Biological Psychology 92 (2013) 282–291

Contents lists available at SciVerse ScienceDirect

Biological Psychology

journal homepage: www.elsevier.com/locate/biopsycho

Differential brain response to alcohol cue distractors across stages of alcohol dependence

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ARTICLE INFO

Article history:
Received 12 June 2012
Accepted 12 October 2012
Available online 3 November 2012

Keywords:
Abstinence
Alcoholism
Amygdala
Anterior cingulate
Cognitive control
Distraction
Inferior parietal lobule

ABSTRACT

Altered attention to alcohol-related cues is implicated in the craving and relapse cycle characteristic of alcohol dependence (ALC). Prior cue reactivity studies typically invoke explicit attention to alcohol cues, so the neural response underlying incidental cue exposure remains unclear. Here, we embed infrequent, task-irrelevant alcohol and non-alcohol cues in an attention-demanding task, enabling evaluation of brain responses to distracting alcohol cues. Alcohol dependent individuals, across illness phase ($n = 44$), and controls ($n = 20$) performed a cue-reactivity fMRI target detection task. Significant Group-by-Distractor effects were observed in dorsal anterior cingulate cortex (ACC), inferior parietal lobule, and amygdala. Controls and long-term abstainers increased recruitment of attention and cognitive control regions, while recent and long-term abstainers decreased limbic recruitment to alcohol distractors. Across phases of ALC, self-reported craving positively correlated with cue-related activations in ventral ACC, medial prefrontal cortex, and cerebellum. Results indicate that brain responses elicited by incidental alcohol cues differentiate phases of ALC.

1. Introduction

Alcohol dependence (ALC) is a chronic condition, characterized by repeated cycles of anticipation, binge/intoxication, and withdrawal (Koob and Volkow, 2010). Drug craving is a prominent feature of the anticipatory stage of the addictive cycle. Attention to alcohol-related environmental cues is associated with heightened craving for alcohol in individuals with ALC (Field and Cox, 2008). Cue-induced craving is thought to be an important mechanism involved in the development and maintenance of ALC, as well as a potential antecedent to relapse in recovering alcoholics (Koob and Volkow, 2010). Accordingly, craving plays a central role in the incentive-sensitization theory of addiction, which holds that with repeated use, drugs of abuse and their associated stimuli (i.e., cues) become imbued with salience, leading to hypersensitizing changes in mesolimbic dopaminergic signaling, which then perpetuate the addictive cycle (Robinson and Berridge, 1993).

Functional magnetic resonance imaging (fMRI) has been helpful in characterizing the neuroanatomical regions that subserve alcohol craving. A widely used cue-reactivity task design presents participants with alcohol-related sensory stimuli during MRI acquisition (Bragulat et al., 2008; Braus et al., 2001; Filbey et al., 2008; George et al., 2001; Grüsser et al., 2004; Heinz et al., 2007; Kareken et al., 2004; Myrick et al., 2004; Schneider et al., 2001; Tapert et al., 2003, 2004; Vollstadt-Klein et al., 2010, 2011; Wrase et al., 2002, 2007). The anterior cingulate (ACC), medial prefrontal (PFC), and orbitofrontal cortices, striatum and amygdala are among the most consistent regions to show increased activation to alcohol cues (vs. control conditions) in individuals with ALC (Heinz et al., 2009), though quantitative meta-analysis of existing cue reactivity studies suggests that mesolimbic and prefrontal response to alcohol cues may not distinguish individuals with ALC from controls (Schacht et al., in press). Reduced ventral striatal D2 receptor binding observed via PET positively related to ACC and medial PFC cortical fMRI activation to alcohol cues and to self-reported craving in individuals with ALC (Heinz et al., 2004). These findings suggest that alterations in PFC regions along with increased dopaminergic signaling in the striatum, may result in pathological processing of drug cues that is reflected in the subjective experience of craving. Cue reactivity studies examining other substances of abuse have

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http://dx.doi.org/10.1016/j.biopsycho.2012.10.004

implicated similar neuroanatomy, and many of these brain areas, including PFC (orbitofrontal, medial and cingulate regions), basolateral amygdala, insula and hippocampus, form a circuit thought to subserve the anticipatory stages of drug use (Koob and Volkow, 2010).

Most prior fMRI cue reactivity studies of alcohol have involved blocked task designs with relatively long cue presentation (typically up to several seconds per stimulus) (Bragulat et al., 2008; Braus et al., 2001; Filbey et al., 2008; George et al., 2001; Grüsser et al., 2004; Kareken et al., 2004; Myrick et al., 2004; Schneider et al., 2001; Tapert et al., 2003, 2004; Vollstadt-Klein et al., 2010, 2011; Wrase et al., 2002), often with explicit instructions for subjects to attend to alcohol cues. To facilitate craving phenomena, some studies have used a pre-task cue induction strategy such as providing participants with a priming sip of alcohol (George et al., 2001; Myrick et al., 2004). While the prior fMRI cue reactivity literature has been informative, the presence of "demand characteristics," in which the investigator's aims are relatively transparent to study participants, may complicate this work. In the context of demand characteristics, study participants may invoke different response strategies, including (i) attempting to "crave" in order to comply with perceived investigator expectations, or (ii) attempting to suppress craving in order to make a good impression or appear in control of responses to alcohol. Moreover, demand characteristics may interact with clinical stage of ALC. For example, recovering ALC patients, who are maintaining abstinence from alcohol, may have developed strategies to suppress or minimize craving responses, whereas currently drinking alcoholics may not feel ambivalent about allowing themselves to crave. In this study, we sought to minimize the role of demand characteristics by investigating brain responses to infrequent, task-irrelevant alcohol cues that represent distractors in the context of a primary attention-demanding target detection task. Accordingly, we developed a modified cue reactivity paradigm in which low-probability non-target distractors (alcohol and non-alcohol beverage pictures) were embedded within a visual oddball target detection task, similar to the emotional oddball paradigms developed by McCarthy and colleagues to evaluate brain responses to affective distractors during cognitive performance (Fichtenholtz et al., 2004; Wang et al., 2005, 2008; Yamasaki et al., 2002). This task enabled us to examine brain responses to alcohol cues in the context of cognitive-affective processing interactions.

Because alcohol-related brain alterations may be subject to repair and/or reorganization during periods of abstinence (Crews et al., 2005), functional brain responses to alcohol cues may depend on whether an individual is currently drinking, in early recovery, or in sustained remission. Therefore, in addition to healthy controls, we recruited subjects at three different clinical stages of alcoholism (current drinkers, recent abstainers, and long-term abstainers). Based on previous research suggesting partial reversal of ALC-associated brain damage with abstinence (Crews et al., 2005), our overarching hypothesis was that brain response to task-irrelevant alcohol distractors would differ among the three ALC groups in regions relevant for attentional and affective processing of transient distractors, with the long-term abstinent group most closely resembling healthy control response patterns. However, we also evaluated the alternative possibility that individual subjective craving ratings of alcohol cues would be a determinant of variation in cue-elicited brain activations, by conducting a correlational analysis of self-reported craving and brain response to alcohol cues, collapsed across ALC clinical stage.

2. Materials and methods

2.1. Participants

Four groups of participants (ages 21–60) were included in this study: Current Drinkers (CD, $n = 16$) were non-treatment seeking; Recent Abstainers (RA, $n = 15$) were undergoing treatment for ALC; Long-term Abstainers (LTA; $n = 13$) were maintaining sustained ALC recovery; Healthy Comparisons (HC; $n = 20$) had no history of ALC. CD, RA, and LTA participants met DSM-IV-TR (American Psychiatric Association, 2000) ALC criteria, with the following course specifiers: CD met criteria for continuous ALC (mean last use 1.7 days); RA last used alcohol within 5–30 days (mean last use 20.5 days); and LTA met criteria for sustained full remission, with a minimum of 1 year since last alcohol use (mean last use 1989.0 days). The Structured Clinical Interview for DSM-IV (SCID) (First et al., 2002) was used to confirm a diagnosis of ALC in LTA, RA, and CD groups and to document a negative history of exclusionary psychiatric disorders in all participants. Participants were excluded for meeting lifetime DSM-IV-TR criteria for schizophrenia and other psychotic disorders, post-traumatic stress, obsessive–compulsive, panic, and somatoform disorders. Current or past depressive disorder, substance-induced mood disorder, and past (i.e., not current) drug abuse or dependence were permitted in the ALC groups, based on the high co-morbidity between ALC and these conditions (Hasin et al., 2007). In addition, history of delirium tremens or alcohol withdrawal seizures, neurological disease, head trauma with loss of consciousness, or other serious medical conditions were exclusionary. Patients experiencing acute alcohol withdrawal symptoms, defined by a Clinical Institute of Withdrawal Assessment-Revised (CIWA-Ar) score >8, (Sullivan et al., 1989) were not recruited. Current nicotine use was assessed with the Fagerström Test for Nicotine Dependence (Fagerström et al., 1990) and current depressive symptoms were assessed via the Beck Depression Inventory (BDI) (Beck et al., 1979).

Information related to time course of ALC and quantity/frequency of alcohol use was documented through multi-modal assessment based on participant report, clinical measures, treatment provider evaluation, and breathalyzer samples. In addition to SCID interview, the following assessment measures characterized alcohol dependence in ALC groups: Michigan Alcohol Screening Test (Selzer, 1971); Alcohol Dependence Scale (ADS) (Skinner and Horn, 1982); and Alcohol Craving Scale (ACS) (Krystal et al., 1994). Family history of ALC was determined by the Family History Assessment Module (Rice et al., 1995). Abstinence monitoring in the LTA group was further achieved by assessing alcohol use biomarkers (e.g., mean corpuscular volume, gamma-glutamyl transferase), which were reviewed by a study physician (D.H.M.). These biomarkers were not reviewed for RA or CD participants, due to their recency of heavy alcohol use. All participants were asked to refrain from alcohol and drug use for 18 h prior to assessment sessions, and confirmatory breathalyzer samples and urine toxicology screens were collected prior to data collection sessions.

Abstinent participants were recruited from hospital-based (RA) or outpatient (LTA) ALC treatment programs at the West Haven VA Hospital and the Connecticut Mental Health Center. HC and CD participants, and some LTA participants, were recruited from the local community. Written informed consent was obtained from study participants, under protocols approved by the Human Subjects Subcommittee of the VA Connecticut Healthcare System and the Human Investigations Committee of the Yale University School of Medicine.

2.2. fMRI task

Participants performed a visual oddball task that presented 4 trial types in an event-related design: frequents (80% of trials), infrequent targets (10% of trials), non-alcohol distractors (NAD; 5% of trials), and alcohol distractors (AD; 5% of trials). The frequent stimulus was a small blue circle and the target stimulus was a large blue circle. NAD stimuli were color photographs of non-alcoholic beverages (e.g., water, coffee, soda) and AD stimuli were color photographs of alcoholic beverages (e.g., beer, wine, liquor), which were drawn from photograph sets used in prior studies (George et al., 2001; Heinz et al., 2004) supplemented with stimuli developed for the current study. Participants were instructed to respond, via button press, to infrequent target stimuli and to withhold responses to all other stimuli. Trials were presented for 700 ms, with variable inter-stimulus interval (ISI) lengths of 300, 800, 1000, or 1300 ms. Target-to-Target median SOA was 12.5 s (minimum = 4.0 s; maximum = 47.5 s). AD-to-AD median SOA was 22.0 s (minimum = 2.0 s; maximum = 107.0 s). NAD-to-NAD median SOA was 21.8 s (minimum = 4.0 s; maximum = 79.0 s). Median SOA between any two distractor stimuli was 13.0 s (minimum = 2.0 s; maximum = 51.5 s). Task stimuli were inversely projected and viewed through a mirror on the head coil. Behavioral responses were recorded via a fiber-optic response pad. Target accuracy was defined as the percentage of targets that were correctly identified (hits), such that lower accuracy scores reflect omission errors. Commission error rates to both AD and NAD trial types were low across individuals (range: 0–2 errors) and were not subjected to analysis.

2.3. Post-scanner picture rating task

Study participants rated AD and NAD stimuli to assess beverage identification accuracy and elicited craving. For each beverage stimulus, participants were asked to identify the beverage type (possible responses: alcohol, non-alcohol, or unsure). Next, participants answered four questions related to craving for that beverage, each rated on a seven-point Likert scale (see Fig. 1). Mean craving ratings were constructed for AD and NAD stimuli, with higher scores reflecting greater craving. Based on accuracy of responses to the post-scan beverage identification task, 6 alcohol and 6 non-alcohol beverage stimuli were declared ambiguous because