in prefrontal gray matter volume (Raine et al., 2000). Adolescent conduct disorder is characterized by functional and structural changes in brain areas related to emotion (amygdala, insula, striatum, orbital cortex, Fairchild et al., 2011; Fairchild et al., 2013; Sarkar et al., 2013; Sebastian et al., 2012). Changes in prefrontal volume have been associated with aggressive behavior and callousness in CD, with aggressive behaviors being negatively correlated with right dorsolateral prefrontal cortex volume, and emotional callousness being positively correlated with bilateral orbitofrontal cortex volumes (Fairchild et al. 2013). In a relatively small sample of adult psychiatric patients with mixed externalizing disorders, motor impulsiveness was also related to lesser orbitofrontal gray matter (Lee et al., 2011).

Studying healthy community-dwelling subjects without clinical diagnoses, Cho et al., (2013) reported an association between gray matter volume and impulsivity in 34 young adults, with greater impulsivity linked to reduced medial prefrontal, dorsolateral prefrontal and ventral striatal gray matter volumes. An inverse relationship between trait impulsiveness and orbitofrontal gray matter volume in middle age adults has also been reported (Matsuo et al., 2009). Walhovd et al. (2012) similarly showed a negative correlation between conduct problems and left orbitofrontal and supramarginal gyri thickness in children and adolescents. In the large European IMAGEN trial of community dwelling adolescents, externalizing behaviors were related to lower gray matter in left inferior and middle frontal gyri (Montigny et al., 2013), and impulsivity traits related to reductions in orbitofrontal gray matter volume (Schilling et al., 2013b) and superior frontal gyrus cortical thickness (Schilling et al., 2013a). As opposed to self-reported impulsivity, experimentally measured reward impatience (delay discounting) is associated with reduced lateral prefrontal volume in healthy adults (Bjork et al., 2009). Thus, even in healthy individuals who are not the focus of clinical attention, there seem to be relationships between regional brain volume and externalizing personality traits. However, the largest samples are limited to children and adolescents, in whom neocortical development continues in to late adolescence and early adulthood (particularly in the frontal lobes, Groeschel et al., 2010; Lenroot and Giedd, 2006). That is, these relationships between personality traits and brain volume might not persist into adulthood, or perhaps assume a different nature. Moreover, the personality assessments have usually been limited to one particular scale, which limits the dimensionality with which facets of impulsivity can be assessed.

In this study, we examined a large sample of 176 physically healthy young adults with structural MRI and several personality scales of trait impulsiveness and antisocial behaviors, which were analyzed with principal component analysis. Our primary goal was to employ voxel based morphometry (VBM) and analyze relationships between personality components and gray matter partial volume estimates (gmPVE). However, rather than studying clinically diagnosed patients or controls without any indication of pathology, our sample is instead comprised of subjects from neuroimaging studies of alcoholism risk and heavy drinking—a population in which impulsivity and antisocial behaviors are more prevalent (Finn, 2002; Haber et al., 2005; Kendler et al., 2003; Krueger and South, 2009; Moss et al., 2007; Young et al., 2000). We hypothesized that trait impulsivity and antisocial behavior would negatively correlate with prefrontal gmPVE. Secondarily, and given the nature of the sample, we also investigated the effects of alcohol use and familial alcoholism on these externalizing personality components, and on gmPVE.

## 2. Methods

The research procedures in this work were conducted after obtaining from all subjects written informed consent; both the consent form and procedures were approved by the Institutional Review Board (IRB) of Indiana University. All procedures were conducted according to the principles expressed in the Declaration of Helsinki.

### 2.1 Subjects

This study includes the anatomic brain imaging data acquired from 176 subjects who had previously participated in five different functional MRI or PET neuroimaging studies of alcoholism risk, as conducted at the Indiana University School of Medicine (including those subjects published in Kareken et al., 2012; Kareken et al., 2010; Kareken et al., 2013b; Oberlin et al., 2013; Oberlin et al., 2014). One hundred and seventeen of these subjects had participated in studies that involved pulsed arterial spin labeling MRI of regional cerebral blood flow; this subsample was recently reported in (Weafer et al., 2015) to examine relationships between resting brain physiology and impulsive personality traits. The aggregate sample (Table 1) is predominantly male (147 men, 29 women). Exclusion criteria comprised self-reported evidence of neurological disorders of central origin, self-report of symptoms consistent with mood or anxiety disorders, psychoses, bipolar disease, or current psychiatric treatment, including any psychoactive medication. At the time of the study, none of the participants were seeking treatment for alcoholism or had developed drug dependence through their lifetime. All subjects had data from the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA, Bucholz et al., 1994, see below), and 16 (9.1%) subjects satisfied criteria for a lifetime diagnosis of DSM-IV alcohol dependence. Although subjects with histories of illicit drug use were enrolled, 171 (97.2%) tested negatively on urine screens for psychoactive drug use, with 4 (2.3%) testing positive for marijuana, and 1 (0.6%) for opiates. Based on information from the SSAGA, 34 subjects (19.3%) described using marijuana or hashish at least 21 times. The majority ( $n= 157$ ; 89.2%) were non-smokers.

## 2.2 Measures

**2.2.1 Subject assessment**—All subjects were characterized with the SSAGA, using trained raters who underwent observation before examining subjects. The SSAGA's Family History Assessment Module (FHAM) was used to assess each subject's family history of alcoholism (only the subject was available to assess family history), and the Timeline Followback interview was used to measure subjects' recent drinking (TLFB, Sobell et al., 1986) over 90 days prior to study participation. Alcohol Use Disorders Identification Test (AUDIT, Saunders et al., 1993) data were available for 169 subjects. Family history of alcoholism was categorized as: 1) Family history positive (FHP) having at least one first degree affected relative; 2) A more ambiguous family history (FHAmbig) consisting of one or more second degree affected relatives; and 3) A negative family history of alcoholism (FHN), as defined by no affected first or second degree relatives. Subjects with mothers who were affected with probable dependence were excluded to rule out fetal alcohol effects.

**2.2.2 Personality trait measurement**—Externalizing traits and self-reported behaviors were assessed with: (1) the Zuckerman Sensation Seeking Scale (Zuckerman, 1994) whose subscales reflect enjoyment of socially conventional adventure and thrill seeking (Thrill/Adventure Seeking), a liking of less conventional and more unusual sensory experiences (Experience Seeking), a preference for occasions that afford the opportunity to "let loose" (Disinhibition), and a tendency to bore easily with repetitive or sedate activity (Boredom Susceptibility), (2) the Eysenck I<sub>7</sub> (Eysenck et al., 1985) Impulsivity scale, whose subscales reflect a tendency to act without thinking (Impulsiveness), adventure seeking (Venturesomeness), and emotional concern for others (Empathy), and (3) an in-house, computerized modification of Section M of the SSAGA semi-structured interview on which subjects endorsed or denied a variety of antisocial acts occurring after the age of 15 (total ranging from 0 – 44, see Oberlin et al., 2012). These instruments were adapted to a computer self-administration format using E-Prime software (Psychology Software Tools, Inc, Sharpsburg, PA). For all scales, higher scores represent a greater magnitude of the measured trait.

**2.2.3 MRI acquisition**—Imaging was performed in a Siemens (Siemens Healthcare, Erlangen, Germany) 3T Magnetom Trio-Tim scanner with a 12-channel head coil array at the Center for Neuroimaging of the Indiana University School of Medicine. A whole-brain high resolution anatomical MRI was collected using a 3D Magnetization Prepared Rapid Acquisition Gradient Echo (MP-RAGE) with imaging parameters optimized according to the ADNI (Alzheimer's Disease Neuroimaging Initiative) protocol, and as implemented in a large cohort study of Alzheimer's disease, mild cognitive impairment and normal subjects (160 sagittal slices in 9.14 minutes,  $1.0 \times 1.0 \times 1.2 \text{ mm}^3$  voxels).

## 2.3 Analyses

**2.3.1 Personality trait data**—As a data reduction strategy, principal component analysis with varimax rotation (SPSS, v. 20) was conducted on the antisocial behavior inventory and the subscales of the Zuckerman Sensation Seeking and Eysenck I<sub>7</sub> inventories. As some variables were abnormally skewed, they were transformed prior to inclusion in the PCA using the most appropriate transformation to reduce skewness (square root transformation

for antisocial behavior count and Venturesomeness from the Eysenck I<sub>7</sub>; Log10 transformation for Thrill and Adventure Seeking from the Sensation Seeking Scale). Personality data were derived from an original superset of 198 subjects who had participated in these studies (165 men; mean age 24.3, SD=3.2). However, 22 of these subjects were eventually excluded from the VBM analyses given either incomplete data about their marijuana use (n=14) or imaging data that were acquired using a different head coil (n=8).

**2.3.2 Image processing**—The optimized VBM method (Good et al., 2001) was implemented within SPM8 (Wellcome Trust Centre for Neuroimaging) by first segmenting brain tissues into gray matter, white matter and cerebrospinal fluid. Subsequently, each subject's gray matter images were normalized to the MNI gray matter template using a modulation step to adjust for spatial distortions introduced by non-linear image deformations. The gray matter images were then smoothed using a 12mm full-width at half-maximum (FWHM) isotropic Gaussian kernel, which allows the application of cluster-level statistics (Silver et al., 2011). Estimated total intracranial volume (eTIV) was derived from FreeSurfer version 5.1 (<https://surfer.nmr.mgh.harvard.edu/fswiki/FreeSurferMethodsCitation>) and used as a covariate to adjust for inter-individual differences in head size in the VBM analysis (see below). Freesurfer eTIV was employed, as it has a higher correlation with the gold standard of manual measurements than does SPM8 eTIV (Malone et al., 2015).

**2.3.3 Image analyses**—A multiple regression model in SPM8 was implemented to perform voxel-wise correlations between personality traits components derived from the PCA (independent variables of interest) and gmPVE from the modulated images. Given the centrality of impulsivity (acting without adequate thought/planning) and antisocial (socially deviant) behaviors in alcohol use disorders (rather than social use, per se, Finn, 2002; Gunn et al., 2013), we focused the analyses on the two components that predominantly loaded on trait impulsivity and the endorsement of antisocial acts. The regression model also included covariates to control for any effects from age (inverse transformed to minimize skewness), gender, drinking (drinks/week, square root transformed to minimize skewness), eTIV (as reported by FreeSurfer), smoking status, and lifetime marijuana/hashish use of greater than 21 times, as derived from the SSAGA. Smoking and marijuana use were both dummy-coded as binary variables.

Statistical inferences for VBM were made using cluster statistics ( $p_{FWE} < 0.05$ , correcting for whole brain gray matter family-wise error [FWE]) with the cluster-forming (height) threshold  $p < 0.001$  (uncorrected, Silver et al. 2011). The mean cluster values of each significant region were extracted for all subjects using MarsBar (Brett et al., 2002) at the cluster forming threshold to illustrate the nature of significant relationships between average gmPVE and personality components, and to assure that they were not driven by outliers.

## 3. Results

### 3.1 Personality Traits

After performing principal components analysis (PCA) on the antisocial behavior count, and the subscales of the Eysenck I<sub>7</sub> and Sensation Seeking Scale (Table 2), three principal

components emerged with eigenvalues greater than 1.0 that explained 64.9% of the total variance after varimax rotation (Table 3). The components and their pattern of loadings can be characterized as dimensions of: 1) Boredom Susceptibility and Impulsivity (BS/IMP), 2) Thrill Seeking (TS), and 3) High Empathy and Low Antisocial Behaviors (EMP/LASB).

### 3.2 Relationships between gmPVE and Personality Traits

BS/IMP was neither positively nor negatively correlated with gray matter volume at FWE-corrected cluster level significance. Given our recent finding of an inverse relationship between right prefrontal (premotor) regional cerebral blood flow and Eysenck I<sub>7</sub> impulsivity subscale (Weafer et al. 2015), we secondarily examined this scale individually, and also found no significant inverse relationship between gmPVE and impulsivity. There was, however, a left frontal cluster where the I<sub>7</sub> impulsivity subscale was *positively* related to gmPVE in the inferior frontal/posterior-lateral orbitofrontal and insula areas; a similar cluster was present on the right, albeit of trend level significance ( $p_{FWE} = 0.065$ ; Figure 1, Table 4).

Four clusters (three frontal) of gmPVE correlated positively with EMP/LASB: a left dorsolateral prefrontal region, a right dorsolateral prefrontal cluster, and a left ventromedial prefrontal region (Figure 2; Table 5). The remaining cluster was in occipital cortex (Table 5). There were no clusters of negative correlation between gmPVE and EMP/LASB.

### 3.3 Relationships between alcohol use, familial alcoholism, personality traits, and gmPVE

Average number of drinks/week from the Timeline Followback interview was related positively with BS/IMP (Spearman's rho,  $\rho = 0.37$ ,  $p < 0.001$ ), negatively with EMP/LASB ( $\rho = -0.16$ ,  $p = 0.03$ ), but unrelated to TS ( $\rho = 0.13$ ,  $p = 0.09$ ). Average drinks/drinking day showed similar relationship with BS/IMP ( $\rho = 0.20$ ,  $p = 0.008$ ), EMP/LASB ( $\rho = -0.21$ ,  $p = 0.006$ ); and TS ( $\rho = 0.06$ ,  $p = 0.42$ ). The AUDIT was related with BS/IMP ( $\rho = 0.43$ ,  $p < 0.001$ ), but not with TS or EMP/LASB ( $ps > 0.11$ ).

One-way analyses of variance (ANOVA) showed small, but significant mean differences between the three family history groups (FHP,  $n = 62$ ; FHamb,  $n = 45$ ; and FHN,  $n = 69$ ) in age ( $F_{2,173} = 6.3$ ,  $p = 0.002$ ; FHP=23.4, SD= 2.5; FHamb= 24.9, SD=3.6; Tukey's least significant difference [LSD],  $p = 0.019$ ), but not education, or any of the personality components ( $F_s < 1.9$ ,  $ps > 0.16$ ); the FHA groups also did not differ in gender ( $\chi^2 = 1.3$ ,  $p > 0.5$ ). The family history groups were, however, different in drinks/week ( $F_{2,173} = 3.9$ ,  $p = 0.022$ ) and AUDIT scores ( $F_{2,173} = 5.2$ ,  $p = 0.006$ ), although not in drinks/drinking day. Tukey's LSD showed that for drinks/week, FHN subjects (14.7, SD= 10.8) were lower than FHamb (19.1, SD= 11.0,  $p = 0.038$ ). For AUDIT, FHN subjects (9.3, SD=4.3) were lower than both FHamb (12.1, SD=5.4) or FHP (11.9, SD=6.0;  $ps < 0.02$ ). As analyzed in separate SPM ANOVA models (co-varying for age, gender, drinks/week, smoking, cannabis use, and eTIV), there were no differences between the three family history groups in gmPVE.

There were no significant clusters of correlation between the SPM model covariates of drinks/week, smoking, or cannabis use and gmPVE.

## 4. Discussion

In this retrospective sample of undiagnosed community-dwelling subjects recruited for studies of risky drinking, we tested for significant relationships between frontal gmPVE and impulsive/externalizing personality traits. We reasoned that such a sample should increase the variance of these traits (Finn, 2002; Haber et al. 2005; Kendler et al. 2003; Krueger and South, 2009; Moss et al. 2007; Young et al. 2000)— a rationale supported by the statistically significant relationships in this sample between drinking and the derived externalizing personality components comprising elements of impulsivity (BS/IMP) and antisocial behavior (EMP/LASB). We hypothesized that elevated trait impulsivity and antisocial behaviors would negatively correlate with prefrontal gray matter volume as observed in externalizing disorders.

### 4.1 Relationship between BS/IMP and gmPVE

Unlike prior studies (Boes et al., 2009; Cho et al., 2013; Lee et al. 2011; Matsuo et al. 2009; Schilling et al. 2013a; Schilling et al. 2013b; Walhovd et al., 2012), including a smaller study of patients diagnosed with DSM-IV alcohol abuse and matched controls (Asensio et al., 2015), we did not find that gmPVE correlated negatively with self-reported impulsive behavior, either as a function of our BS/IMP component (consisting of significant loadings from scales reflecting boredom susceptibility, impulsive acts, antisocial behaviors, social disinhibition, and a desire to seek out unusual experiences), or when looking specifically at the Impulsivity subscale of the Eysenck I<sub>7</sub> inventory. The Impulsivity subscale of the Eysenck I<sub>7</sub> inventory did, however, correlate positively with bilateral gmPVE in lateral/posterior orbital cortex and insula. While not a typical finding, some studies have reported positive correlations between impulsiveness and either insula or medial frontal gray matter (e.g., Cho et al. 2013; Kaag et al., 2014; Lee et al. 2011). Differences in sample characteristics, age or approach to measuring impulsivity could account for the contradictory results found between the literature and our study (e.g., many studies use the Barratt Impulsivity Scale, Barratt, 1959).

### 4.2 Relationship between EMP/LASB and gmPVE

We found significantly large clusters where frontal gmPVE (dorsolateral prefrontal extending into the ventromedial and insula areas) correlated with EMP/LASB. Of note, neither of the independent scales of Eysenck I<sub>7</sub> empathy or antisocial acts (the primary constituents of the EMP/LASB component) was significantly associated with gray matter volume when examined independently. This suggests that statistically aggregating these anti-correlated elements allowed detecting a behavioral phenotype that is more reflective of gray matter structure.

Empathy (which by I<sub>7</sub> inventory items includes elements of “emotional contagion,” perspective taking, and sympathy) dominates the EMP/LASB component. In the clinical neurological literature, the loss of the ability to empathize can result from acquired lesions of ventromedial prefrontal cortex (Hillis, 2014; Shamay-Tsoory et al., 2003). In 118 healthy young adults, Banissy et al. (2012) found that empathic concern was associated with *reduced* gray matter volume in the left precuneus, left inferior frontal gyrus/insula, and left

anterior cingulate. However, a large study of 261 children (ages 5 – 15 years) found that parent-rated empathy derived from the Children's Empathy Quotient and Systemizing Quotients scale (Auyeung et al., 2009) correlated positively with gray matter volume in the left fronto-opercular and superior temporal cortex (Sassa et al., 2012; also see Sterzer et al., 2007). Most recently, higher “affective empathy” (experiencing others’ emotions) in 176 undergraduate psychology majors was associated with increased gray matter density in the insula, while “cognitive empathy” (understanding others’ motivations) was related to higher gray matter density in the middle cingulate and dorsomedial prefrontal cortex (Eres et al., 2015).

Antisocial acts loaded negatively on the EMP/LASB component, and the absence of empathy is a component of antisocial personality disorder and sociopathy. That is, the EMP/LASB component can be interpreted as the inverse of a sociopathic personality constellation. In this context, a number of studies have shown that, compared to controls, there is reduced frontal gray matter and amygdala volume in subjects with ASPD, violent offenders, and criminal psychopaths (de Oliveira-Souza et al., 2008; Gregory et al., 2012; Laakso et al., 2002; Müller et al., 2008; Pardini et al., 2014; Raine et al. 2000; Tiihonen et al., 2008). Similar anatomic locations have been implicated in 23 boys (ages 10 – 13), in whom callous-unemotional traits were related to increased gray matter concentration in medial orbital and anterior cingulate cortex, and increased gray matter volume and concentration in the bilateral temporal lobes (De Brito et al., 2009). In this case, the relative increase in gray matter in children might reflect competitive pruning during cortical maturation (Lenroot and Giedd, 2006). In older adolescent boys with conduct disorder (ages 16 – 21), Fairchild et al. (2011) found gray matter volume reductions in the amygdala and insula. The same group also noted gray matter reductions in adolescent girls with conduct disorder in the bilateral insula and right striatum, with aggressive CD symptoms negatively correlating with right dorsolateral prefrontal volume, but callous traits correlating positively with orbital volume (Fairchild et al. 2013).

A connection between antisocial behavior and dorsolateral prefrontal neocortex is certainly intuitive, as this region is well known to regulate the ability to plan, regulate, shift strategy, and exert cognitive inhibitory control (Fuster, 1997). However, antisocial activity often comprises a lack of empathy and regard for others’ well-being. In that vein, our findings extended into ventral regions of prefrontal cortex, where acquired brain lesions are most likely to result in violence (Grafman et al., 1996). Ventromedial frontal cortex also activates during moral reasoning (Shenhav and Greene, 2014), and lesions to this region most alter decisions in ethical dilemmas where subjects must decide upon actions that result in harm to others (Koenigs et al., 2007; Thomas et al., 2011). A key aspect to the ventromedial prefrontal cortex here is its role in coding the visceral sensations experienced when contemplating both the loss of assets when gambling (Bechara et al., 1999), and harm caused to others by one’s behaviors (Moretto et al., 2010). Given our results and others’ findings, it is then possible that reduced ventromedial frontal gray matter interfere with the visceral sensations that occur when contemplating how one’s actions affect others’ well-being.



In addition to the frontal findings, the whole brain VBM identified an occipital cluster that was highly correlated with the EMP/LASB component. Although not obviously implicated in disorders of behavioral control, alterations in these regions have been identified in CD and ASPD populations. Bertsch et al. (2013) showed that across different types of ASPD subjects there were common clusters of reduced gray matter volumes within the frontal pole and the occipital cortex. Sundram, et al. (2012) observed reduced white matter integrity in the inferior fronto-occipital fasciculus (the white matter tract connecting the frontal lobe and the posterior portion of the inferior occipital gyrus) in the right frontal lobe of ASPD subjects. Moreover, this altered white matter integrity was negatively correlated with measures of psychopathy. Dalwani et al.'s (2011) work also showed that boys with serious CD and substance use problems have lower gray matter volume in left DLPFC and right lingual gyrus (but higher gray matter volume in the right precuneus). A first step in empathy is to perceive another's emotional state, and such visual processing centers play an important role in the visual identification of facial emotion (Kitada et al., 2010). One could then speculate that visual centers might, in this way, relate to empathy.

### 4.3 Personality traits, alcohol use, familial alcoholism, and gmPVE

Finally, although the externalizing personality traits did relate to drinking, neither alcohol consumption itself nor familial alcoholism was significantly related to gmPVE. Many studies have shown significant gray matter loss in the prefrontal cortex of alcohol-dependent individuals (up to 20% in the dorsolateral frontal cortex, e.g., Chanraud et al., 2006; Fein et al., 2002; Pfefferbaum et al., 1997). Given the nature of our sample, however, the lack of our own findings might well be accounted for by the limited range of drinking and the lack of heavy, chronic exposure. Some studies have also shown that alcohol-naïve subjects from high-risk families have alterations in frontal gray and white matter volumes (Cservenka, 2015). For example, Benegal et al. (2007) found that the alcohol naïve offspring of alcoholic parents, when compared to controls, had significantly smaller volumes of superior frontal and cingulate areas, with the left superior frontal gyrus volume correlating with externalizing symptoms. Hill's group has found that the offspring of alcoholic relatives had lower [right > left] asymmetry ratios of combined gray and white orbital volume, and that orbital white matter asymmetry in these offspring correlated with greater impulsivity (Hill et al., 2009). The same group (Hill et al., 2001, 2013) and Dager et al (2015) also detected loss of right amygdala volume in the adolescent offspring of families with alcoholism. Most recently, Cservenka et al (2015) reported that family history density was related to left nucleus accumbens volume in adolescents, although only in girls. Our large smoothing kernel may have precluded us from detecting effects in smaller subcortical regions. Having said that, we did observe a small subthreshold effect (299 voxels at  $p < 0.005$ ) in the right amygdala, where FHP subjects had reduced gmPVE when compared to FHN subjects (similar to the Hill and Dager studies above). A second consideration in our lack of findings related to this genetic risk is familial density of affected relatives, as subjects in our study could have only one first-degree affected relative, whereas the density of affected relatives in other studies was higher (e.g., Hill et al. 2001; Hill et al. 2009). Also, only the subject was available to interview with regard to family history, without the added reliability from interviewing collateral family. This could affect the nature of the family history outcome.

#### 4.4 Limitations

Although our study is comprised of a large sample of well characterized subjects, it has limitations. First, the predominantly male sample complicates generalizing the findings to women. Second, given that the subjects were selected for their elevated drinking, it may not be possible to generalize these results to samples characterized by more social levels of alcohol consumption. Some subjects with lower empathy and higher antisocial behavior were in the age range of 27 – 35, making it difficult to tease out interactions between age and these other factors.

#### 4.5 Conclusions

This study of 176 young healthy drinkers found significant relationships between dorsolateral/ventromedial prefrontal and occipital gray matter volume and a personality trait component reflecting a combination of high empathy and low sociopathic behavior. Trait impulsivity was unexpectedly associated with increased lateral inferior frontal/insular gray matter volume. Thus, aspects of externalizing personality traits in community-dwelling non-patients are, as in clinical samples, related to regional differences in frontal and limbic gray matter volume.

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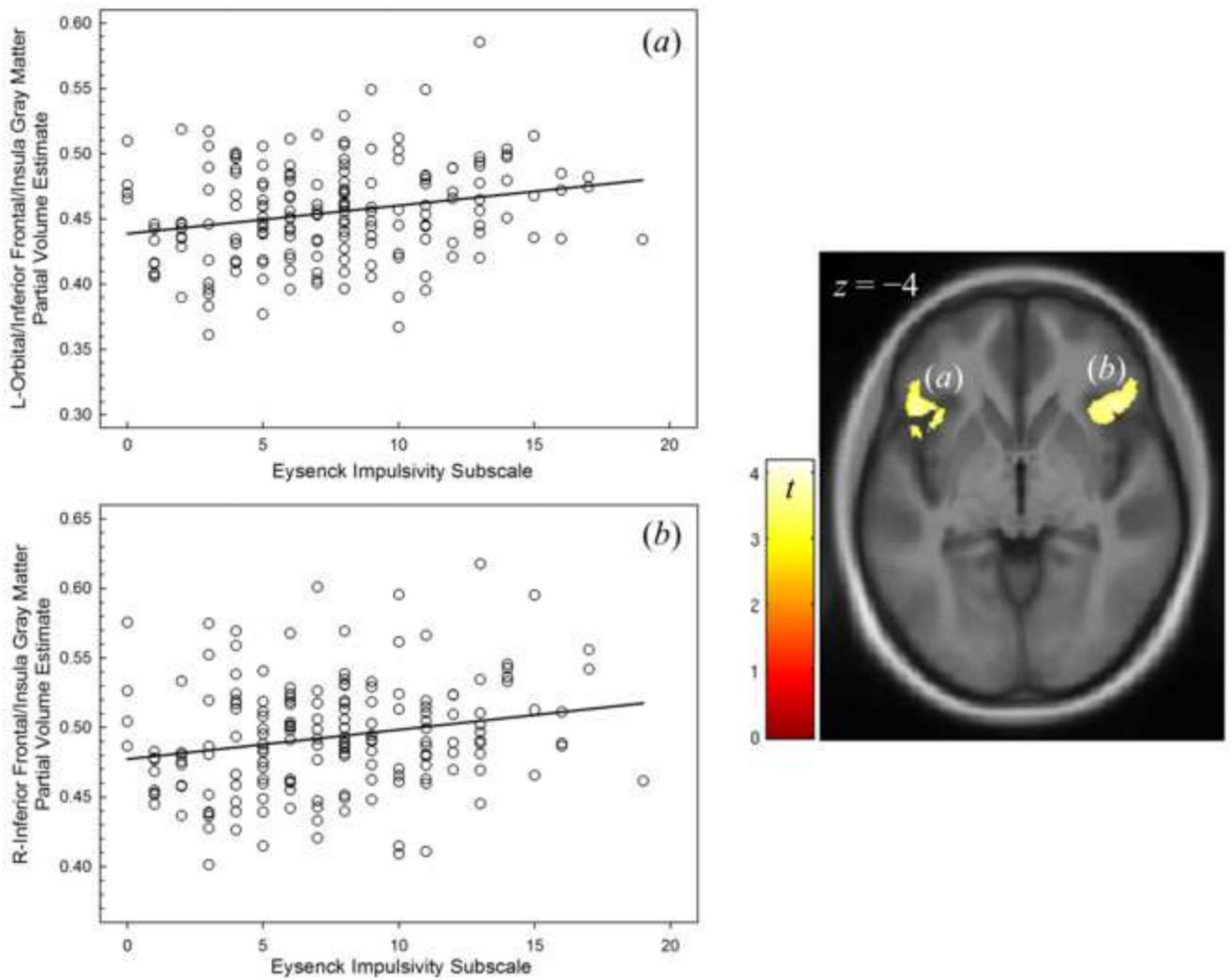
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### Highlights

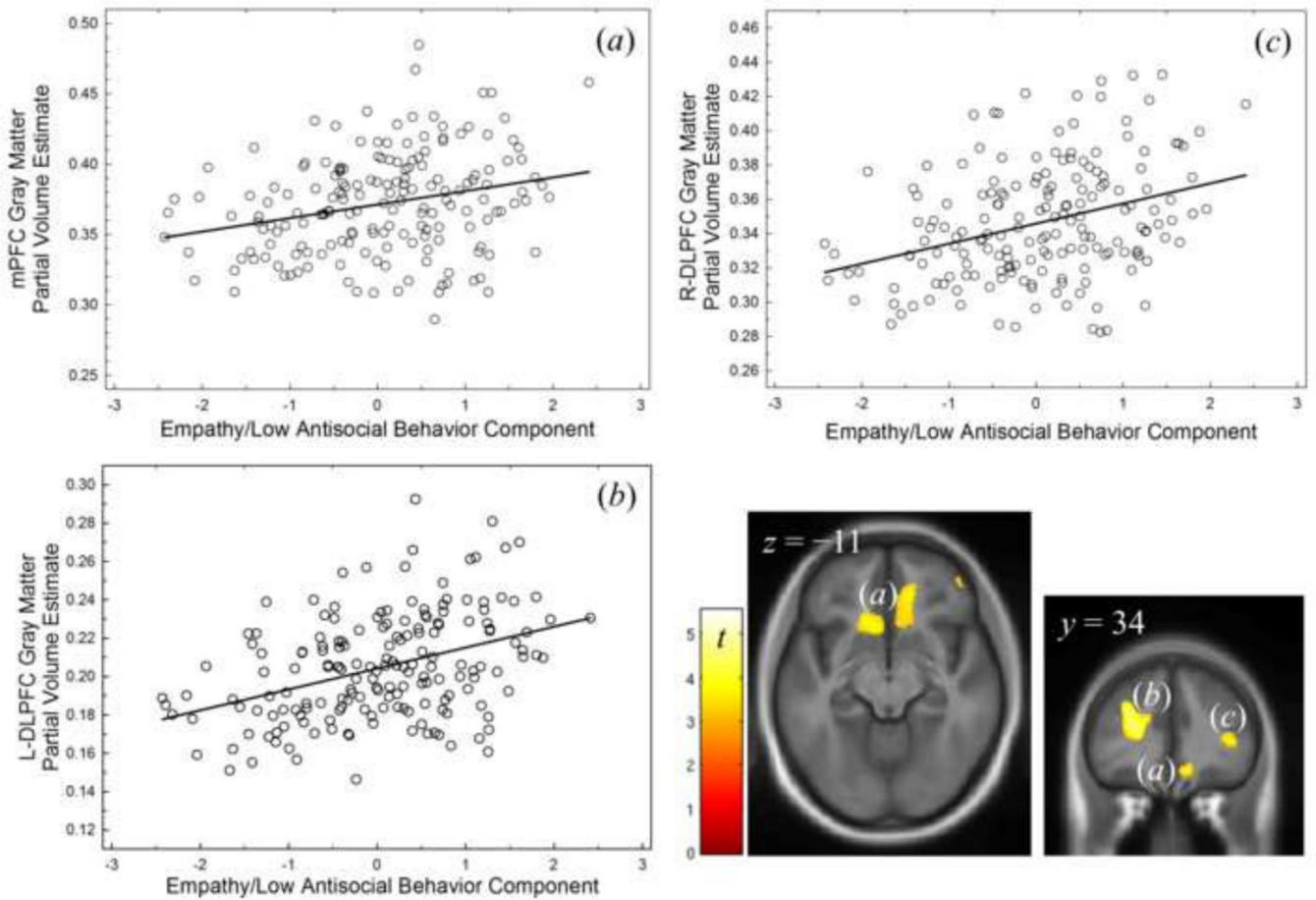
- We tested for relationships between externalizing behaviors and gray matter volume.
- High empathy/low sociopathic behavior correlated with frontal gray matter.
- Impulsivity positivity correlated with frontal/insula gray matter volume.
- Frontal gray matter is related to externalizing personality traits.





**Figure 1.**

Regions of positive correlation between the Impulsivity scale of Eysenck's  $I_7$  inventory and gray matter partial volume estimates (gmPVE) in (a) left orbital/inferior frontal/insula and (b) right inferior frontal/insula regions. Display  $p < 0.001$  uncorrected voxel height, showing (a) significant ( $p_{FWE} < 0.05$ ) and (b) trend-level significant ( $p_{FWE} = 0.065$ ) clusters after correcting for whole brain family-wise error.



**Figure 2.** Regions of positive correlation between the EMP/LASB component and gmPVE in (a) Left/right medial prefrontal and (b) left and (c) right dorsolateral prefrontal cortex. Display  $p < 0.001$  uncorrected voxel height, showing only clusters of significance after correcting for whole brain family-wise error ( $p_{FWE} < 0.05$ ).

Table 1

Subject characteristics.

	Total (n=176)			Men (n=147)			Women (n=29)		
	Mean	SD	n (%)	Mean	SD	n (%)	Mean	SD	n (%)
Age (years)	24.0	2.9		24.0	3.1		23.9	2.3	
Education (years)*	15.2	1.6		15.0	1.6		15.8	1.4	
AUDIT*	10.9	5.4		11.4	5.6		8.0	2.3	
Drinks/week <sup>1, 3*</sup>	17.2	11.5		18.5	12.0		10.6	5.2	
Drinks/drinking day <sup>1*</sup>	5.8	3.4		6.2	3.3		3.9	1.7	
<i>Subjects as Classified by NIAAA-Recommended Drinking Limits<sup>2</sup></i>									
Exceed neither weekly nor daily limits			46 (26.1)			38 (25.8)			8 (27.6)
Exceed only weekly limit			32 (18.2)			22 (15.0)			10 (34.5)
Exceed only daily limit			23 (13.1)			21 (14.3)			2 (6.9)
Exceed both weekly & daily limits			75 (42.6)			66 (44.9)			9 (31.0)

Notes: AUDIT= Alcohol Use Disorders Identification Test (n= 169);

<sup>1</sup> Drinking patterns derived from Timeline Followback Interview (Sobell et al. 1986) and compared to

<sup>2</sup> recommended limits from the National Institute on Alcohol Abuse and Alcoholism for daily and weekly alcohol consumption (daily limit 5/4 drinks per day for men/women, respectively; weekly limit 14/7 drinks per day for men/women, respectively).

<sup>3</sup> Drinks/week was analyzed using a square root transform; for comprehensibility, data in the table are untransformed;

\* Men different than women ( $p < 0.05$ ) via *t*-test.

Table 2

Personality trait raw scores.

	Total (n=176)		Men (n=147)		Women (n=29)	
	Mean	SD	Mean	SD	Mean	SD
Antisocial Behavior Count *	5.6	4.9	6.0	5.0	3.5	3.3
<i>Eysenck I<sub>7</sub> Inventory</i>						
Impulsivity	7.5	4.1	7.6	4.0	7.0	4.4
Venturesomeness	11.9	3.0	12.1	2.8	10.9	3.5
Empathy	12.4	3.3	12.3	3.4	12.9	2.8
<i>Sensation Seeking Scale</i>						
Thrill/Adventure Seeking	7.9	2.2	8.1	2.1	7.6	2.6
Experience Seeking	6.0	2.0	6.0	1.9	5.9	2.5
Disinhibition	6.3	2.2	6.4	2.2	6.0	2.5
Boredom Susceptibility	3.4	2.0	3.5	1.9	2.8	2.3

Note:

\* Men greater than women via *t*-test,  $p < 0.05$ .

**Table 3**

## Principal Component Loadings

	<b>1. Boredom Susceptibility/Impulsivity</b> (BS/IMP; 26.2%)	<b>2. Thrill Seeking</b> (TS; 25.1%)	<b>3. Empathy/Low Antisocial Behavior</b> (EMP/LASB; 13.7%)
Antisocial Behavior Count	<b>0.660</b>	0.017	<b>-0.364</b>
<i>Eysenck I<sub>7</sub> Inventory</i>			
Impulsivity	<b>0.695</b>	-0.199	0.221
Venturesomeness	-0.123	<b>0.920</b>	0.155
Empathy	-0.052	0.125	<b>0.917</b>
<i>Sensation Seeking Scale</i>			
Thrill/Adventure Seeking	-0.028	<b>0.925</b>	-0.012
Experience Seeking	<b>0.416</b>	<b>-0.479</b>	-0.046
Disinhibition	<b>0.669</b>	-0.060	-0.210
Boredom Susceptibility	<b>0.732</b>	-0.125	0.049

*Notes:* Percentage of variance accounted for by the rotated components appears in parentheses beneath the component labels. Component loadings larger than | 0.3 | appear in boldface type.

Positive correlations between I<sub>7</sub> impulsivity and gray matter partial volume estimates (gmPVE).

**Table 4**

	Voxel Statistics			Cluster Statistics		
	MNI Coordinate (mm)			Size ( <i>k</i> )	<i>p</i> (FWE)	
	<i>x</i>	<i>y</i>	<i>z</i>			
Left Inferior Frontal/Orbital/Insula	-38	29	-17	4.05	8,595	0.001
Right Inferior Frontal/Insula	47	29	-8	3.97	3,002	0.065

*Notes:* MNI= Montreal Neurological Institute. Voxel statistics refer to peak effects within a cluster (all *p*-values < 0.001 uncorrected). Cluster statistic reflects a greater number of contiguous voxels exceeding height threshold (*p*<0.001, uncorrected) than expected by chance, controlling for whole brain family-wise error (FWE).

**Table 5**

Positive correlations between EMP/LASB and gmPVE.

	Voxel Statistics			Cluster Statistics		
	MNI Coordinate (mm)			Peak Z	Size (k)	p(FWE)
	x	y	z			
Left DLPFC	-23	29	17	5.3	4,974	0.012
Right DLPFC	37	24	15	4.5	7,043	0.002
Ventromedial Prefrontal/Ventral Anterior Cingulate	-10	20	-8	4.0	4,559	0.016
Occipital	-9	-83	17	3.7	3,785	0.032

*Notes:* MNI= Montreal Neurological Institute. DLPFC= dorsolateral prefrontal cortex. Voxel statistics refer to peak effects within a cluster (all  $p$ -values < 0.001 uncorrected). Cluster statistic reflects a greater number of contiguous voxels exceeding  $p < 0.001$  height threshold (uncorrected) than expected by chance, controlling for whole brain family-wise error (FWE).