Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Research Paper

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

Malak Abu Shakra [a], Marco Leyton [a,b,c], Hussein Moghnieh [e], Jens Pruessner [d], Alain Dagher [c], Robert Pihl [a,b,*]

[a] *Department of Psychology, McGill University, Montreal, Quebec, Canada*
[b] *Department of Psychiatry, McGill University, Montreal, Quebec, Canada*
[c] *Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada*
[d] *Department of Psychology, University of Konstanz, Konstanz, Baden-Württemberg, Germany*
[e] *FastPay Financial Institution, Beverly Blvd, Los Angeles, CA, United States*

ARTICLE INFO

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.

© 2017 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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

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.

Table 2
Demographic characteristics and baseline self-report measures (study phase II).

	TRAs	Non-TRAs	Group difference P value
HASS, No. (%)	8 (44.4)[c]	10 (55.6)	
HSSS, No. (%)	5 (29.4)	12 (70.6)	
Women, no. (%)			
HASS	4 (50.0)	4 (40.0)	
HSSS	1 (16.7)	6 (54.5)	
Age, mean (SD), y			
HASS	23.50 (1.10)	22.83 (1.33)	ns
HSSS	23.25 (2.86)	23.28 (2.03)	ns
Race, no. (%)			
Caucasian			
HASS	8 (100)	8 (80.0)	
HSSS	4 (66.7)	7 (63.6)	
Asian			
HASS	0	0	
HSSS	0	2 (18.2)	
Other			
HASS	0	2 (20.0)	
HSSS	1	1 (10)	
Years of education, mean (SD)			
HASS	14.50 (0.76)	13.90 (0.88)	ns
HSSS	14.00 (1.26)	14.09 (1.04)	ns
Follow-up clinical measures, mean (SD)			
MAST score			
HASS	6.25 (3.99)	0.00 (0.00)	0.003
HSSS	7.33 (3.93)	0.18 (0.60)	0.006
Alcoholic drinks per week			
HASS	22.00 (5.15)	6.00 (2.79)	<0.001
HSSS			
Anxiety disorder, no. (%)			
HASS	7 (87.5)[a]	3 (30.0)	
HSSS	0	0	
Major depression, no. (%)			
HASS	3 (37.5)	1 (10.0)	
HSSS	1 (16.7)[b]	1 (9.1)	

Abbreviations: TRAs, Transitioners; Non-TRAs, Non-Transitioners; HASS, high anxiety sensitivity subjects; HSSS, high sensation seeking subjects; MAST, Michigan Alcohol Screening Test; ns, nonsignificant.

[a] Symptom worsening (relative to severity at study entry) reportedly preceded escalating use but was further exacerbated after.
[b] Substance-induced.
[c] For the TRA HSSS, environmental adversity (job loss, dumped by romantic partner) reportedly occurred in the aftermath of and as a direct result of drug misuse.

mood was visually self-rated and salivary cortisol levels recorded repeatedly throughout the experiment (eMethods in the Supplement). After the MIST and prior to the end of MRI session, a 10-minute structural scanning period occurred as subjects rested. Total scanning time approximated 55 min. Subjects were sent home 1.5–2 h after the end of scanning session, or until BAC fell below 0.02 g%. Neuroimaging data acquisition parameters and preprocessing steps are detailed in eMethods in the Supplement.

2.2.1.1. fMRI Data Analyses. Functional images were processed using the Statistical Parametric Mapping software package (SPM8; Wellcome Trust Center for Neuroimaging, London, UK; eMethods in the Supplement).

Contrasts of interest were, for the event-related FEPT, Negative Face (averaged fearful, disgusted, angry and sad trials) > Neutral Face trials (NEG − NEU) and for the block-designed MIST, Experimental > Control condition (Stress − NonStress).

Regions-of-interest (ROIs) and stringent exploratory voxel-wise analyses were performed.

ROIs were selected a priori based on research implicating them in the processing of the sort of emotional material used here (Hefner and Curtin, 2012). These were, for the FEPT, the (bilateral) AMYG and aINS, and, for the MIST, mOFG, pgACC and NAc (eMethods in the Supplement).

2.2.1.2. Statistical Analyses. eMethods in the Supplement provides detailed description of the analyses performed on our behavioral (performance), endocrine and subjective data.

2.2.2. Phase II

Subjects underwent a phone (n = 14) or Skype (n = 21) interview performed by a trained doctoral student of Clinical Psychology (MAS). The SCID-NP[42] was administered to assess the possible development of major non-substance related psychiatric conditions and the DSM-IV diagnostic criteria for AUDs and substance use disorders (SUDs) were used to determine the presence of problem use of alcohol and illicit drugs, respectively (eMethods in the Supplement). Subjects who classified as TRAs if they met 2 or more criteria for either or both AUDs and SUDs. TRAs were compared to their same-personality non-TRAs counterparts on baseline demographic characteristics and self-report measures, to assess for variables that might require further covariation. Given sample attrition at follow-up, our fMRI analyses were limited to our previously specified ROIs (eMethods in the Supplement).

3. Results

3.1. Phase I: Baseline Data

There were no group differences in demographic characteristics or testing variables (eTable 1 in the Supplement).

3.1.1. FEPT

3.1.1.1. Behavioral Results. Face emotion detection accuracy was high in the entire sample under placebo (M = 17.91, SE = 1.5), with no effects of personality, sex or an interaction being seen. Condition had a main effect on this measure ($F_{(1,39)} = 5.17$, $P < 0.029$, $\eta p^2 = 0.120$), with a decrease seen under the alcohol (M = 22.15, SE = 19.84) vs. placebo (M = 17.58, SE = 14.46) condition ($t_{(41)} = 2.43$, $P = 0.019$).

3.1.1.2. ROI Analyses Results. The NEG-NEU contrast yielded main effects of personality reflecting greater activations in the HASS vs. HSSS in bilateral AMYG (L: $F_{(1,36)} = 18.87$, $P < 0.001$, $\eta p^2 = 0.344$; R: $F_{(1,36)} = 21.19$, $P < 0.001$, $\eta p^2 = 0.371$; eTable 2 in the Supplement) and left aINS ($F_{(1,36)} = 9.93$, $P = 0.003$, $\eta p^2 = 0.216$; eTable 2 in the Supplement). The same contrast also yielded a condition-by-personality interaction effect in the bilateral AMYG (L: $F_{(1,36)} = 12.46$, $P = 0.002$, $\eta p^2 = 0.236$; R: $F_{(1,36)} = 13.19$, $P = 0.001$, $\eta p^2 = 0.268$; Fig. 1), with HAS participants showing decreased activation under alcohol compared with placebo (L: $t_{(19)} = -4.94$, $P < 0.001$; R: $t_{(19)} = -5.22$, $P < 0.001$) while the HSS group remained comparatively unresponsive during both sessions (L: $P > 0.30$; R: $P > 0.08$). The aINS showed a similar 2-way interaction, though not robustly enough to survive correction for multiple comparisons.

3.1.1.3. Exploratory Voxel-wise Analyses Results. Under placebo, the NEG-NEU contrast yielded a main personality effect on the activation of two brain clusters that were localized to the bilateral AMYG and more strongly activated in HAS than HSS participants (eResults and eFigure 4 in the Supplement). Condition-by-personality interaction effects in multiple brain clusters were also found (eTable 3 in the Supplement), with widespread ethanol-induced limbic deactivations in group HAS, including peak effects in the left AMYG, and no change in the HSS group (Fig. 2, eTable 4 in the Supplement).

3.1.2. Mist

3.1.2.1. Behavioral Results. Under placebo, there was a main effect of personality on task performance ($F_{(1,38)} = 6.09$, $P = 0.018$, $\eta p^2 = 0.135$), with a higher rate of correct answers being given by HSS (M = 45.46, SE = 0.91) than HAS participants (M = 42.09, SE = 1.02). There was
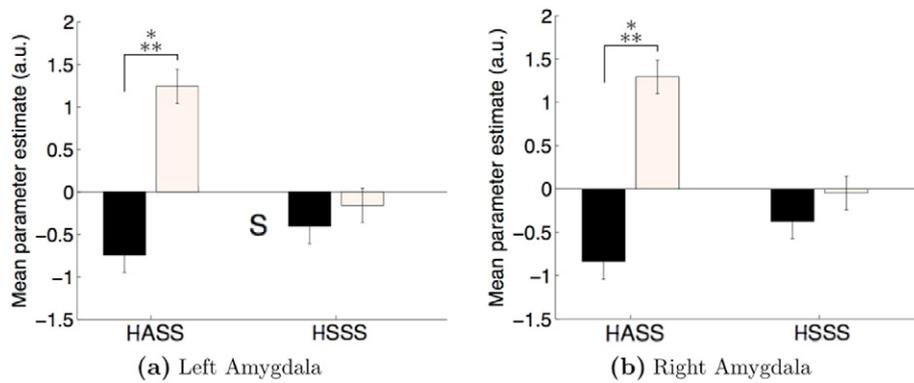
Fig. 1. The Effects of Alcohol on AMYG Activation to Negative Faces by Personality Group. Mean parameter estimates (arbitrary units) of mean activation (y-axes) to negative versus neutral faces within the left (a) and right (b) AMYG by personality group (High Anxiety Sensitivity Subjects [HASSS] and High Sensation Seeking Subjects [HSSS]; x-axes) under the under alcohol (dark bars) and placebo (light bars) conditions. Significant condition × personality interaction effects were indicated by 3-way mixed-design ANOVAs and survived alpha adjustment to correct for multiple comparisons. ***$P \leq 0.001$ (paired t-test). Error bars indicate SEM. For values, see eTable 3 in the Supplement.

also a condition-by-personality interaction on the same performance outcome measure ($F_{(1,37)} = 16.38$, $P < 0.001$, $\eta p^2 = 0.307$), with the HAS group performing better under alcohol (M = 28.99, SE = 3.02) relative to placebo (M = 34.56, SE = 3.14) condition ($t_{(19)} = 3.18$, $P = 0.005$) and the HSS group performing worse (respectively, M = 35.60, SE = 2.90 and M = 36.98 SE = 3.01; $t_{(21)} = -2.55$, $P = 0.019$).

3.1.2.2. Subjective Mood Results. Under placebo, there was a main effect of time on stress-related increments in self-rated embarrassment ($F(1,32) = 11.16$, $P = 0.002$, $\eta p^2 = 0.259$) and anger ($F(1,32) = 29.37$, $P < 0.001$, $\eta p^2 = 0.497$) from pre- to post-manipulation. There was also a personality-by-sex interaction effect on the changes in subjective embarrassment ($F(1,32) = 4.74$, $P = 0.037$, $\eta p^2 = 0.129$), with a significant increase being shown by the HSSM subgroup ($t_{(18)} = 3.02$, $P = 0.003$). No effects of condition or an interaction were statically significant.

3.1.2.3. Endocrine Results. Personality and personality-by-sex interaction effects on cortisol AUCi under placebo stood out ($F_{(1,36)} = 9.49$, $P = 0.004$, $\eta p^2 = 0.209$ and $F_{(1,36)} = 6.75$, $P = 0.014$, $\eta p^2 = 0.158$, respectively), with greater physiological responsiveness being seen in HASS (M = 0.35 nmol/l, SD = 1.22) compared with HSSS (M = −0.52 nmol/l, SD = 0.74) and in HASMS than HASFS (eFigure 5 in the Supplement).

Cortisol AUCi also showed condition-by-personality and condition-by-personality-by-sex interaction effects ($F_{(1,34)} = 7.83$, $P = 0.040$, $\eta p^2 = 0.12$; and $F_{(1,34)} = 7.83$, $P = 0.008$, $\eta p^2 = 0.19$, respectively), with a decrease seen in HASS, especially males, and an increase in HSS participants, especially males, under alcohol relative to placebo (eFigure 6 in the Supplement). Correlational analyses revealed that cortisol AUCi under placebo, in the entire sample combined, was uniquely

correlated with MIST-elicited increments in embarrassment ($r(33) = 0.69$, $P < 0.001$; eFigure 5 in the Supplement), but no psychoendocrine covariance was detected under alcohol.

3.1.2.4. fMRI Results. In response to the Stress − NonStress contrast under placebo, ROI analyses found a personality-by-sex interaction effect on bilateral mOFC activity (L: $F_{(1,38)} = 9.16$; $P = 0.004$, $\eta p^2 = 0.194$; R: $F_{(1,38)} = 7.01$, $P = 0.012$, $\eta p^2 = 0.156$), with HSSMS showing stronger activation that HASMS and HSSFS (eFigure 7 in the Supplement). A condition-by-personality interaction effect in the left mOFC activity was also revealed ($F_{(1,37)} = 5.95$, $P < 0.020$, $\eta p^2 = 0.139$) and mainly driven by the HSS group, who showed statistically decreased activation under the alcohol (M = −0.29, SE = 0.22) compared with placebo (M = 0.14, SE = 0.22) condition ($t_{(21)} = -3.14$, $P = 0.005$), as opposed to HAS who exhibited no significant changes ($P > 0.6$). A condition-by-personality-by-sex interaction effect was also present within the bilateral mOFC (L: $F_{(1,37)} = 24.12$, $P < 0.001$, $\eta p^2 = 0.395$; R: $F_{(1,36)} = 20.04$, $P < 0.001$, $\eta p^2 = 0.358$), pgACC (L: $F_{(1,37)} = 8.53$, $P = 0.006$, $\eta p^2 = 0.187$; R: $F_{(1,37)} = 16.82$, $P < 0.001$, $\eta p^2 = 0.312$) and NAc (L: $F_{(1,37)} = 9.11$, $P = 0.005$, $\eta p^2 = 0.198$; R: $F_{(1,37)} = 9.34$, $P = 0.004$, $\eta p^2 = 0.202$; Fig. 3). These 3-way interactions were mainly driven by male subjects, with alcohol compared with placebo increasing activity in the bilateral mOFC (L: $t_{(10)} = 4.05$, $P = 0.002$; R: $t_{(10)} = 4.034$, $P = 0.002$), right pgACC ($t_{(10)} = 3.15$, $P = 0.010$) and bilateral NAc (L: $t_{(10)} = 2.34$ $P = 0.041$; R: $t_{(10)} = 2.60$, $P = 0.027$) in HASMS, and decreasing bilateral mOFC responses in HSSMS (L: $t_{(12)} = 4.96$, $P < 0.001$; R: $t_{(12)} = 3.64$, $P = 0.003$). Mean condition differences for the subgroups are displayed in eTable 5 in the Supplement. Exploratory whole-brain analyses yielded no significant results.
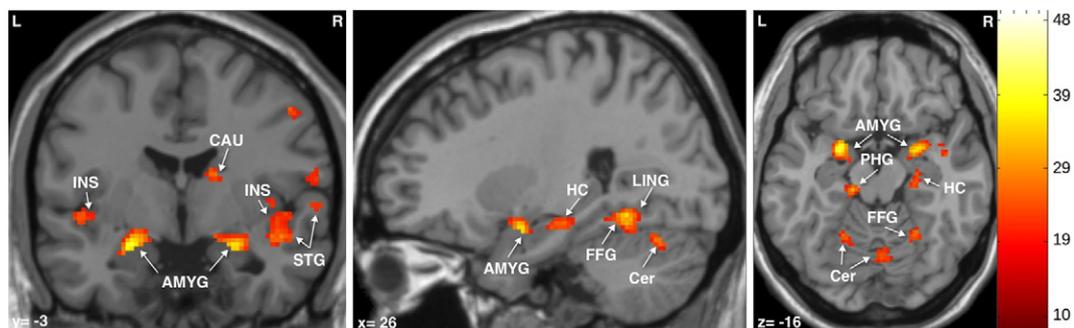

Fig. 2. Alcohol-by-personality interaction effect on regional brain activation to emotional (− neutral) faces. The main effects of alcohol were observed in, among other areas, core limbic structures (e.g., AMYG, HC and thalamus), the FFG, PHG, MCC and ACC. In comparison, the condition-by-personality interaction effect was more localized to core limbic regions, other sub-cortical sites (e.g., caudate) and the insular cortex. x, y, z = sagittal, coronal and horizontal view in MNI coordinates. The color map represents the corresponding F-value (see eTable, in the Supplement). L and R indicate, respectively, the left and right sides of the brain; AMYG, amygdala; CAU, caudate; INS, insula; PrecG, precentral gyrus; HC, hippocampus.
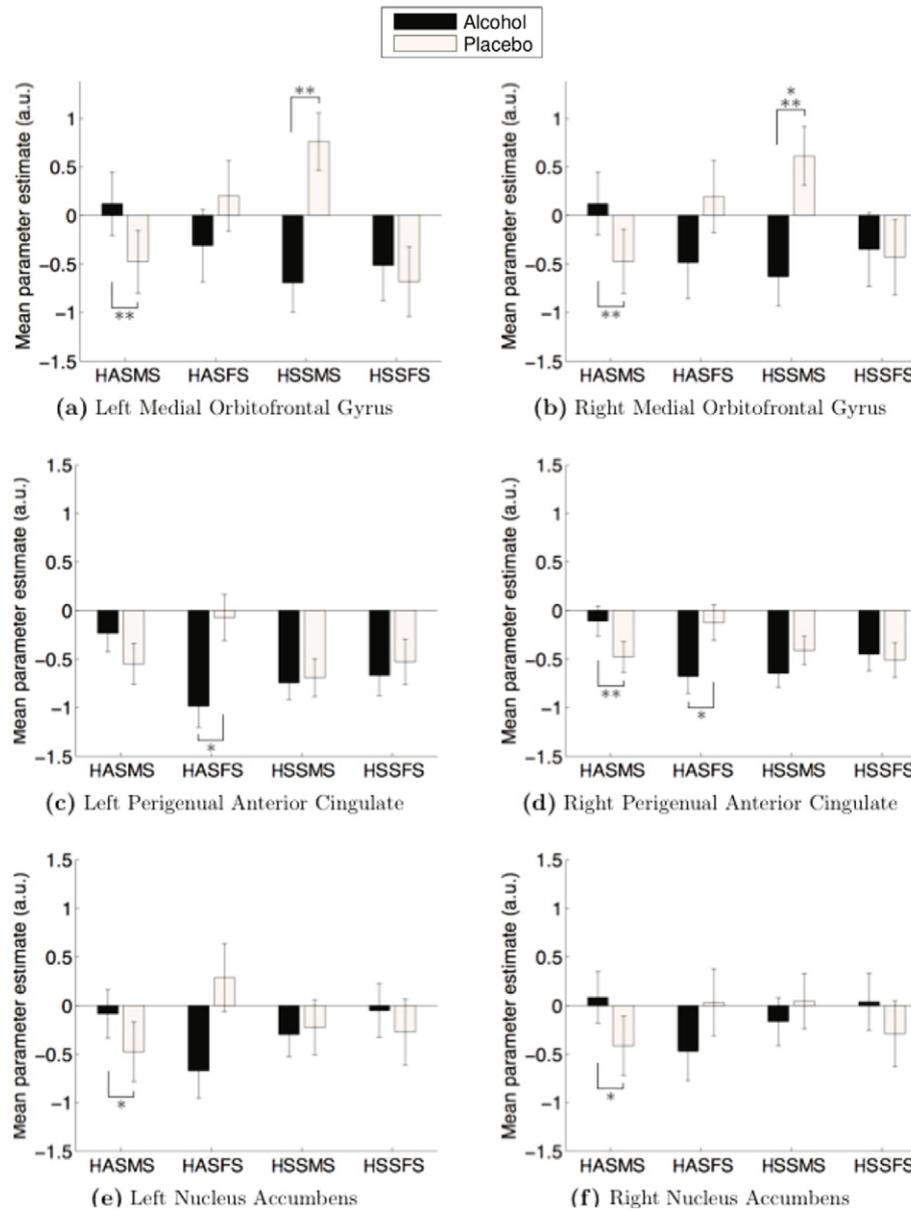
Fig. 3. The Effects of Alcohol on mOFC, pgACC and NAc Activation to Acute Social Stress. *a–d* Means of parameter estimate activity (*y*-axes) of the, respectively, left and right mOFC (*a–b*) pgACC (*c–d*) and NAc (*e–f*) under stress versus nonstress conditions in high anxiety-sensitivity male and female subjects (respectively, HASMS and HASFS) and high sensation0seeking male and female subjects (respectively, HSSMS and HSSFS) subjects (*x*-axes) under alcohol (dark bars) and placebo (light bars). Means for alcohol are BAC-adjusted. All of three ROIs, bilaterally, showed significant condition-by-personality-by-sex effects. *$P \leq 0.05$, **$P \leq 0.0125$ and ***$P \leq 0.001$.

3.2. Phase II: Predicting Outcome at Follow-up.

The eTable 6 in the Supplement displays the demographic characteristics and scores on baseline self-report measures for the TRA and non-TRA subjects by personality group. The HSS TRA subgroup showed male preponderance and both TRA subgroups showed a higher prevalence of familial AUDs. Because of these group differences, biological sex and familial AUDs were covaried for in all subsequent analyses.

3.2.1. FEPT

3.2.1.1. ROI Analyses. There was a significant condition-by-personality-by-transitioning status effect in the bilateral AMYG (L: $F_{(1,26)} = 7.40$, $P = 0.011$, $\eta p^2 = 0.222$; R: $F_{(1,26)} = 3.52$, $P = 0.026$, $\eta p^2 = 0.176$, Fig. 4). This 3-way interaction was mainly driven by HAS, especially HAS TRAs in whom the alcohol vs. placebo effect was most

pronouncedly significant, in the AMYG, particularly the right hemisphere (eTable 7 in the Supplement).

Hierarchical linear regression analyses performed on the HAS group showed that adding the alcohol vs. placebo contrast in left and right AMYG activation to the model covarying for sex and familial AUDs increased the predictive capacity of the model from (respectively) 27.3% to 63.9% (R Square change = 0.336, $t = -0.363$, $P = 0.003$) and from 16.9% to 60.4% (R Square change = 0.331, $t = -0.30$, $P = 0.006$). Meaning, 33.6% and 33.1% of the variance in transitioning status within the HAS group was predicted by the contrast between alcohol and placebo in the (respectively) left and right AMYG activation to the NEG-NEU face contrast.

3.2.2. Mist

3.2.2.1. ROI Analyses. ROIs analyses found a condition-by-transitioning status-by-personality effect on the bilateral mOFC activation to acute
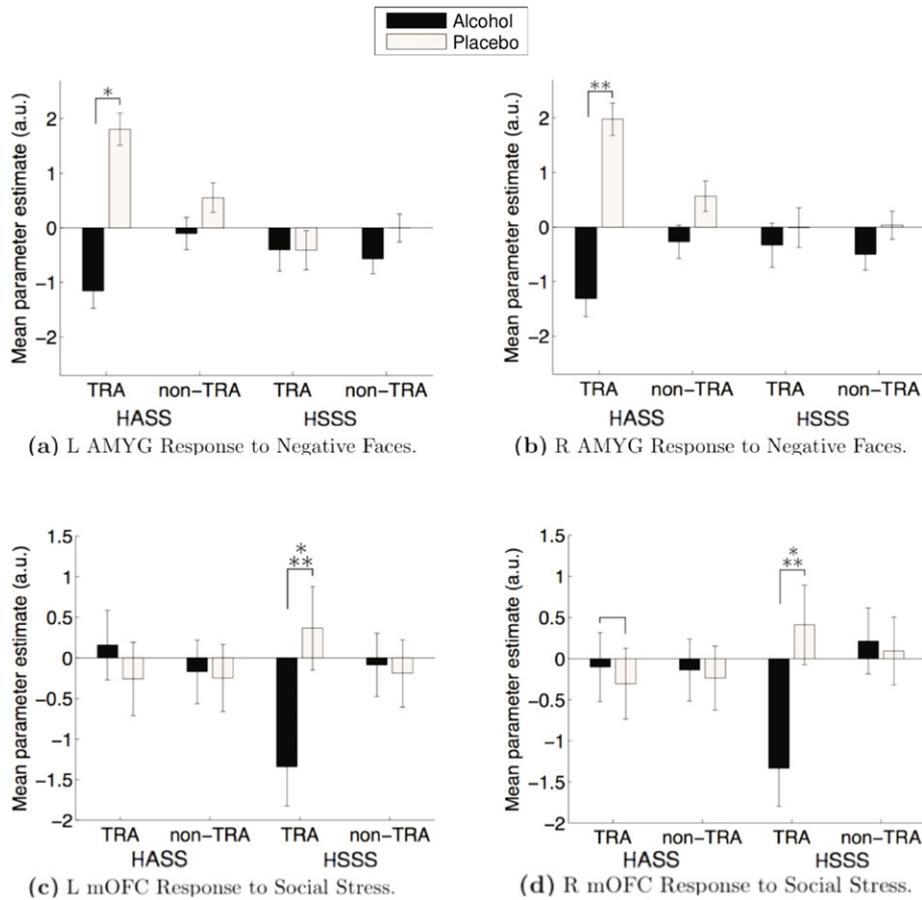
Fig. 4. Prospective Association Between ROI Activations to Emotionally Challenging Material and Escalating Alcohol and/or Illicit Drug Use. a–d, Mean parameter estimates (arbitrary units) of AMYG activity in response to negative (fearful, angry, disgusted and sad) vs. neutral faces (a–b) and mOFC activity in response to acute social stress vs. a control condition (c-d) in high anxiety-sensitivity subjects (HASS) and high sensation-seeking subjects (HSSS) who classified as transitioners (TRA) and non-transitioners (non-TRA) to substance use problems within 3 years after the fMRI testing under alcohol (dark bars) and placebo (light bars) conditions. **$P \leq 0.0125$ (Bonferroni adjusted alpha); *$P \leq 0.02$. Error bars indicate SEM.

social stress (L: $F_{(1,27)} = 10.11$, $P = 0.004$, $\eta p^2 = 0.273$ and R: $F_{(1,26)} = 8.27$, $P = 0.008$, $\eta p^2 = 0.235$). This 3-way interaction was mainly driven by HSS-TRAs, the only subgroup in which the contrast in the mOFC activity between the testing conditions was statistically significant (Fig. 3, eTable 8 in the Supplement).

Hierarchical linear regression analyses performed on HSS showed that adding the alcohol vs. placebo contrast in left and right mOFC activation to the model covarying for sex and familial AUDs increased the predictive capacity of the model from (respectively) 18.6% to 52.0% (R Square change = 0.334, F Change = 8.35, $P = 0.014$) and from 16.3% to 45.8% (R Square change = 0.295, F Change = 5.98, $P = 0.032$), respectively. Meaning, 33.4% and 29.5% of the variance in transitioning status within the HSS group was predicted was predicted by the contrast between alcohol and placebo in the (respectively) left and right mOFC activation to the MIST Stress − NonStress contrast.

4. Discussion

To our knowledge, this is the first study to characterize ethanol-induced neurobiological responses to emotionally challenging stimuli in distinct personality risk pathways for AUDs. It also provides the first evidence that personality-specific brain regional activations to drug ingestion predict escalating substance use at follow-up. The predictive power was relatively large, above and beyond that provided by other measured risk factors.

In the HAS group only, threatening stimuli activated the AMYG and these responses were reversed by alcohol. These changes were statistically significant using both ROI and stringently corrected voxel-wise

analyses. Previous fMRI studies have identified ethanol-induced attenuations of AMYG (Gilman et al., 2008, 2012a; Sripada et al., 2011) and, less prominently, aINS (Gilman et al., 2008; Padula et al., 2011) activations during threatening face processing when testing healthy adults not differentiated by personality risk factors and using less stringent statistical thresholds (Gilman et al., 2008, 2012a; Sripada et al., 2011). Together with the present results, these findings support proposals that a subgroup of drinkers with high threat sensitivity has distinct emotional and neurobiological responses to alcohol ingestion.

It is notable that the aforementioned changes in fMRI when HASS were under the influence of alcohol co-occurred with an increased tendency to mistake negative faces expressions for neutral. According to several theoretical accounts of alcohol use, acute alcohol intoxication attenuates fear and bring an perceived and/or actual relief from aversive affect by impairing recognition accuracy of threatening faces (Borrill et al., 1987), and hampering attention to and negative appraisal/perceived salience of the socio-emotional threat cues (Gilman et al., 2008, 2012a; Gorka et al., 2013; Stevens et al., 2008, 2009).

Our behavioral observation of alcohol-induced disruption of negative face emotion identification accuracy compatible with these models and empirical evidence supporting them, or aspects thereof. For example, showed that alcohol has been found to be more robustly anxiolytic when ingested before exposure to, and thus prior to appraisal of, stressors or threat signals than after (Sayette et al., 2001), with indications that this might be especially or specifically true when the aversive stimulus is temporally unpredictable, and the threat it signals, uncertain (Moberg and Curtin, 2009; Hefner and Curtin, 2012).

Personality trait specific effects were also seen during the performance-based social stress task. Exposure to the MIST, under placebo, activated the mOFC in HSSMS, but not other subgroups. Following alcohol ingestion, the MIST (Dedovic et al., 2005) increased mOFC, pgACC and NAc activity in HASMS and decreased the mOFC response in HSS, especially males. These brain regional effects of ethanol co-varied with increased vs. decreased physiological responsiveness to the MIST in HASMS vs. HSSMS, and improved vs. hindered task performance in HAS and HSS, respectively. Together, these personality trait specific effects support the existence of distinct risk pathways for AUDs (Conrod et al., 1998; Stewart and Kushner, 2001; Pihl and Peterson, 1995) and might help explain why ethanol has not been consistently found to either dampen stress and defensive reactivity (Cappell, 1987)or risky decision making and aggressivity (Gilman et al., 2012b). The stimulatory effect on HPAA activation shown by HSSMS resonates with evidence derived from human and animal studies suggesting that that for certain subjects, stimulation of the stress systems along with resultant increase in glucocorticoid secretion could suggest that alcohol acted as an energizer and euphoriant (Piazza et al., 1993; Deroche et al., 1993). In this framework, the present endocrine findings could be seen as lending further support to the sensation-seeking hypothesis, which predicts that inherent hypoarousal leads to the deliberate seeking-out of substances of abuse in order to increase arousal (Goeders, 2003; Koob and Kreek, 2007).

The regions engaged for each risk pathway are of interest given the associated personality traits. The mOFC influences the regulation of negative affective states (LeDoux, 2015), including approach-oriented anger (Coccaro et al., 2007). Its deactivation during exposure to the MIST (Pruessner et al., 2008; Dedovic et al., 2009) and comparable forms of anxiety-evoking paradigms (Wang et al., 2005) has been found in healthy volunteers, frequently in association with elevated cortisol release (Pruessner et al., 2008), and the response is thought to be stress-related, potentially diminishing the ability to cope effectively (Pruessner et al., 2008; Wang et al., 2005). Strikingly, in the present study HSSMS exhibited the converse response: exposure to the MIST increased mOFC activity, and this effect was reversed by ethanol ingestion. Since the HSS participants who exhibited the largest ethanol-induced decrease had substance use problems at follow-up, these findings support the supposition that vulnerable HSS individuals might be distinguished by their susceptibility to alcohol-heightened dyscontrol over ill-advised impulses, perhaps especially during emotionally challenging conditions (Pihl and Sutton, 2009).

The HAS participants were distinguished most clearly by hyper-reactive AMYG responses to the negative faces, potentially reflecting difficulty disengaging from threat signals when sober (Blackford et al., 2013). Exaggerated AMYG activations to emotional faces have been recently linked to disordered drinking via anxious, depressive symptomatology (Nikolova et al., 2016). The present study extends these observations with the finding that ethanol ingestion reversed this AMYG response preferentially in those who developed escalated alcohol use at follow-up. Studies in laboratory animals suggest that stress and drug cue-induced activations of the AMYG foster the attractiveness of drug related cues (Stringfield et al., 2016), perhaps much as other negative states can enhance the incentive salience of food (Dickinson and Balleine, 1994) and heroin-paired (Hutcheson et al., 2001) cues.

The present results should be considered in light of the following. Despite their internal consistency, they will require replication in larger and more randomly selected samples, and should be interpreted in the context of several limitations, including sample attrition at follow-up and not controlling for menstrual cycle phase. It also remains unclear whether the identified prospective associations are bidirectional, reverse or better explained by a third factor. Notwithstanding, this study adds to the evidence that there are distinct premorbid risk pathways for AUDs, and identifies for the first time risk pathway specific differences in alcohol-induced brain responses during emotional challenges that predict, over 2–3 years, escalations in alcohol and other drug use. AUD subtypes might benefit from pathway-specific interventions.

Conflicts of Interest

The authors declare no conflict of interest.

Funding

Author Contribution

Malak Abu Shakra, Robert Pihl, Marco Leyton, Alain Dagher and Jens Pruessner contributed to the initial study design. Malak Abu Shakra and Hussein Moghnieh contributed to the data analyses. All listed authors contributed to the manuscript writing, literature search, and final approval of the manuscript. All authors contributed to data interpretation.

Acknowledgment

Appendix A. Supplementary Data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ebiom.2017.11.025.

References

Blackford, J.U., Allen, A.H., Cowan, R.L., Avery, S.N., 2013. Amygdala and hippocampus fail to habituate to faces in individuals with an inhibited temperament. Soc. Cogn. Affect. Neurosci. 8 (2), 143–150.

Borrill, J.A., Rosen, B.K., Summerfield, A.B., 1987. The influence of alcohol on judgement of facial expressions of emotion. Br. J. Med. Psychol. 60 (1), 71–77.

Britt, J.P., Benalioud, F., McDevitt, R.A., Stuber, G.D., Wise, R.A., Bonci, A., 2012. Synaptic and behavioral profile of multiple glutamatergic inputs to the nucleus accumbens. Neuron 76 (4), 790–803.

Cappell, H., 1987. Alcohol and tension reduction: what's new. Stress and Addiction. Brunner/Mazel, New York.

Coccaro, E.F., McCloskey, M.S., Fitzgerald, D.A., Phan, K.L., 2007. Amygdala and orbitofrontal reactivity to social threat in individuals with impulsive aggression. Biol. Psychiatry 62 (2), 168–178.

Conrod, P.J., Pihl, R.O., Vassileva, J., 1998. Differential sensitivity to alcohol reinforcement in groups of men at risk for distinct alcoholism subtypes. Alcohol. Clin. Exp. Res. 22 (3), 585–597.

Dedovic, K., Renwick, R., Mahani, N.K., Engert, V., Lupien, S.J., Pruessner, J.C., 2005. The Montreal Imaging Stress Task: using functional imaging to investigate the effects of perceiving and processing psychosocial stress in the human brain. J. Psychiatry Neurosci. 30 (5), 319.

Dedovic, K., Rexroth, M., Wolff, E., et al., 2009. Neural correlates of processing stressful information: an event-related fMRI study. Brain Res. 1293, 49–60.

Deroche, V., Piazza, P.V., Le Moal, M., Simon, H., 1993. Individual differences in the psychomotor effects of morphine are predicted by reactivity to novelty and influenced by corticosterone secretion. Brain Res. 623 (2), 341–344.

Dickinson, A., Balleine, B., 1994. Motivational control of goal-directed action. Learn. Behav. 22 (1), 1–18.

Gilman, J.M., Ramchandani, V.A., Davis, M.B., Bjork, J.M., Hommer, D.W., 2008. Why we like to drink: a functional magnetic resonance imaging study of the rewarding and anxiolytic effects of alcohol. J. Neurosci. 28 (18), 4583–4591.

Gilman, J.M., Ramchandani, V.A., Crouss, T., Hommer, D.W., 2012a. Subjective and neural responses to intravenous alcohol in young adults with light and heavy drinking patterns. Neuropsychopharmacology 37 (2), 467–477.

Gilman, J.M., Smith, A.R., Ramchandani, V.A., Momenan, R., Hommer, D.W., 2012b. The effect of intravenous alcohol on the neural correlates of risky decision making in healthy social drinkers. Addict. Biol. 17 (2), 465–478.

Goeders, N.E., 2003. The impact of stress on addiction. Eur. Neuropsychopharmacol. 13 (6), 435–441.

Gorka, S.M., Fitzgerald, D.A., King, A.C., Phan, K.L., 2013. Alcohol attenuates amygdala–frontal connectivity during processing social signals in heavy social drinkers. Psychopharmacology 229 (1), 141–154.

Haber, S., Kim, K., Mailly, P., Calzavara, R., 2006. Reward-related cortical inputs define a large striatal region in primates that Interface with associative cortical connections, providing a substrate for incentive-based learning. J. Neurosci. 26 (32), 8368–8376.

Hefner, K.R., Curtin, J.J., 2012. Alcohol stress response dampening: selective reduction of anxiety in the face of uncertain threat. J. Psychopharmacol. 26 (2), 232–244.

Hutcheson, D., Everitt, B., Robbins, T., Dickinson, A., 2001. The role of withdrawal in heroin addiction: enhances reward or promotes avoidance? Nat. Neurosci. 4 (9), 943–947.

Koob, G., Kreek, M.J., 2007. Stress, dysregulation of drug reward pathways, and the transition to drug dependence. Am. J. Psychiatry.

LeDoux, J., 2015. Anxious: The Modern Mind in the Age of Anxiety. Oneworld Publications.

Leyton, M., 2017. Altered dopamine transmission as a familial risk trait for addictions. Curr. Opin. Behav. Sci. 13, 130–138.

Lundqvist, D., Flykt, A., Öhman, A., 1998. The Karolinska directed emotional faces (KDEF). CD ROM from Department of Clinical Neuroscience, Psychology Section. Karolinska Institutet, pp. 91–630.

Moberg, C.A., Curtin, J.J., 2009. Alcohol selectively reduces anxiety but not fear: startle response during unpredictable versus predictable threat. J. Abnorm. Psychol. 118 (2), 335.

Mujica-Parodi, L., Carlson, J.M., Cha, J., Rubin, D., 2014. The fine line between 'brave' and 'reckless': amygdala reactivity and regulation predict recognition of risk. NeuroImage 103, 1–9.

Nikolova, Y.S., Knodt, A.R., Radtke, S.R., Hariri, A.R., 2016. Divergent responses of the amygdala and ventral striatum predict stress-related problem drinking in young adults: possible differential markers of affective and impulsive pathways of risk for alcohol use disorder. Mol. Psychiatry 21 (3), 348–356.

Padula, C., Simmons, A., Matthews, S., et al., 2011. Alcohol attenuates activation in the bilateral anterior insula during an emotional processing task: a pilot study. Alcohol Alcohol. 46 (5), 547–552.

Piazza, P.V., Deroche, V., Deminiere, J.-M., Maccari, S., Le Moal, M., Simon, H., 1993. Corticosterone in the range of stress-induced levels possesses reinforcing properties: implications for sensation-seeking behaviors. Proc. Natl. Acad. Sci. 90 (24), 11738–11742.

Pihl, R.O., Peterson, J.B., 1995. Alcoholism: the role of different motivational systems. J. Psychiatry Neurosci. 20 (5), 372.

Pihl, R.O., Sutton, R., 2009. Drugs and aggression readily mix; so what now? Subst. Use Misuse 44 (9–10), 1188–1203.

Price, J.L., 2007. Definition of the orbital cortex in relation to specific connections with limbic and visceral structures and other cortical regions. Ann. N. Y. Acad. Sci. 1121 (1), 54–71.

Pruessner, J., Dedovic, K., Khalili-Mahani, N., et al., 2008. Deactivation of the limbic system during acute psychosocial stress: evidence from positron emission tomography and functional magnetic resonance imaging studies. Biol. Psychiatry 63 (2), 234–240.

Reiss, S., Peterson, R., Gursky, D., McNally, R., 1986. Anxiety sensitivity, anxiety frequency and the prediction of fearfulness. Behav. Res. Ther. 24 (1), 1–8.

Sayette, M.A., Martin, C.S., Perrott, M.A., Wertz, J.M., Hufford, M.R., 2001. A test of the appraisal-disruption model of alcohol and stress. J. Stud. Alcohol 62 (2), 247–256.

Sripada, C.S., Angstadt, M., McNamara, P., King, A.C., Phan, K.L., 2011. Effects of alcohol on brain responses to social signals of threat in humans. NeuroImage 55 (1), 371–380.

Stein, M.B., Simmons, A.N., Feinstein, J.S., Paulus, M.P., 2007. Increased amygdala and insula activation during emotion processing in anxiety-prone subjects. Am. J. Psychiatry 164 (2), 318–327.

Stevens, S., Gerlach, A.L., Rist, F., 2008. Effects of alcohol on ratings of emotional facial expressions in social phobics. J. Anxiety Disord. 22 (6), 940–948.

Stevens, S., Rist, F., Gerlach, A.L., 2009. Influence of alcohol on the processing of emotional facial expressions in individuals with social phobia. Br. J. Clin. Psychol. 48 (2), 125–140.

Stewart, S.H., Kushner, M.G., 2001. Introduction to the special issue on anxiety sensitivity and addictive behaviors. Addict. Behav. 26 (6), 775–785.

Stringfield, S.J., Higginbotham, J.A., Fuchs, R.A., 2016. Requisite role of basolateral amygdala glucocorticoid receptor stimulation in drug context-induced cocaine-seeking behavior. Int. J. Neuropsychopharmacol. 19 (12), pyw073.

Wang, J., Rao, H., Wetmore, G.S., et al., 2005. Perfusion functional MRI reveals cerebral blood flow pattern under psychological stress. Proc. Natl. Acad. Sci. U. S. A. 102 (49), 17804–17809.

Zuckerman, M., 1979. Sensation Seeking; beyond the Optimal Level of Arousal. Lawrence Erlbaum Associates, Hillsdale, NJ.