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Corticotropin-Releasing Factor receptor 1 (CRF1) antagonism in patients with alcohol use disorder and high anxiety levels: effect on neural response during Trier Social Stress Test video feedback

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In preclinical models of alcohol use disorder, the corticotropin-releasing factor (CRF) receptor is upregulated, particularly in the extended amygdala. This upregulation is thought to play a role in stress-induced relapse to drinking by a mechanism that is independent of the hypothalamic-pituitary-adrenal axis. As part of a double-blind, placebo-controlled clinical study with pexacerfont, a selective, orally available, and brain-penetrant CRF1 receptor antagonist which has anti-anxiety effects in preclinical studies, we examined the effect of pexacerfont on the neural response to a social stress task adapted to fMRI. Subjects were 39 individuals (4 women) with high trait anxiety and moderate to severe alcohol use disorder randomized to receive pexacerfont or placebo. The task involved feedback of videoclips of an individual performing the Trier Social Stress Test. Pexacerfont had no effect on the neural response to self-observation under stress. The neural response to viewing oneself under stress vs an unknown other under stress activated prefrontal brain regions including insula, inferior frontal gyrus as well as medial, superior frontal gyri. These regions of activation overlap with those found in studies using similar paradigms. Potential applications of this task to probe neurocircuitry that is disrupted in addiction is discussed.

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INTRODUCTION

In preclinical models of alcohol use disorder (AUD) [1], the corticotropin-releasing factor-1 (CRF1) receptor is upregulated, particularly in the extended amygdala which contains extrahypothalamic CRF neurons located in the bed nucleus of the stria terminalis and central nucleus of the amygdala [2]. This upregulation is thought to play a role in stress-induced relapse to drinking by a mechanism that is independent of the hypothalamic–pituitary–adrenal (HPA) axis [3, 4]. This effect is most pronounced in animals with high levels of anxiety-like behavior [3].

CRF1 receptor antagonists have been evaluated in clinical populations with anxiety and depression with largely negative results [5, 6]. Central administration of a CRF1 receptor antagonist blocked alcohol withdrawal-induced anxiety in rodents [7]. Peripheral administration of a CRF1 receptor antagonist reduced alcohol self-administration in a rodent model of alcohol dependence and in rats genetically bred to prefer alcohol [8]. It also blocked reinstatement of stress-induced alcohol seeking in these two animal models related to AUD [8]. The effect of CRH1 antagonists to reduce these stress-induced behaviors is independent of the HPA axis [9, 10].

In patients with moderate to severe AUD [1] and high trait anxiety, Kwako et al. conducted a double-blind, placebo-controlled clinical study with pexacerfont [11]. The aim was to investigate whether pexacerfont, reduced stress-induced craving for alcohol. Stress was induced with two laboratory procedures: the Trier Social Stress Test (TSST) [12] and with personalized stress scripts [13]. Pexacerfont did not reduce subjective stress or craving reported as a consequence of these two laboratory stress provocations [11]. The drug also had no effect on blood-oxygen level dependent (BOLD) responses to alcohol cues or affective [fearful vs neutral stimuli from the International Affective Picture System (IAPS) [14]]. Pexacerfont, consistent with preclinical studies, did not reduce HPA-related biomarkers which are reliably activated in the TSST such as plasma cortisol or adrenocorticotropic hormone (ACTH), and did not affect these markers in the dexamethasone/CRF stimulation test.

Notwithstanding the absence of a drug effect on these aforementioned outcomes, the TSST itself (regardless of drug condition: pexacerfont or placebo), produced a robust stress response with significant plasma cortisol and ACTH concentration elevations over baseline 20 min after the TSST. Accordingly, there

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was a significant elevation in subjective stress response as measured by the Subjective Units of Distress Scale (SUDS; [15]) at 20 min post-TSST and in alcohol craving as measured by the Alcohol Urge Questionnaire (AUQ; [16]) at 40 min post-TSST. These results are consistent with the large body of literature reporting that the TSST is a reliable laboratory paradigm for stress induction as measured by these objective and self-report measures.

We previously developed an fMRI task that involved video feedback of oneself performing the TSST during fMRI scanning [17]. This task combines self-referential processing under conditions of stress compared to viewing an unknown other under the same stress conditions (TSST). Task-based connectivity on similar tasks with the amygdala as a seed was sensitive to treatment for anxiety [18] and for predicting levels of clinical anxiety [19]. We examined whether there was an effect of pexacerfont on BOLD response to viewing SELF vs OTHER during the TSST among individuals with moderate to severe AUD and high trait anxiety. Since the putative mechanism of the CRH1 receptor antagonist, pexacerfont, dampens CRF-induced upregulation in the extended amygdala in AUD, we investigated whether pexacerfont modulated the neural response during this self-referential processing task using a seed-based analysis with right/left amygdala as a region of interest (ROI). Further, we explored, as regions of interest, other brain areas known to be activated in self-referential processing [20], anterior cingulate cortex (ACC), left, right inferior frontal gyrus (IFG)/insula. Of note, these were the regions we found to be robustly activated in the SELF vs OTHER contrast in our previous study of this task [17]. We also investigated whether neural modulation was related to the magnitude of the stress response while performing the actual TSST as measured by cortisol, ACTH, and subjective report of stress and of alcohol craving.

METHODS

Participants

Methods have been reported previously [11]. We report here the results from the subset of subjects from the parent study [11] who completed the TSST and fMRI sessions with the TSST video feedback task ($N = 39$; 4 female). For subject characteristics, see Table 1. Trait anxiety was assessed with the Spielberger State Trait Anxiety Inventory-Trait version (STAI-T; [21]; the study inclusion criterion score for this instrument was a STAI-T score >39. There were no significant group differences in age or scores on the Addiction Severity Index (ASI) [22], Childhood Trauma Questionnaire (CTQ) [23], Neuroticism factor of the NEO Personality Inventory-Revised (NEO; [24] or Spielberger State-Trait Anxiety Inventory-Trait Version (STAI-T) [21] between the pexacerfont and placebo groups(Table 1). Subjects were right-handed and diagnosed with alcohol dependence (AD) (DSM-IV) [25] which is equivalent to moderate to severe AUD [1]. Participants were excluded if they had other significant psychiatric or medical disorders. Informed consent was obtained as approved by the NIH Institutional Review Board. Details of eligibility criteria are provided at http://www.clinicaltrials.gov/ct2/show/NCT01227980.

Table 1. Demographic characteristics of subjects by drug group.

	Pexacerfont	Placebo	Total
Number	19	20	39
Age (years)	42.8 ± 9.9	44.8 ± 8.8	43.8 ± 9.2
Gender(m/f)	16/3	19/2	35/5
Race (Caucasian)	8	2	10
ASI Score	2.0 ± 0.6	2.1 ± 0.5	2.0 ± 0.5
CTQ Total Score	45.1 ± 22.5	38.8 ± 15.7	41.9 ± 19.2
STAIT Score	56.2 ± 9.4	52.2 ± 5.4	54.1 ± 7.8
N Factor Score	59.5 ± 12.6	57.3 ± 8.3	58.3 ± 10.4

ASI Addiction Severity Index; [22] *CTQ* Childhood Trauma Questionnaire; [23] *STAI-T* Spielberger State/Trait Anxiety Inventory-Trait version [21]. Scores and age are expressed as mean (±SD).

Study drug administration

Subjects were randomized to pexacerfont or matched placebo, which was administered for 30 days. They received a loading dose of 300 mg of pexacerfont given once daily for the first 7 days, followed by 100 mg once daily for 23 days, or placebo. A separate pharmacokinetic (PK) study was conducted using this dosing regimen in which cerebrospinal fluid was sampled in steady state in a group of healthy volunteers; data were presented in the parent study. PK modeling based on this study provided support for >90% central CRF1 receptor occupancy. All participants remained hospitalized throughout the study and were simultaneously in standard inpatient treatment for AUD.

TSST and cue reactivity session (TSST/CR)

Stress induction was achieved in the laboratory using the TSST. This procedure took place on Day 18. The TSST was immediately followed by an alcohol cue reactivity (CR) session. The TSST consisted of the subject delivering a 5-min oral presentation in front of a panel of unfamiliar individuals. Then subjects were instructed to carry out mental arithmetic (serial subtraction) for 5 min. The TSST was videotaped for the fMRI task. Throughout the TSST/CR session, subjective anxiety was rated with the SUDS and alcohol craving was rated with the AUQ. The endocrine response (ACTH and cortisol) was measured with serial blood draws every 10 min from −20 to 90 min. approximately.

fMRI task

The video feedback task for the TSST was similar to that described previously [17]. Audio-visual recordings were reviewed and edited into 30 s video clips, numbering 7. These video clips were chosen during periods when participants appeared uncomfortable or were making errors. Seven similar clips were obtained from a volunteer "other" who was unknown to the participant and who was the same gender and race as the participant. Clips were chosen from "other" during periods where the subject's performance was unremarkable to avoid the confound of an empathetic or envious response to another's performance. The fMRI task consisted of random alternating presentation in fixed order of SELF and OTHER videoclips, each of 30 s duration, totaling 7-SELF and 7-OTHER video clips for a total imaging time of 900 s (15 min).

fMRI scanning session

Scanning session took place on Day 23 of the study. Three other tasks were conducted in this session involving stimuli from the International Affective Picture System, alcohol cues and emotional faces and are reported elsewhere [11]. The order of presentation of the four tasks was randomized across participants. Subjects underwent an fMRI scan on a 3 Tesla General Electric MRI Scanner using a standard quadrature head coil. The functional MRI (fMRI) scans consisted of 450 temporal (with TR, repetition, or sampling time, of 2 s or as previously mentioned a total time of 900 s) volumes ($64 \times 64 \times 36$) consisting of 3.8 mm thick slices with in-plane sampling of 3.75×3.75 mm using a T2* weighted echo planar sequence. Structural scans were acquired using a T1-weighted MP-RAGE sequence with $256 \times 256 \times 144$ voxels with 0.9375×0.9375 mm in plane sampling and slice thickness of 1 mm.

Analysis

All preprocessing and statistical tests on functional images were performed on an Apple Mac Pro 3.33 GHz 6-Core Intel Xeon computer using the Analysis of Functional NeuroImaging (AFNI) software package [26]. The functional images were blurred to a 6 mm full-width at half-maximum resolution (composed of intrinsic or acquired smoothing plus the application of a Gaussian smoothing filter of 4 mm) and slice-time corrected to account for difference in acquisition times between slices in each volume. Motion correction of the fMRI was done to the third temporal image (and 12 motion correction regressors from this correction were used in later statistical analyses). Also note that voxels showing spatial aligned temporal corrections greater than 0.3 mm where censored in later analyses. The fMRI volumetric sequence was then aligned to the MP-RAGE image and ultimately transformed to Talairach space.

For each subject, a voxel-wise generalized least squares time series fit was constructed using AFNI 3dREMLfit that included estimation of the temporal auto-correlation structure. A boxcar design corresponding to the 30 s trier stimulus intervals (AFNI BLOCK duration 30 and magnitude 1 option) convoluted with a standard hemodynamic transfer function (HTF) was used as the primary regressors as well as the previously mentioned motion regressors.

For Group analysis, 3dMVM [27], a group analysis program from AFNI that performs traditional ANOVA and ANCOVA style computations, was used. The resultant activation maps were presented in standard (Talairach) space and displayed as 3.5 × 3.5 × 3.5 mm voxels. The SELF versus OTHER contrast (SELF > OTHER) was tested at a per voxel *p* value of 0.0001 (all subjects combined regardless of drug group: pexacerfont or placebo). Then *t* tests were conducted comparing the SELF vs OTHER contrast for the pexacerfont group compared to the placebo group. To further help control for multiple voxel tests only voxel cluster sizes greater than 20 at cluster threshold of 0.05 were deemed significant.

In an exploratory analysis, we examined further the effect of Pexacerfont on the SELF > OTHER contrast by adding psychological characteristics to the model and examining whether there was an interaction between each of these measures and DRUG (pexacerfont vs Placebo) on SELF vs OTHER. The measures were addiction severity (ASI), history of childhood trauma (CTQ), Neuroticism (NEO-PR), trait anxiety (STAI-T), post-traumatic stress disorder symptom severity (PTSD Symptom Severity Interview—PSSI) [28].

Objective measures of stress (cortisol and ACTH), as well as subjective measures of alcohol craving (AUQ) and distress (SUDS) (all entered as peak change from baseline post-TSST), were entered as covariates in the SELF > OTHER analysis to determine whether the experienced stress during the actual TSST affected the neural response to viewing the SELF under stress.

For the ROI analysis, bilateral insula, left IFG, right IFG, ACC, left amygdala, right amygdala were ROIs. The p-values were determined for difference in average fMRI response in each ROI between drug conditions (pexacerfont vs placebo). ROIs were based on AFNI segmentation map re-sampled to fMRI grid for each subject. In addition, for each drug condition (pexacerfont or placebo), the correlation between BOLD activation in each ROI and psychometric/stress variable listed above were compared.

RESULTS

There was no significant effect of DRUG on BOLD response for the SELF > OTHER contrast. There was no significant DRUG x Psychological/Stress response interaction on SELF vs OTHER in the whole brain or ROI analyses. SELF > OTHER for the entire group, regardless of DRUG condition yielded significant activations in bilateral insula, superior, medial, and inferior frontal gyri (Table 2, Fig. 1). Covarying for psychological/stress response measures did not alter neural activation of the SELF vs OTHER contrast in the whole brain or ROI analyses (see Table 3 and Fig. 2 for cortisol covariate as an example).

DISCUSSION

We report here the neural response to viewing the self under stress in individuals with moderate-severe AUD with high trait anxiety. We found no effect of pexacerfont, a CRF1 receptor antagonist on this response. In addition, baseline psychological factors (addiction severity, trait anxiety, PTSD symptoms, childhood trauma, neuroticism) did not interact with the drug condition to affect the neural response to the observation of oneself under stress compared to an unknown other. The subjects experienced an objective and subjective stress response during the actual TSST [11] as exemplified by the significant elevation in plasma cortisol and ACTH as well as distress ratings compared to baseline at the 20-min timepoint (post-TSST). As we know from the original study [11], there was no drug effect on these TSST outcomes and during the dexamethasone/CRF stress test, there was also no effect of pexacerfont on either cortisol or ACTH plasma concentrations. This was not unexpected as CRF1 antagonists exert their anxiolytic, anti-stress effect in a manner independent of the HPA axis, perhaps by modulating neurocircuitry related to the extended amygdala.

Therefore, we wanted to explore whether pexacerfont may modulate the neural response to viewing oneself undergoing the TSST even though it did not modulate the peripheral HPA axis response provoked by the TSST in real time. We found that it did not, neither in whole brain nor in ROI analyses that included the amygdala. Similarly, in the parent study [11], there was no effect of pexacerfont on amygdala BOLD activation in response to fearful vs neutral faces. This latter brain region is where the CRF system is upregulated in AUD and where, theoretically, CRF1 antagonists exert their effect to suppress alcohol self-administration [reviewed in ref. [3]] in preclinical studies. Notwithstanding preclinical studies of alcohol self-administration in animal models of AUD, pexacerfont did not modulate biological markers of stress during the actual TSST [11] or neural activation during viewing oneself under stress as reported here.

Table 2. SELF > OTHER across all subjects showing cluster size, peak activation (t-statistic), and peak coordinate within each cluster (clusters greater than 20 voxels).

Region (Focus point)	Cluster size (voxels)	Peak value *t*	Peak coordinates within cluster (Talairach Atlas - AFNI) X	Y	Z
Right Medial Frontal Gyrus	249	7.3	2	31	31
Right Insula	139	7.3	40	17	3
Right Inferior Frontal Gyrus	51	8.0	47	6	24
Left Insula	35	6.7	−33	13	6
Right Superior Frontal Gyrus	22	5.9	5	10	59
Left Superior Frontal Gyrus	20	6.1	−26	41	27

Threshold set per voxel at $p \leq 0.0001$.

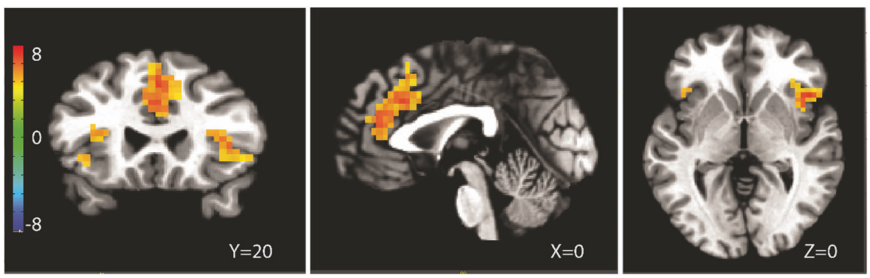

Fig. 1 SELF vs OTHER comparison. Representative activations of t-statistic for SELF minus OTHER comparison across all subjects showing activations in bilateral Cingulate Gyrus and Insula in three orthogonal slices. Color bar shows approximate t-statistical values.

Table 3. SELF minus OTHER with cortisol level as covariate, across all subjects showing cluster size, peak activation (t-statistic) and peak coordinate within each cluster (clusters greater than 20 voxels).

Region (Focus point)	Cluster Size (voxels)	Peak value *t*	Peak coordinates within cluster (Talairach Atlas - AFNI) X Y Z		
Left Cingulate Gyrus	206	6.9	−2	24	31
Right Insula	58	7.0	40	17	3
Right Inferior Frontal Gyrus	49	8.3	47	6	24
Right Superior Frontal Gyrus	37	6.2	36	48	17
Left Insula	26	6.2	−33	13	7

Threshold set per voxel at $p \leq 0.0001$.

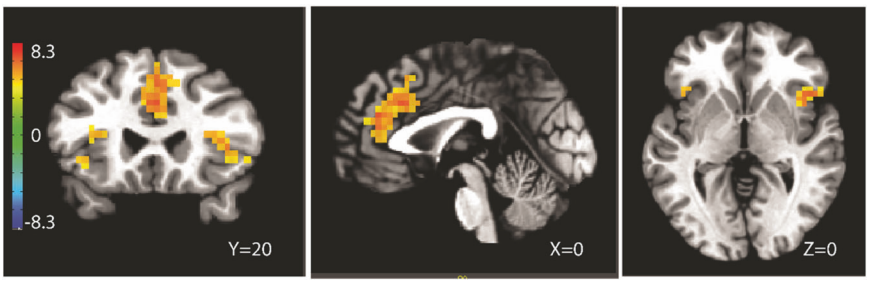

Fig. 2 SELF vs OTHER comparison with covariates. Representative activations of t-statistic for SELF minus OTHER comparison, with cortisol level as covariate, across all subjects showing activations in bilateral Cingulate Gyrus and Insula in three orthogonal slices. Color bar shows approximate t-statistical values.

A limitation of the present study is that we did not have subjective ratings of affect or stress during the fMRI video feedback task. We do know from our pilot study of this task in healthy controls [17] that the task did engender subjective report of stress where stress ratings viewing the SELF were significantly greater than viewing OTHER. Further, we previously reported gender differences in neural activation to SELF vs OTHER where males activated right insula/IFG as well as superior, middle frontal gyrus, cingulate gyrus to a greater degree than women while reporting less stress during the actual TSST. We were unable to examine gender differences in the SELF vs OTHER contrast in the present study due to the small number of women ($n = 4$), however, when we examined these outcomes in males only, the results were unchanged. Another limitation is that the sample size ($N = 50$) for the parent study which was calculated based on the effect size of naltrexone to reduce cue induced alcohol craving in a laboratory session. This may not be adequate to detect a pexacerfont effect on the neural response to the self under stress and further, the sample size for imaging from the parent study [11] was smaller, i.e., $N = 39$. Three other tasks were conducted with the task reported here, however, the order of the tasks was randomized across participants so as to minimize an order effect on task outcome. Lastly, we considered that since both the SELF and OTHER conditions included viewing a stress induction task (TSST), the neural response to the stress component of the task may have been diminished. Examining the effect of pexacerfont on the response to SELF vs baseline or OTHER vs baseline yielded no significant results.

Importantly, in this group of individuals with moderate-severe AUD with high trait anxiety, the brain regions activated while viewing the SELF versus an unknown OTHER under stress, overlap with those previously reported with this same task in healthy control subjects [17], namely prefrontal cortical and limbic regions, including the superior, medial, inferior frontal gyri as well as insula. These regions have been shown to be activated in a meta-analysis of self-face recognition apart from stress conditions [20]. In addition to the frontal lobes other brain regions are involved in self-recognition including regions of the parietal, temporal and occipital lobes [29]. While the regions found in the results of the present study overlap partially with those found in self-recognition/observation tasks that do not involve stress, the stress condition added to this study makes comparison difficult.

The effect of observing oneself vs another in pain vs no pain [30] significantly activated in similar brain regions reported in the present study: inferior and middle frontal gyri and insula. Self-observation in patients with social anxiety disorder (compared to controls) was associated with greater connectivity between insula and amygdala [18]. Activation in the insula and middle frontal gyrus during self-observation was also sensitive to social anxiety disorder treatment (cognitive behavioral therapy or acceptance commitment therapy), where the activation in these regions during self-observation decreased with treatment.

Self-observation is related to self-monitoring which is impaired in addiction [31]; the salience network, which mediates self-monitoring, is structurally [32, 33] and functionally [34–36] impaired in AUD. Targeting nodes in the salience network such as insula or ACC with noninvasive brain stimulation is a potential therapeutic approach for addiction [37]. This fMRI task robustly engages nodes in the salience network. Therefore, this kind of task could be used in conjunction with noninvasive brain stimulation approaches to activate targeted salience network nodes. Further, combining this task with alcohol/drug cue exposure could help to elucidate how drugs of addiction can shift salience and alter salience network functioning.

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AUTHOR CONTRIBUTIONS

MH, RM, LK, MRL designed experiments; LK, DTG performed experiments. DR, MRL analyzed data. MH, RM, LK, MRL, DTG, MRL wrote and edited the manuscript.

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COMPETING INTERESTS

MH is an Associate Editor for Neuropsychopharmacology. The other authors declare that they have no competing conflicts of interest.

ADDITIONAL INFORMATION

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