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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 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.

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 and Costa, 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 and Costa, 2004). Those high in neuroticism

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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 et al., 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 and Costa, 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