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Structural deficits in salience network regions are associated with increased impulsivity and compulsivity in alcohol dependence

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ABSTRACT

Background: Convergent preclinical and clinical evidence has linked the anterior insula to impulsivity and alcohol-associated compulsivity. The anterior insula is functionally connected to the anterior cingulate cortex, together comprising the major nodes of the salience network, which serves to signal salient events, including negative consequences. Clinical studies have found structural and functional alterations in the anterior insula and anterior cingulate cortices of alcohol dependent individuals. No studies have yet investigated the association between morphometric abnormalities in salience network regions and the phenotype of high levels of impulsivity and compulsivity seen in alcohol dependent individuals.

Methods: In the current study, we compared self-report impulsivity, decisional impulsivity, self-report compulsivity, and structural neuroimaging measures in a sample of alcohol dependent individuals ($n = 60$) and a comparison group of healthy controls ($n = 49$). From the structural magnetic resonance images, we calculated volume and cortical thickness for 6 regions of interest: left and right anterior insula, posterior insula, and anterior cingulate.

Results: We found that alcohol dependent individuals had smaller anterior insula and anterior cingulate volumes, as well as thinner anterior insula cortices. There were no group differences in posterior insula morphometry. Anterior insula and anterior cingulate structural measures were negatively associated with self-report impulsivity, decisional impulsivity, and compulsivity measures.

Conclusions: Our results suggest that addiction endophenotypes are associated with salience network morphometry in alcohol addiction. These relationships indicate that salience network hubs represent potential treatment targets for impulse control disorders, including alcohol addiction.

1. Introduction

Problematic alcohol use is a serious public health issue. In the United States, alcohol misuse contributes to 88,000 deaths per year and is estimated to cost \$245 billion each year due to lost productivity, health care costs, law enforcement, and associated criminal justice expenses (General, 2016). An estimated 6% of people (15.7 million) in the United States meet criteria for a current alcohol use disorder (Quality, 2016). A hallmark of alcohol use disorders, as well as other drug addictions, is compulsive drug use (NIDA, 2012). Compulsive drug use is behaviorally manifested by the tendency to continue seeking and taking a drug, despite negative or aversive consequences.

Impulsivity is a multi-dimensional construct that has been linked to addiction. Broadly defined, impulsive actions are premature, unplanned or poorly planned, and often conducted in inappropriate contexts

(Moeller et al., 2001). Self-report trait impulsivity, behavioral impulsivity, and decisional impulsivity scores are higher in addicted individuals than non-addicted controls (MacKillop et al., 2011; Verdejo-Garcia et al., 2008). Impulsivity is also thought to contribute to the development of addictive disorders. Children with a family history of substance use disorders are more impulsive than lower risk children prior to drug and alcohol exposure (Verdejo-Garcia et al., 2008). Trait impulsivity is also higher in non-drug using siblings pairs of stimulant dependent individuals (Ersche et al., 2010). Further, impulsive behavior can predict alcohol-related problems, comorbid alcohol and drug use, and the number of illicit drugs used independently of parental alcohol dependence (Nigg et al., 2006). Together, these data provide evidence for the hypothesis that impulsivity is an endophenotype for addiction, where impulsivity is both a vulnerability factor for and impacts the severity of addiction (Ersche et al., 2012b).

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The insula has been identified as a key region in addiction. Smokers with insula damage were more likely to experience a complete disruption of addiction, described by an ability to stop smoking immediately after an insular brain lesion, without relapse, and a loss of craving, than individuals with a non-insular brain lesion (Naqvi et al., 2007). Animal models have also implicated the insula as a critical region for impulsivity and compulsivity. Seif and colleagues found that the glutamatergic inputs from the anterior insula to the nucleus accumbens were necessary for compulsive alcohol seeking (Seif et al., 2013). When these anterior insula inputs were optogenetically inhibited, rats reduced their consumption of alcohol paired with an aversive consequence, but did not reduce their consumption of unpaired alcohol (Seif et al., 2013). Belin-Rauscent and colleagues found that motor impulsivity was inversely related to anterior insula cortical thickness in rats and that anterior insula lesions resulted in a decrease in motor impulsivity specifically in high impulsive rats (Belin-Rauscent et al., 2016). Moreover, they found that bilateral anterior insula lesions both prevented the development of schedule-induced polydipsia, a measure of compulsive behavior, and reduced the level of schedule-induced polydipsia in high compulsive rats (Belin-Rauscent et al., 2016). Together, these studies indicate that the anterior insula may be a core neural substrate for maladaptive impulse control disorders, including alcohol addiction.

The anterior insula (AI) is functionally connected to the anterior cingulate cortex (ACC), together representing the key nodes of the salience network (Menon and Uddin, 2010). In the salience network, the AI facilitates a bottom-up signal to the ACC to signal salient events. This process often involves task-switching, where one's attention is "switched" through the Salience Network (SN) to other large scale networks. EEG studies evaluating the detection of deviant stimuli have provided the temporal resolution to measure this bottom-up salience signal. Initially, sensory areas are activated during the detection of novel stimuli. Next, this signal is transmitted to the AI and then the ACC, where top-down control signals are generated and sent to further neocortical regions. Finally, the ACC facilitates the response to the salient stimuli through connections to motor areas (Menon and Uddin, 2010). In addictive disorders, the detection of salient events including negative consequences may be disrupted. Preclinical studies have also implicated the ACC in impulsive responding. Lesions of the ACC result in increases in motor impulsivity in rats (Muir et al., 1996).

Previous studies have identified volume reductions in the insula and ACC in alcohol dependent individuals (Demirakca et al., 2011; Durazzo et al., 2014; Durazzo et al., 2011). Alcohol dependent individuals have decreases in right AI volume (Makris et al., 2008), and bilateral AI volume (Senatorov et al., 2015). Alcohol dependent individuals also had smaller volume of the right caudal and left rostral ACC compared to controls (Durazzo et al., 2011). Further morphometric damage has also been described in alcohol dependent individuals. Previous studies have also identified reductions in insula and ACC cortical thickness (Durazzo et al., 2011; Momenan et al., 2012). Durazzo and colleagues identified alcohol-associated decreases in the cortical thickness of the right caudal and left rostral ACC (Durazzo et al., 2011).

Despite the importance of the insula in addiction, and the indication that it is a critical region for compulsive and impulsive behavior, there have been no studies investigating the relationship between insula morphometry, impulsivity, and compulsivity in addiction. Here we investigate the volume and cortical thickness of the AI, posterior insula (PI), and ACC in alcohol dependent individuals (ALC) and light-drinking healthy controls (HC). We also investigated self-report impulsivity, decisional impulsivity, and self-report compulsivity in the same group. We hypothesized that there would be lower volumes and thinner cortices in the anterior insula and anterior cingulate cortex in the ALC group. We further hypothesized that there would be a negative association between impulsivity/compulsivity measures and AI morphometric measures.

2. Materials and methods

2.1. Participants

Participants were selected from individuals enrolled in inpatient and outpatient screening protocols at the National Institute on Alcohol Abuse and Alcoholism (NIAAA) from 2014 to 2016, who underwent a structural magnetic resonance imaging (MRI) scan. The screening protocols were approved by an NIH Institutional Review Board. Participants provided written informed consent. Participants were all right-handed individuals, ages 21–60. Exclusion criteria included significant medical illness (including diabetes and untreated hypertension), neurological disorders, history of psychotic symptoms, history of head trauma, ferrous metal in the body, pregnancy, and positive urine drug tests. Individuals with high levels of alcohol withdrawal symptoms (scores ≥ 8 on the Clinical Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar)) were also excluded.

As part of the screening visit, the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID IV-TR; (First et al., 1997)) was administered to all participants. Participants were divided into two groups based on their current drinking behavior and DSM-IV SCID alcohol diagnosis: HC and ALC. Diagnoses of psychotic disorders were exclusionary, other Axis I diagnoses were not exclusionary (see Table S1 for breakdown of Axis I diagnoses). The presence or absence of Axis I disorders beyond alcohol dependence was coded as 1 or 0 and included as a covariate. HC ($n = 49$) were individuals who drank at or below NIAAA recommendations for low risk drinking (maximum 7 drinks/week and no more than 3 drinks/day for women and 14 drinks/week and no more than 4 drinks/day for men; <https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/moderate-binge-drinking>). ALC ($n = 60$) were individuals who were undergoing inpatient treatment for their alcohol use and met DSM-IV criteria for alcohol dependence. ALC were in early abstinence (< 1 month since date of last drink) at the time of the study (see Table 1 for demographic information).

2.2. Alcohol and smoking measures

Participants completed several alcohol-related questionnaires: Timeline Followback (TLFB), Alcohol Use Disorders Identification Test (AUDIT), and Alcohol Dependence Scale (ADS). The TLFB is a self-report measure of alcohol consumption over the past 90 days (Sobell et al., 1996). The AUDIT was designed as a screening tool for hazardous alcohol use; it assesses alcohol consumption, drinking behaviors, and alcohol-related problems (Saunders et al., 1993). The ADS measures elements of alcohol dependence including loss of control over alcohol use, salience of alcohol-seeking behaviors, tolerance, and withdrawal, and produces a composite score that describes an individual's level of alcohol dependence (Skinner and Horn, 1984). To determine smoking status, participants completed the Fagerstrom Test for Nicotine Dependence (FTND) (Heatherton et al., 1991). Participants also completed the State-Trait Anxiety Inventory (STAI), Form Y-2, which measured their trait anxiety levels (Spielberger, 1983).

2.3. Impulsivity and compulsivity measures

Participants completed the Barratt Impulsiveness Scale (BIS-11; (Patton et al., 1995)), a self-report measure, which evaluates 3 dimensions of impulsivity: attentional impulsiveness, motor impulsiveness, and non-planning impulsiveness. They also completed a delay-discounting task, which measures decisional impulsivity (Mitchell, 1999). This task presents a series of choices to participants, where the participant must choose between a smaller, immediate monetary reward (\$10-\$90) or a fixed, larger reward (\$100) that is delayed in time (0–30 days). The rate of discounting, or devaluing, the delayed outcome is represented by k , the delay discounting factor. For analysis purposes,

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