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Blunted amygdala functional connectivity during a stress task in alcohol dependent individuals: A pilot study

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ABSTRACT

Background: Scant research has been conducted on neural mechanisms underlying stress processing in individuals with alcohol dependence (AD). We examined neural substrates of stress in AD individuals compared with controls using an fMRI task previously shown to induce stress, assessing amygdala functional connectivity to medial prefrontal cortex (mPFC).

Materials and methods: For this novel pilot study, 10 abstinent AD individuals and 11 controls completed a modified Trier stress task while undergoing fMRI acquisition. The amygdala was used as a seed region for whole-brain seed-based functional connectivity analysis.

Results: After controlling for family-wise error ($p = 0.05$), there was significantly decreased left and right amygdala connectivity with frontal (specifically mPFC), temporal, parietal, and cerebellar regions. Subjective stress, but not craving, increased from pre-to post-task.

Conclusions: This study demonstrated decreased connectivity between the amygdala and regions important for stress and emotional processing in long-term abstinent individuals with AD. These results suggest aberrant stress processing in individuals with AD even after lengthy periods of abstinence.

1. Introduction

Experience of early stressful life events significantly increases the odds of developing alcohol dependence (AD) (Pilowsky et al., 2009), and recent stress increases alcohol consumption in the short- and long-term (Vlahov et al., 2002, 2004). In Koob's and colleagues' (Koob and Volkow, 2010; Koob and Le Moal, 1997) three-stage model of addiction, stress is hypothesized to play several key roles. For example, in the second "withdrawal and negative affect" stage, stress increases withdrawal effects through release of corticotropin-releasing factor (CRF) and norepinephrine in the extended amygdala—a brain region comprised of the bed nucleus of the stria terminalis, the central nucleus of the amygdala, and the shell subregion of the nucleus accumbens (Koob and Volkow, 2010). Subsequent to this withdrawal phase, the third stage is further influenced by stress, which often leads to relapse. Importantly, Koob and colleagues hypothesize that addiction leads to an overall allostatic shift, a readjustment of hedonic response as a result of repeated and compulsive drug use and over-compensating by the stress response system (Koob and Le Moal, 1997; Koob, 2013). As physiological adjustments occur, it may be that there are not enough resources available to effectively inhibit the stress response. Alternatively, the stress response may also become sensitized, making it easier to be triggered in response to a stressor.

The relationship between stress and AD is complex. Stress may predispose vulnerable individuals to develop alcohol problems (Koob and Kreek, 2007), with stress system dysfunction conversely being suggested as a consequence of AD (Adinoff et al., 2005). Individuals with AD are often characterized as having a blunted cortisol response (Lovallo et al., 2000) and elevated basal cortisol levels (Lovallo et al., 2000; Thayer et al., 2006), yet as Stephens and Wand (2012) point out, specific glucocorticoid supply levels differ depending on what stage in the addiction cycle an individual is in,

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amongst other factors. To date, only one known study specifically examined the neural response to stress in an AD sample (Seo et al., 2013). Results showed blunted activity in the ventromedial PFC and anterior cingulate cortex (ACC) during an idiographic stress script, with hyperactivity in the amygdala and other regions during a neutral script. Since recently abstinent AD individuals have a blunted cortisol response (Lovallo et al., 2000), they may have an altered response to a stressor as a result of an inhibited negative feedback loop. For example, connectivity between the amygdala and medial PFC (mPFC) may be important since the mPFC has been suggested to play a key role in controlling motivated behavior in alcohol consumption (George et al., 2012) as well as the mPFC being key to modulate the inhibitory response to stress in healthy individuals (Kern et al., 2008).

The present study investigated the effects of AD on amygdala functional connectivity during an fMRI stress task, given the important role proposed for the amygdala in the neurobiology of addiction (Koob and Volkow, 2010). It was hypothesized that abstinent AD subjects demonstrate decreased connectivity (George et al., 2012) between the amygdala and mPFC during the stress task, compared with controls.

2. Materials and methods

The present study analyzed data previously collected as part of a pilot imaging genetics study derived from two larger parent studies (NCT00226694, NCT01200901). Twenty-one participants (10 AD, 11 controls) were recruited from the original parent studies that examined hormonal changes with stress (for details see (Anthenelli et al., 2009)). Participants completed psychological questionnaires related to stress and trauma history and performed an fMRI stress task.

2.1. Participants

A total of 21 individuals (23-55 years-old) completed the fMRI stress task. Ten abstinent individuals with AD (6 females) were recruited from the parent study that examined endocrine and behavioral responses to pharmacological stressors (Anthenelli et al., 2009) (NCT00226694). Eleven non-depressed controls (6 females) were recruited from the community as part of a larger study examining stress and brain response in depression (NCT01200901). The IRBs at the University of Cincinnati and Cincinnati Veterans Affairs Medical Center approved all aspects of the study, and all participants provided written informed consent.

AD participants met lifetime DSM-IV-TR criteria for AD in sustained or early full remission and were in treatment when they enrolled in the parent study. Participants were abstinent from all substances except for tobacco for at least one month prior to the MRI session. AD participants had largely maintained abstinence since their participation in the parent study, as measured by Timeline Follow-Back, though only one month of abstinence was required for this pilot imaging study. Although current PTSD was exclusionary, sub-threshold symptoms of PTSD and history of trauma were not. Controls had no history of any Axis I or Axis II disorders, including substance use disorders (SUD). Current use of psychotropic medication; lifetime history of serious neurologic injuries or disorders; severe medical illness; diagnosis of an independent Axis I anxiety, mood or psychotic disorder (or Axis II personality disorder in controls); use of oral contraceptives; current pregnancy or lactation in women; or MRI contraindications were exclusionary in both groups. Recent (past several days) abstinence from substance use was confirmed by drug toxicology testing (DrugTestStrips.com™12 Panel drug test), and breathalyzer (FC10 Breath Alcohol Tester® to verify 0.000 BAC) in AD individuals.

2.2. Procedure

Eligible participants were consented to this phase of the study, and Timeline Follow-Back (TLFB) data were collected to fill in alcohol and drug use from the parent study's conclusion to the present study. Women underwent urine pregnancy testing. All participants were given psychological questionnaires to assess mood and trauma history. Participants then completed the neuroimaging protocol.

2.3. Measures

2.3.1. Stress and craving measures

Subjective stress and craving for alcohol was measured by calculating change scores from baseline (initial moments in the scanner) to post-scan (immediately after the stress task) with participants rating their level subjective stress and craving on a 100-point scale.

2.4. Data acquisition

Imaging was conducted at the University of Cincinnati's Center for Imaging Research, using a 4.0 T Varian, Unity INOVA Whole Body MRI/MRS System (Varian, Inc., Palo Alto, CA). To provide an anatomical reference for the fMRI data, a T1-weighted, 3-D anatomical brain scan was first obtained using a modified driven equilibrium Fourier transform sequence (T_{MD} = 1.1 s, TR = 13 ms, TE = 6 ms, FOV = 25.6 × 19.2 × 19.2 cm, matrix 256 × 192 x 96 pixels, flip angle = 20°, 15″). fMRI scans were acquired using an RF-spoiled FAST 3-D acquisition technique. Functional images were collected while performing the stress task using a T2*-weighted gradient-echo echoplanar imaging (EPI) pulse sequence (TR/TE = 2000/30 ms, FOV = 25.6 × 25.6 cm, matrix 64 × 64 pixels, slice-thickness = 4 mm, flip angle = 75°, 35 slices in coronal orientation). Sixteen minutes of the hour-long scan were dedicated to the control (5 min) and stress tasks (11 min), respectively (see *fMRI Stress Task* below). A neuroradiologist assessed each scan for brain abnormalities and found none.

2.5. Amygdala mask

Automated left and right amygdala masks were created for each subject, and then hand nudged to more accurately reflect neuroanatomy.

2.6. fMRI stress task

Stress was induced through a variation on the Trier Social Stress Test (TSST) (Allendorfer et al., 2014; Kirschbaum et al., 1993). The task includes two math components; a stress-inducing test and a "control" test. The control task (not used in the present study) was first and included 60 different basic subtraction problems. They then completed the stress task, which consisted of 80 subtraction problems that were considerably more difficult and contained three possible answers rather than two. As this task was about to begin, participants saw a video on their goggles worn into the scanner of two confederate "doctors" sitting in the scanner console room. Participants were told these "experimenters," who introduced themselves as doctors, would be rating them and giving feedback on their performance (six different pre-recorded messages that informed them they were not performing up to the task, regardless of their actual performance). Participants were also told that they would have between 1 and 5 s to answer each question, but would not be told how long was left. If they went over the allotted time, their answer would not count. Finally, participants