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Research Paper

Neurobiological Correlates and Predictors of Two Distinct Personality Trait Pathways to Escalated Alcohol Use

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ABSTRACT

Background: The delineation of the behavioral neurobiological mechanisms underlying the heterogeneous pathways for alcohol use disorders (AUDs) is ostensibly imperative for the development of more cost-effective treatments predicated on better understanding of this complex psychopathology.
Methods: 1) Forty-eight high anxiety sensitive (HAS) and high sensation seeking (HSS) psychopathology-free emerging adults (mean (SD) age: 20.4 (1.9) years) completed a Face Emotion Processing Task and a social stress paradigm (Montreal Imaging Stress Task) during functional magnetic resonance imaging sessions with and without alcohol ingestion (1 ml/kg of 95% USP alcohol, p.o.). Drug and alcohol use was reassessed during follow-up interviews 2–3 years later.
Outcomes: The effects of alcohol (versus placebo) ingestion depended upon the task and risk group. In response to negative (versus neutral) faces, alcohol diminished amygdala (AMYG) activations in HAS but not HSS subjects. In response to psychosocial evaluative stress, alcohol enhanced activations of the medial orbitofrontal cortex (mOFC), perigenual anterior cingulate cortex, and nucleus accumbens in HAS male subjects (HASMS), but decreased mOFC activity in HSS male subjects (HSSMS). At follow-up, a greater alcohol versus placebo differential for threat-related AMYG activations predicted escalating drinking and/or illicit drug use among HAS but not HSS participants, whereas a greater differential for mOFC activations during acute social stress predicted escalating substance use among HSS but not HAS participants.
Interpretation: This double dissociation provides evidence of distinct neurobiological profiles in a priori identified personality trait-based risk groups for AUDs, and links these signatures to clinically relevant substance use outcomes at follow-up. AUD subtypes might benefit from motivationally and personality-specific ameliorative and preventative interventions.

1. Introduction

High levels of the traits anxiety sensitivity (AS, fear of fear) (Reiss et al., 1986) and sensation seeking (SS, the tendency to seek and take risk for the sake of novel and emotionally intense experiences) (Zuckerman, 1979) are risk factors for alcohol use disorders (AUDs). Some evidence suggests that these personality dimensions are associated with distinct motives for drinking and trait-specific effects of alcohol ingestion (Conrod et al., 1998). For example, high AS (HAS) individuals often report drinking "to forget" and are highly susceptible to alcohol-induced anxiolysis (Stewart and Kushner, 2001), whereas those high in SS (HSS) tend to report drinking because it is "fun" and exhibit hypersensitivity to alcohol-induced stimulation (Conrod et al., 1998).

Neurobiological correlates of these vulnerable phenotypes have been tentatively identified. In response to threatening stimuli, HAS individuals, as compared to healthy controls, overactivate in the brain's "defensive survival circuit" (Stein et al., 2007), which is anchored by, among other regions, the amygdala (AMYG) and anterior insula (aINS) (LeDoux, 2015). In comparison, threat-related stimuli yield relatively few activations of this circuit in HSS individuals (Mujica-Parodi et al., 2014).

The source of these differential threat responses might include differences in cortical input. The AMYG receives inhibitory projections from the perigenual anterior cingulate cortex (pgACC) and medial orbitofrontal cortex (mOFC) (Price, 2007). These pathways can influence the processing of threatening events (LeDoux, 2015), with the

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mOFC being particularly important for the suppression of stimulus triggered impulsive acts including the urge to aggress against others (Coccaro et al., 2007). Input from all three regions (AMYG, mOFC, pgACC) is integrated in the ventral striatum (Haber et al., 2006), which influences the ability of motivationally relevant cues to elicit approach (Britt et al., 2012) and exhibits functional irregularities in populations at risk for addictions (Leyton, 2017).

Activations of the defensive circuit by threatening stimuli can be reduced by ethanol ingestion (Gilman et al., 2008, 2012a; Sripada et al., 2011), and this effect might be particular important for highly anxious individuals. Sensation seekers, in comparison, appear to be particularly susceptible to alcohol-heightened impulsive, aggressive behaviors (Pihl and Sutton, 2009), making it is plausible that the pgACC and mOFC contribute to their alcohol-related behaviors. These proposals noted, it remains unknown whether these brain regional effects of alcohol vary as a function of personality traits. Obtaining an understanding of the hypothesized differential responses might be informative about why the substance is used and misused (Pihl and Peterson, 1995).

To investigate these hypothesized processes explicitly, the current study tested (Reiss et al., 1986) whether different at-risk populations exhibit distinct ethanol-induced changes in their brain regional processing of emotionally challenging material, and (Zuckerman, 1979) whether differences in the proposed risk-trait specific neurobiological responses prospectively predict escalations in alcohol and other drug use patterns. The design was a placebo-controlled double-blind repeated-measures prospective study of two cohorts of HAS and HSS volunteers. In phase I, participants were alcohol and placebo challenged on separate fMRI sessions as they completed two emotionally challenging tasks that differed in both form and affect. In phase II, two to three years after their fMRI testing, participants had a follow-up interview about their mental health and substance use.

Based on the extant literature, we predicted that (Reiss et al., 1986) ethanol-induced reductions in threat- related activations within the "defensive survival circuit" would be significant only in HAS participants, (Zuckerman, 1979) ethanol would decrease activations within top-down regions that subserve emotion regulatory functions and increase the activity of regions that participate in reward and motivation processing in the context of a performance-based social stressor only in HSS volunteers, and (Conrod et al., 1998) the magnitude of these personality-specific effects of alcohol would be largest in those who exhibited escalated substance use at follow-up.

2. Materials and Methods

2.1. Subjects

Forty-eight right-handed healthy young adults (23 women) who classified as HAS or HSS were recruited via advertisements (eMethods in the Supplement). Study protocols were approved by the McGill Institutional Review Board. All participants provided written informed consent and were fully debriefed at the end of testing.

A total of four subjects failed to complete the two MRI sessions or showed excessive head movement, leaving us with a final sample of 20 HAS (9 women) and 24 HSS (10 women) volunteers (Table 1). Out of these, nine were lost to the multi-year follow-up. The remaining 35 (18 HAS; 7 women and 17 HSSS; 7 women) were reassessed for alcohol and drug use status. Fifteen of these participants (8 HAS; 4 women and 7 HSS, 1 woman) had escalated to clinical relevant alcohol or other substance use problems, and were classified as 'transitioners' (TRAs). The rest, who had not developed the clinical outcome, were classified as Non-TRAs (Table 2).

2.2. Procedure

2.2.1. Phase I

On scanning days, subjects reported to the MNI's Brain Imaging Centre at least 1 h prior to start of testing. They changed their clothing (into scrubs) and rested for 45–60 min. The alcohol/placebo challenge procedure (detailed in eMethods in the Supplement) then started and when completed, placement in a 3.0 T Siemens Magnetom Trio Tim scanner (Erlangen, Germany) immediately occurred, at or near the height of the blood alcohol curve (BAC = 0.08; range = 0.075–0.10).

In the scanner, subjects first performed a Face Emotion Processing Task (FEPT), in which they passively viewed and then identified emotional and neutral faces, taken from the Karolinska Directed Emotional Faces (KDEF) (Lundqvist et al., 1998) set (eMethods and eFigure 2 in the Supplement). Subjects then completed the Montreal Stress Imaging Task (MIST) (Dedovic et al., 2005), a social stress paradigm mental arithmetic is performed under time pressure. A failure rate of 40–50% was enforced and visually displayed on a 'performance scale'. Additional negative feedback was provided by the study investigators who entered the scanner rooms after each test segment (eMethods and eFigure 3 in the Supplement). Subjective

Table 1
Demographic characteristics and baseline self-report measures.

	HASS (N = 23)	HSSS (N = 24)	Group difference *P* value
Women, No. (%)	11 (47.80)	11 (44.00)	
Age, mean (SD), y	20.52 (1.65)	20.4 (2.20)	*ns*
Race, No. (%)			
Caucasian	21 (91.30)	18 (75.00)	
Black	0	0	
Asian	0	2 (8.30)	
Other	2 (8.70)	4 (16.70)	
Years of education, mean (SD)	14.17 (0.89)	14.18 (1.07)	*ns*
Personality and clinical measures scores, mean (SD)			
SURPS-AS subscale	16.95 (1.70)	6.20 (1.25)	<0.001
SURPS-SS subscale	10.35 (1.22)	22.37 (1.95)	<0.001
ASI-Global	34.60 (6.61)	10.45 (4.73)	<0.001
ASI-PC subscale	17.58 (5.35)	3.45 (3.00)	<0.001
ASI-MIC subscale	5.64 (2.87)	3.62 (1.66)	0.006
ASI-SC subscale	7.17 (2.12)	4.79 (1.91)	<0.001
SPSRQ-SP subscale	13.40 (4.79)	6.21 (4.03)	<0.001
SPSRQ-SR subscale	10.90 (3.27)	16.04 (2.82)	<0.001
MAST subscale	0.57 (1.46)	0.24 (0.88)	*ns*
Alcoholic drinks per week	8.20 (4.10)	10.54 (7.27)	*ns*
Lifetime regular smokers (n (%))	0	0	*ns*

Abbreviations: HASS, high anxiety sensitivity subjects; HSSS, high sensation seeking subjects; ASI, Anxiety Sensitivity Index; PC, physical concerns; MIC, mental incapacitation concerns; SC, social concerns; SURPS, Substance Use Risk Profile Scale; AS, anxiety sensitivity; SS, sensation seeking; SPRSQ, SPSRQ, Sensitivity to Punishment and Sensitivity to Reward Questionnaire; MAST, Michigan Alcohol Screening Test; ns, nonsignificant at $P < 0.05$.
No statistical effects of sex or personality-by-sex interaction were found for any of the presented variables.

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