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Analysis of alcohol use disorders from the Nathan Kline Institute-Rockland Sample: Correlation of brain cortical thickness with neuroticism*

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Abstract

Background—Although differences in both neuroanatomical measures and personality traits, in particular neuroticism, have been associated with alcohol use disorders (AUD), whether lifetime AUD diagnosis alters the relationship between neuroticism and neuroanatomical structures remains to be determined.

Methods—Data from 65 patients with lifetime AUD diagnoses and 65 healthy comparisons (HC) group-matched on age, sex and race were extracted from the Nathan Kline Institute - Rockland Sample data set. Each subject completed personality trait measures and underwent MRI scanning. Cortical thickness measures at 68 Desikan-Killiany Atlas regions were obtained using FreeSurfer 5.3.0. Regression analyses were performed to identify brain regions at which the neuroticism-cortical thickness relationship was altered by lifetime AUD status.

Results—As expected, AUDs had higher neuroticism scores than HCs. Correlations between neuroticism and cortical thickness in the left insula and right fusiform differed significantly across groups. Higher neuroticism score in AUD and the interaction between the insular cortical

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Conflict of interest

The authors declared no conflicts of interest related to this research.

Contributors

Author YZ processed and analyzed the imaging and personality data, interpreted the results and wrote the manuscript. ZLZ interpreted results and wrote the manuscript. FXC provided expertise in data interpretation and revised the manuscript.

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thickness-neuroticism correlation and AUD status were confirmed in a replication study using the Human Connectome Project data set.

Conclusions—Results confirmed the relationship between neuroticism and AUD and suggests that specific cortical regions, particularly the left insula, represent anatomic substrates underlying this association in AUD.

Keywords

Personality; Neuroticism; Alcohol Use Disorders; Insula; Fusiform gyrus; Chronic pain disorder

1. INTRODUCTION

Alcohol use disorders (AUD), including alcohol abuse and alcohol dependence, continue to be a major and complex public health problem (Reilly et al., 2014; Zahr et al., 2011). The detrimental consequences of AUD include brain damage leading to executive function impairment and memory loss. To reduce deleterious health impacts and the associated economic loss, mechanistic understanding of AUD pathogenesis is required for developing more effective strategies for AUD prevention and treatment (Johnson, 2010; Litten et al., 2015; Reilly et al., 2014; Zahr et al., 2011). Decades of studies have suggested biological factors and social and interpersonal influences as the major risk factors for the development of AUD.

Among the many risk factors, personality traits have been long recognized as important contributors to the development of AUD (Cloninger et al., 1988; Hakulinen et al., 2015; Hicks et al., 2012; Martin and Sher, 1994). The Five Factor Model (FFM) is a widely accepted framework that organizes personality traits along five dimensions: openness, conscientiousness, extraversion, agreeableness and neuroticism (Funder, 2001; McCrae, 2004). Neuroticism, the most frequently examined of these in AUD studies, entails the tendency to experience negative emotions including anger, anxiety, depression and vulnerability. Neuroticism can be quantified with the standardized NEO Five-Factor Inventory (NEOFFI; McCrae, 2004). Those high in neuroticism are more likely to be impacted by persistent negative feelings. While personality traits, including neuroticism, are considered stable and enduring aspects of individuals with substantial heritability (Munafo and Flint, 2011), it has been argued that personality can affect alcohol consumption or shape the development of AUD. Studies have indicated that neuroticism is positively correlated with AUD (Hicks et al., 2012; Martin and Sher, 1994; Mitrovic, 2014) or variation in drinking patterns (Hakulinen et al., 2015). Hicks et al. reported the interesting finding that negative emotionality traits at age 11 predict the onset and course (persistence vs. desistence) of AUD and that the course of AUD can affect the rate of personality change (Hicks et al., 2012). This finding suggests that neuroticism and AUD can have reciprocal effects during development, indicating a complex relationship between AUD and neuroticism.

A number of studies have focused on the neural correlates of neuroticism and AUD, using various brain imaging technologies such as structural magnetic resonance imaging (sMRI) and functional MRI (fMRI). With regard to the brain correlates of neuroticism, several sMRI

studies have reported negative correlations of neuroticism with global grey matter volume (Liu et al., 2013), thickness of the left orbitofrontal cortex (Wright et al., 2006), white matter volume in the superior medial frontal gyrus (Liu et al., 2013), volumes in several prefrontal regions (DeYoung et al., 2010; Kapogiannis et al., 2013) and volumes in left medial temporal lobe and in cingulate gyrus (DeYoung et al., 2010). More than a dozen fMRI studies that included cognitive tasks involving emotional conflict or facial stimuli processing have suggested that neuroticism is strongly associated with activity in amygdala and anterior cingulate cortex (ACC) although medial prefrontal cortex, hippocampus and insula are also involved (Kennis et al., 2013; Ormel et al., 2013; Servaas et al., 2013). In addition, a recent fMRI study found that right superior parietal cortex activation in the task-independent default mode network was negatively correlated with neuroticism (Sampaio et al., 2014). Taken together, the findings from these brain imaging studies suggest that neuroticism is related to certain specific brain regions that are involved in the perception of negative stimuli and/or exert their control over such stimuli (Ormel et al., 2013).

Similar brain imaging studies have been performed on AUD, and the observed structural and functional changes in the brain that are strongly associated with the development and/or severity of AUDs have been summarized in several recent reviews or meta-analyses (Buhler and Mann, 2011; Monnig et al., 2013; Oscar-Berman and Marinkovic, 2007; Reilly et al., 2014; Schacht et al., 2013; Schulte et al., 2012; Welch et al., 2013; Xiao et al., 2015). Although the brain structure-functional networks that underlie the development or consequence of AUD remain to be definitively identified, studies have started to shed some light on the structural and functional correlates of AUD. In general, AUD is associated with structural changes, including reductions in grey matter and white matter volume and cortical thickness in multiple brain regions from the neocortex (in particular the frontal lobes), the limbic system (including hippocampus, amygdala, hypothalamus and anterior cingulate) and the cerebellum. These structural features reflect alterations in various functional domains including personality.

Despite increasing efforts to examine the relationships between AUD and neuroticism and between AUD or neuroticism and neuroanatomy, no study linking AUD, neuroticism and neuroanatomical measures has been reported yet. In this work, we focused on brain cortical thickness, a measure that has been regarded as an indicator of cortical integrity and the most invariant brain size parameter across species (Makris et al., 2008). Specifically, we attempted to gain initial insights into the possible correlation of brain cortical thickness phenotypes with neuroticism scores and AUD diagnostic status, using the community-based Nathan Kline Institute-Rockland Sample (NKI-RS; Nooner et al., 2012). In the NKI-RS, volunteers from Rockland County, New York, are deeply phenotyped with advanced neuroimaging and DNA samples available to the research community, with the goal of accelerating the pace of discovery science in psychiatry (Zhao and Castellanos, 2016). As of September, 2015, behavioral measurements and structural imaging data were available for 494 subjects. After screening, we had 65 individuals with a lifetime history of AUD. Sixty-five healthy comparisons (HC) were selected to match the cases on age, sex, and race as closely as possible. To confirm the replicability of our results, we used data from the Human Connectome Project (Van Essen et al., 2013).

2. MATERIALS AND METHODS

2.1. Participants

Participants were drawn from the first eight releases of the NKI-RS (Nooner et al., 2012). As part of a larger battery of measures, each participant completed the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID). Study staff provided a diagnostic summary for each participant based on semi-structured interviews. Among 494 subjects with publicly available behavioral measurements and structural image data as of September 2015, those who met any of the following criteria were excluded: 1) age below 18 years; 2) diagnosis of other psychiatric disorders without AUD; 3) a diagnosis of epilepsy and/or a history of seizures; 4) subjects who ever lost consciousness due to head injury; 5) missing data on age, sex, race, age at drinking onset, neuroticism, and/or brain structural measure; and 6) subjects with AUD diagnosis history but reporting no lifetime alcohol consumption. Also exclusionary for healthy comparisons were 7) substance (including alcohol, cannabis, opioid, cocaine et al.) involvement scores greater than 3 (Who Assist Working Group, 2002); and 8) inconsistency regarding substance use between self-report and lab results. This screen resulted in a total of 172 subjects. From these, 65 patients with AUD comprised our disease group, and 65 subjects with no Axis I diagnosis, group-matched on age, sex and race, were selected as HC.

2.2. MRI image pre-processing and data processing

T1-weighted structural imaging was obtained using a magnetization prepared, rapid-acquisition gradient-echo (MPRAGE) sequence with 1 mm isotropic resolution (TR=1900 ms). The structural images were preprocessed using the recon-all pipeline from FreeSurfer version 5.3.0 (Fischl et al., 2002, 2004), which is an extensively used robust pipeline optimized for 1 mm isotropic data. Mean cortical thicknesses of 68 gyral regions based on the Desikan-Killiany atlas (Desikan et al., 2006) were extracted for each participant. Quality control of cortical measurements followed the steps outlined in the ENIGMA protocol (<http://enigma.ini.usc.edu/protocols/imaging-protocols/>). Briefly, subjects with outlying cortical thickness were identified and visually checked to make sure that they were properly segmented. In addition, we visually inspected the snapshots of cortical surface segmentations from both internal slices and external surfaces of the brain to make sure that cortical regions were properly segmented and labeled.

2.3. Personality trait assessments and covariates

Scores for neuroticism and other personality traits were calculated based on 60 items from the NEO Five-Factor Inventory (NEO-FFI; McCrae, 2004). All analyses controlled for the covariates of age, sex, race (i.e., Caucasian or not), full scale intelligence based on Wechsler abbreviated scale of intelligence quotient (IQ), past childhood traumatic event status, smoking and marijuana use status, and age at drinking onset. Hollingshead four-factor index of socioeconomic status (SES) and laterality index from Edinburgh handedness questionnaire (handedness) were also considered as possible confounders. However, their inclusion did not alter the pattern of results and degraded prediction accuracy. Accordingly, they were not included in analyses

2.4. Statistical analyses

Two sample *t*-tests and chi-square tests were used to test for differences in continuous and categorical covariates between participants with lifetime AUD diagnosis and healthy comparisons. Multiple linear regression analyses were used to estimate group differences in personality traits. Personality traits from the NEO five-factor model were our primary behavioral measures. In the subsequent analysis of brain-behavior relationship we focused only on neuroticism, as this was the only measure showing a significant group difference.

To identify brain regions where a lifetime history of AUD moderated the relationship between neuroticism and cortical thickness, a two-stage procedure, namely screening and formal model testing, was used. Rational for the use of this two-stage procedure can be found in Supplementary Material S2¹. We assumed that only few brain regions were relevant. In screening stage, the main goal is to identifying a subset of potentially relevant brain regions. The L₂Boosting algorithm (Bühlmann, 2006) was used to select a subset of potentially relevant brain regions. Specifically, a linear model with neuroticism as response variable was fitted by least squares method. Predictors in the linear model include cortical thickness in 68 regions, their interactions with AUD status, and a set of confounding variables. Next, L₂Boosting iteratively fit the linear model to current least square residuals. The final boosting estimator was constructed via a linear combination of multiple estimates. To avoid overfitting, the Akaike Information Criterion stopping rule was employed to stop boosting at a suitable number of iterations. Analyses of brain-behavior relationships were focused only on the regions selected by the L₂Boosting algorithm. In model testing stage, linear regression models, with each selected brain region as an outcome measure, were used to test whether there was a significant group by neuroticism effect. All tests are two-sided at false discovery rate (FDR) (Benjamini and Hochberg, 1995) adjusted significance level of 0.05. Multiple comparisons were adjusted for behavioral measures and brain-behavior relationships, respectively. Finally, vertex-based analysis was performed to localize significant findings. Specifically, we pre-smoothed the cortical thickness data by full width half maximum of 10 mm onto the surface fsaverage6 for each subject. Multiple linear models were used to test the interaction effects of group and neuroticism on the cortical thickness at each vertex on the above three regions. Analyses were performed using R version 3.4.0 (The R Project for Statistical Computing).

3. RESULTS

3.1. Sample characteristics

The HC and AUD subjects did not differ in age, sex, race, IQ, handedness, SES, or age at drinking onset. More AUD subjects reported having experienced childhood traumatic events (78.5%) as opposed to 52.3% for HC subjects. There was a significant difference in tobacco and marijuana use status. More AUD subjects reported to be current (35.4%) and past (44.6%) tobacco user as opposed to 16.9% and 29.2% for HC subjects. The prevalence of current and past marijuana user was higher in AUD subjects (29.2% and 52.3%, respectively) than in HCs (10.8% and 36.9%). Only 20.0 % and 18.5% AUD subjects,

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compared to 53.9% and 52.3% in HC subjects, reported they had never smoked and never used marijuana, respectively (Table 1). There were no significant group differences in estimated total intracranial volume or mean cortical thickness in either hemisphere.

3.2. AUD subjects had higher neuroticism scores

Multiple linear regression models were used to test group differences in NEO-FFI personality traits (Table 2). Neuroticism was the only trait differing significantly between groups after multiple comparison adjustments. Specifically, controlling for age, sex and race, AUDs had significantly higher neuroticism scores than HCs ($q=0.043$; q -values represent FDR adjusted p -values). Group status alone explained 4.3% of the variation in neuroticism scores. The estimated mean neuroticism score in AUDs was 3.5 points higher than in HCs. The finding of elevated neuroticism score in AUDs was consistent with prior reports (Hicks et al., 2012; Martin and Sher, 1994; Mitrovic, 2014).

3.3. Lifetime AUD diagnosis alters correlations between cortical thickness and neuroticism

A two-step procedure was used to assess whether a lifetime history of AUD altered the relationship between neuroticism and cortical thickness in certain brain regions. In Step 1, three brain regions, i.e., left insula, postcentral gyrus and right fusiform, were selected by L_2 Boosting, indicating lifetime AUD history might alter the association between neuroticism and cortical thickness at these brain regions. In Step 2, multiple linear models were used to assess the relationship. Regression analyses showed that lifetime AUD diagnosis altered the relationship between neuroticism and cortical thickness at left insula ($q=0.019$) and right fusiform ($q=0.011$). We failed to detect a significant diagnosis by neuroticism interaction at left postcentral gyrus ($q=0.918$).

Subsequent subgroup analysis revealed that in HCs a positive but non-significant correlation between neuroticism and cortical thickness was observed in the left insula ($\beta=0.002$, $P=0.465$) and right fusiform ($\beta=0.005$, $P=0.146$). However, in AUDs the cortical thickness of both regions showed a significant inverse correlation with neuroticism in the left insula ($\beta=-0.005$, $P=0.040$) and right fusiform ($\beta=-0.007$, $P=0.008$), respectively (Fig. 1). These results indicate that AUD diagnosis affected the correlations between cortical thickness and neuroticism.

To facilitate interpretation, secondary vertex-based analysis was performed to localize findings. Multiple linear models were used to assess the interaction effects of group and neuroticism on cortical thickness at each vertex for the three implicated regions. As shown in Fig. 3, significant vertices were located mainly in left anterior and posterior insula, and the lateral and medial aspects of the right fusiform gyrus. These explicatory results are displayed at p -value of 0.05 without multiple comparison adjustment.

3.4. Validation using the Human Connectome Project

To determine the replicability of our findings, we examined AUD samples from the HCP data set (Van Essen et al., 2013). Using similar criteria (Supplementary Material S1²), we

²Supplementary material can be found by accessing the online version of this paper at <http://dx.doi.org> and by entering doi:...

selected 107 AUD subjects and 107 HC. As in the NKI-RS data set, controlling for age, gender, race, smoking and marijuana use status, age at drinking onset, and age-adjusted picture vocabulary score as a proxy for IQ, we found that a high neuroticism score was associated with AUD ($\beta=-3.06$, $P=0.03$) (Fig. 2A). With regard to the brain regions in which lifetime AUD history was associated with distinct cortical thickness and neuroticism correlations in NKI-RS, the result for the left insula ($P=0.003$) was unequivocally significant (Fig. 2B). Similar to the finding for the NKI-RS data (Fig. 1A), subgroup analysis revealed the correlation between neuroticism and cortical thickness at the left insula was significant in AUD ($\beta=-0.005$, $P=0.002$) but not in HC ($\beta=0.002$, $P=0.258$). The result for fusiform gyrus was also significant ($P=0.041$), though subgroup analysis did not show significant correlations between cortical thickness and neuroticism in AUDs ($\beta=-0.002$, $P=0.275$) and HCs ($\beta=0.003$, $P=0.073$). Due to the dense nature of HCP data and computational limitations, vertex level explicatory analyses were not performed for the HCP data.

4. DISCUSSION

We confirmed that individuals with lifetime AUDs had higher neuroticism scores than healthy comparisons in both NKI-RS and HCP data sets; we did not confirm associations of other personality traits, such as extraversion or conscientiousness, with AUDs (Hakulinen et al., 2015; Hicks et al., 2012; Martin and Sher, 1994; Mitrovic, 2014). This could be partly due to our using community-based samples in which more than 95% of participants with AUDs had a past rather than a current AUD diagnosis, with less extreme behavior measures than found in treatment-seeking AUD subjects. This suggests the link between neuroticism and AUD may be more enduring than other personality traits.

The impact of AUD status on the relationship between neuroticism and cortical thickness has not previously been reported. In the NKI-RS, we found a significant negative correlation between neuroticism and cortical thickness in the left insula and right fusiform in participants with lifetime AUD diagnosis. By contrast, this relationship was not observed in HCs. The lack of correlation between cortical thickness of the left insula and right fusiform in HC is consistent with prior studies in healthy samples (Bjornebekk et al., 2013; Wright et al., 2006). Our novel finding that lifetime AUD diagnosis impacts the correlation between neuroticism and cortical thickness at specific brain regions is a step towards dissecting the complex relationship between brain structure, AUD and neuroticism. It also supports the utility of community-based samples for identifying biological and psychological risk factors impacting AUD (Nooner et al., 2012).

The most compellingly replicable result was our observation of negative correlations between left insular cortical thickness and neuroticism in AUD subjects in both the NKI-RS and the HCP data sets, suggesting that left insular cortical thickness could be a reliable brain endophenotype linking AUD and neuroticism. The insula is involved in multiple processes including perception, motor control, self-consciousness, cognitive functioning, and emotional regulation, and it has been particularly linked to addictive behaviors (Naqvi and Bechara, 2009). Our vertex-based analysis revealed that the correlation between neuroticism and cortical thickness was predominantly affected by AUD status in both anterior and posterior subdivisions of the left insula. The literature on structure-functional relationships

in the insula is conflicted (Droutman et al., 2015). Bilateral insula damage was associated with loss of addictive craving (Naqvi et al., 2007), but reduction in insular cortical thickness has also been reported in cocaine addiction (Makris et al., 2008) and in alcohol dependent subjects (Durazzo et al., 2011). In addition, substance users have been found to show reduced posterior insula activity during risky choice tasks (Stewart et al., 2014), as well as increased insula activity in response to drug-related cues (Schacht et al., 2013). In the same vein, severity of alcohol addiction has been positively associated with cue-induced insula activity (Claus et al., 2011). In cocaine addiction, insula involvement has been understood on the basis of interconnections with the dorsolateral prefrontal cortex in normative functioning of the reward system (Makris et al., 2008). Furthermore, the strong emotional states produced by substance abuse have been proposed to enhance insula connectivity, which in turn leads to strong associations between drugs of abuse and emotional states in drug abusing subjects (Viswanath et al., 2015). Interestingly, several studies have indicated that activation in the anterior subdivision of the left insula is negatively correlated with emotional control-related neuroticism (Iaria et al., 2008; Meriau et al., 2009; Simmons et al., 2011). We speculate that the insula-neuroticism correlation we observed in AUD may reflect the same relationship.

Our finding that AUD impacted the correlation between neuroticism and cortical thickness in the anterior and posterior insula supports the tentative suggestion that this effect may involve pain perception in participants with AUDs. Our vertex-based analysis result pinpointing both anterior and posterior subdivisions of the insula is consistent with the involvement of both these subdivisions in pain perception. Pain sensations evoked from various painful stimuli are relayed to dorsal posterior insula via the spinothalamocortical pathway and then integrated in the anterior subdivision (Bernard et al., 1996; Ostrowsky et al., 2002; Egli et al., 2012). AUD has been increasingly viewed as a chronic pain disorder based on accumulating pathophysiological observation and brain imaging evidence (Egli et al., 2012; Zale et al., 2015). Alcohol administration is believed to trigger an initial rewarding and pain alleviating response, although excessive alcohol intoxication and withdrawal episodes can dysregulate brain stress and reward circuits. Such repeated episodes can lead to a persistent negative affective state that in turn motivates excessive alcohol consumption to restore the normal emotional state (Egli et al., 2012). Neuroticism score, which was higher in participants with AUDs than in HCs, has been reported to be negatively related to pain tolerance (Ralevski et al., 2010). The insula's fundamental role in human pain perception is further supported by its being the most consistently activated region in response to abnormal and induced pain (Egli et al., 2012; Ostrowsky et al., 2002; Segerdahl et al., 2015). Finally, the insula is also activated in subjects with alcohol dependence during reward anticipation (Villafuerte et al., 2012). Therefore, our observation in two independent data sets that the insula cortical thickness-neuroticism correlation differs in participants with AUD versus HCs may also be explained by the intriguing, albeit untested, hypothesis that insula cortex dysfunction, indexed by structural differences, may mediate the impact of alcohol consumption on affective pain states, consequently contributing to the development of AUDs. Clearly, understanding the potential role of the insula in addiction requires further investigation.

The study which reported the association between insular activity and AUD (Claus et al., 2011) also showed associations of AUD with cue-induced activity in fusiform gyrus, among others. In the NKI-RS dataset, we also found a significant negative correlation between right fusiform cortical thickness and neuroticism in AUDs. This correlation was non-significantly positive in HCs. The relationship between AUD history and the correlation between neuroticism and right fusiform cortical thickness replicated in the HCP ($P = 0.041$). However, exploratory subgroup analyses did not replicate strictly. The significant negative neuroticism-right fusiform gyrus correlation in AUDs ($P = 0.008$) in NKI-RS data was not significant ($P = 0.275$) in HCP data. We interpret this result as broadly but not completely convergent with our NKI-RS finding. Despite the lack of complete replication, prior results implicate the right fusiform in AUD or emotional control. Right fusiform cortical thickness was recently found to be negatively correlated with lifetime alcohol use in adolescent alcohol users (Jacobus et al., 2015). Similarly, in subjects with AUD, significant activation in bilateral fusiform gyri correlated with the level of craving to alcohol cues (Claus et al., 2011; Jasinska et al., 2014; Park et al., 2007). In addition, the fusiform gyrus has been linked to neural pathways involved in face recognition and responding to emotional faces (Cservenka et al., 2014). A negative correlation between activation in the right fusiform gyrus and neuroticism during anticipation of visceral pain has also been reported (Coen et al., 2011).

Our study has several limitations. First, the sample sizes from the NKI-RS (130 subjects) and HCP (214 subjects) datasets are relatively small. These resulted from our matched case-control design, which we adopted to reduce possible confounding. Second, about 50% of participants with histories of AUDs were comorbid with at least one other psychiatric disorder. Specifically, 26.2%, 10.8%, 9.2% and 6.1% subjects comorbid with 1, 2, 3, and more than 3 other disorders, respectively (Table 1). The top three comorbidities were cannabis use disorder (23.1%), major depressive disorder (21.5%), and cocaine use disorder (12.3%). Exploratory analysis, using AUD subjects without other comorbid disorders, revealed that the neuroticism-cortical thickness correlation remained to be negative in both brain regions. However, the relationship was not statistically significant. Therefore, the effect of comorbid psychiatric disorders on the cortical thickness-neuroticism relationship warrants further investigation in a larger study. Third, the insula cortex finding was replicated in an independent data set, but the subgroup analysis of fusiform result did not strictly replicate. Thus, the complex relationship among cortical thickness, neuroticism, and AUD status in the fusiform must be interpreted as preliminary. Fourth, our findings do not address cause-effect relationships. Clearly, well-controlled longitudinal studies are needed to delineate the potential causative factors involved in neuroticism and AUD development.

In conclusion, as a first step towards the dissection of the complex relationship among AUD, neuroticism and brain structure, we used a novel machine learning tool to analyze data from two community-based samples. Our results suggest that neuroticism is related to AUD status, which affects the correlation of neuroticism with cortical thickness in the left posterior insula and right fusiform gyrus in both NKI-RS and HCP data sets. Future work on the dissection of the mechanisms underlying AUD-neuroticism interactions will provide further insights into the relationship between specific brain loci, AUD and neuroticism, which may contribute to the development of more effective strategies for preventing and treating AUD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Subjects with AUD diagnosis history had higher neuroticism scores than HCs.
- Neuroticism was correlated with cortical thickness of insula and fusiform in AUDs.
- The AUD-impacted insula cortical thickness-neuroticism correlation was replicated.

Fig. 1. Correlation of brain cortical thickness with neuroticism

(A) Left insula cortex thickness. (B) Right fusiform cortex thickness. HC, healthy comparisons; AUD, alcohol use disorders. P -values for the correlations in HC and AUD are both shown.

Fig. 2. Validation result using the Human Connectome Project data set

(A) Correlation of neuroticism with AUD. The dot in AUD group indicates an extreme neuroticism score. (B) Correlation of the left insula cortex thickness with neuroticism score. P -values for the correlations in HC and AUDS are both shown. HC, healthy comparisons; AUD, alcohol use disorders.

Fig. 3. Vertex-based analysis of the brain cortical regions
(A) Left insula. (B) Right fusiform. Vertices in red represent the region with P -value less than 0.05.

Table 1

Summary of the AUD subjects and health controls used in this study.

Variables	HC (n=65)	AUD (n=65)
<i>Demographics</i>		
Age	44.2 (18.6)	45.6 (17.6)
Sex (Female)	37 (56.9%)	33 (50.8%)
Race (White)	50 (76.9%)	49 (75.4%)
IQ	101.6 (11.9)	101.4 (12.9)
Socioeconomic status	44.0 (14.4)	44.8 (10.6)
Handedness	75.3 (28.5)	71.2 (37.4)
Traumatic events *	34 (52.3%)	51 (78.5%)
Age at drinking onset	17.5 (4.0)	16.8 (2.6)
Tobacco use status *		
Never used tobacco	35 (53.9%)	13 (20.0%)
Past tobacco user	19 (29.2%)	29 (44.6%)
Current tobacco user	11 (16.9%)	23 (35.4%)
Marijuana use status *		
Never used marijuana	34 (52.3%)	12 (18.5%)
Past marijuana user	24 (36.9%)	34 (52.3%)
Current marijuana user	7 (10.8%)	19 (29.2%)
<i>Psychiatric comorbidity</i>		
Number of Comorbidities		
0		31 (47.7%)
1		17 (26.2%)
2		7 (10.8%)
3		6 (9.2%)
>3		4 (6.1%)
Top 3 comorbidities		
Cannabis abuse/dependence		15 (23.1%)
Major depressive disorder		14 (21.5%)
Cocaine abuse/dependence		8 (12.3%)
<i>Global brain measurement</i>		
ICV (cm ³)	1479.5 (128.8)	1491.3 (149.9)
lh_Thickness (mm)	2.49 (0.11)	2.48 (0.10)
rh_Thickness (mm)	2.48 (0.12)	2.47 (0.10)

Notes: HC, healthy comparisons; AUD, alcohol use disorders. ICV, intracranial volume. lh, left hemisphere. rh, right hemisphere.

* indicates $P < 0.05$.

Table 2

Group differences among the five personality traits.

Personality	Descriptive statistics mean (sd)		Model-based group difference	
	HC	AUD	HC-AUD	FDR <i>P</i> value
Neuroticism	15.6 (5.7)	19.0 (7.8)	−3.5	0.043
Extraversion	31.8 (5.1)	29.7 (5.7)	2.0	0.196
Openness	31.5 (5.1)	32.7 (5.4)	−0.7	0.978
Agreeableness	34.7 (5.8)	35.1 (5.9)	−1.8	0.092
Conscientiousness	35.2 (6.4)	34.2 (8.8)	0.6	0.978

Notes: HC, healthy comparisons; AUD, alcohol use disorders.