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Unseen scars: Cocaine patients with prior trauma evidence heightened resting state functional connectivity (RSFC) between the amygdala and limbic-striatal regions

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ABSTRACT

Background: Substance use disorder (SUD) patients with a history of trauma exhibit poorer treatment outcome, greater functional impairment and higher risk for relapse. Endorsement of prior trauma has, in several SUD populations, been linked to abnormal functional connectivity (FC) during task-based studies. We examined amygdala FC in the resting state (RS), testing for differences between cocaine patients with and without prior trauma.

Methods: Patients with cocaine use disorder (CUD; $n = 34$) were stabilized in an inpatient setting prior to a BOLD fMRI scan. Responses to Addiction Severity Index and the Mini-International Neuropsychiatric Interview were used to characterize the No-Trauma ($n = 16$) and Trauma ($n = 18$) groups. Seed-based RSFC was conducted using the right and left amygdala as regions of interest. Examination of amygdala RSFC was restricted to an *a priori* anatomical mask that incorporated nodes of the limbic-striatal motivational network.

Results: RSFC was compared for the Trauma versus No-Trauma groups. The Trauma group evidenced greater connectivity between the amygdala and the *a priori* limbic-striatal mask. Peaks within the statistically significant limbic-striatal mask included the amygdala, putamen, pallidum, caudate, thalamus, insula, hippocampus/parahippocampus, and brain stem.

Conclusions: Results suggest that cocaine patients with prior trauma (versus without) have heightened communication within nodes of the motivational network, even at rest. To our knowledge, this is the first fMRI study to examine amygdala RSFC among those with CUD and trauma history. Heightened RSFC intralimbic connectivity for the Trauma group may reflect a relapse-relevant brain vulnerability and a novel treatment target for this clinically-challenging population.

1. Introduction

Drug addiction is a vital public health concern that exacts a tremendous toll on the brain (Koob and Volkow, 2010; Volkow and Li, 2005). Interestingly, even when patients carry the same substance use disorder (SUD) diagnosis, there is much heterogeneity. Some individuals experience a lifelong struggle with addiction while others respond favorably to treatment. Elucidating the individual differences that underlie such striking variance is key to advancing treatment efforts. One critical factor to consider in understanding individual differences in SUD is prior trauma exposure, which is very common in addiction. As many as 60–90% of treatment seeking SUD patients have experienced a traumatic event (Brady et al., 2004; Farley et al., 2004; Jacobsen et al., 2001; Wu et al., 2010). Co-occurring SUDs and trauma associate with a number of functional impairments, greater rates of relapse, higher treatment costs, poorer outcomes (social functioning, treatment adherence, and drug use) than for those with SUD alone (Back et al., 2000; Driessen et al., 2008; Farley et al., 2004; Gil-Rivas et al., 2009; Norman et al., 2007; Ouimette et al., 2006; Sacks et al., 2008; Tarrier and Gregg, 2004; Tate et al., 2007; Young et al., 2005).

1.1. Trauma exposure and brain function

Certain brain regions are especially sensitive to the stress of trauma

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exposure. Neuroimaging research links traumatic stress to hyperactivity in the amygdala, a structure responsible for processing emotions, fear learning, and orchestrating reactions to environmental threats (Brown et al., 2014; Lanius et al., 2006). In addition to mediating fear responses, the amygdala processes motivational salience underlying reward relevant goals related to appetitive stimuli (Cunningham and Brosch, 2012). Broadly speaking, impairments observed following trauma exposure have been reflected in amygdala hyperactivity to biologically relevant motivational stimuli (i.e., appetitive or aversive).

1.2. Addiction and brain function

Parallel research within the field of addiction also underscores the importance of an over-responsive motivational neural network. For example, findings published by our own (Childress et al., 1999; Franklin et al., 2007; Langleben et al., 2008; Wetherill et al., 2014; Young et al., 2014) and other research laboratories (Chase et al., 2011; Kühn and Gallinat, 2011) examining addiction, have demonstrated that drug cues activate motivational-reward neural circuitry, including the amygdala. Accumulating research suggests that chronic stimulant use leads to mesolimbic hyper-responsiveness to drugs and drug cues as well as other evocative (appetitive and aversive) stimuli (Kalivas and Volkow, 2005; Koob and Volkow, 2010; Robinson and Berridge, 1993, 2008; Volkow et al., 2008; Wyvell and Berridge, 2001). The increased response to acute phasic stimuli (e.g., drugs, cues) may actually occur in the context of an overall down-regulation or tonic decrease of the motivational circuit (Hommer et al., 2011; Volkow et al., 2010, 2011).

1.3. Motivational circuitry: trauma and drugs of abuse

Alterations in the mesolimbic brain reward circuitry among chronic drug users (Goeders, 2003; Sinha, 2008; See and Waters, 2010; Bossert et al., 2013) and among trauma-exposed individuals (D'Angio et al., 1987; Sorg and Kalivas, 1991; Rougé-Pont et al., 1993) have striking parallels. Both animal (Packard, 2009; Packard and Goodman, 2012) and human (Schwabe and Wolf, 2009) studies demonstrate that acute stress causes the brain to focus on the most salient and proximal motivational stimulus (the stressor) – shifting attention and resources away from other flexible goal-directed behavior (Arnsten, 2009; Hermans et al., 2014). These findings have parallels in SUD populations; for example, cocaine patients exposed to stress show greater attentional bias toward drug cues (Tull et al., 2011), a highly salient motivational stimulus. Thus, exposure to trauma triggers activity within mesolimbic motivational circuits, enhancing the response to both aversive and appetitive stimuli (Hermans et al., 2014). Though these prior studies have used a "phasic" cue to probe the motivational circuitry, the current study complements this research by examining the "tonic" resting-state of this circuitry – without the use of an explicit cue.

Although prior studies have used positron emission tomography (PET) to examine resting regional perfusion in PTSD Veterans with cocaine and alcohol abuse history, the earlier technology did not permit assessment of dynamic functional connectivity among nodes of motivational neurocircuitry. These studies (Semple et al., 1996, 2000) detected increased resting perfusion in patients versus controls in the amygdala, but the difference was no longer significant after controlling for multiple comparisons. These early PET studies highlight the need for formal examination of amygdala resting-state functional connectivity (RSFC) with the new technology of BOLD fMRI.

1.4. Resting-State functional connectivity (RSFC)

Prior neuroscience research examining trauma exposure and drug addiction has often used provocation paradigms (e.g., exposure to appetitive drug or aversive fear stimuli). However, recent research highlights resting-state functional connectivity (RSFC) as a unique and complementary tool for understanding brain vulnerability. RSFC measures the strength of the temporal correlation of low-frequency blood oxygen level-dependent (BOLD) fluctuations between discrete anatomical regions (Biswal et al., 1995; Gusnard and Raichle, 2001) when individuals are *not engaged* in cognitively demanding tasks (e.g., instructed to close eyes and not think of anything in particular). RSFC confers an enhanced signal-to-noise ratio over traditional task-based designs, and may circumvent potential limitations of task-based studies (e.g., practice effects; Fox and Greicius, 2010). Importantly, RSFC can be used to distinguish distinctive brain states (McCabe and Mishor, 2011) and to distinguish individuals with and without psychiatric disorders, including SUDs (Sutherland et al., 2012; Whitfield-Gabrieli and Ford, 2012)

Previous RSFC studies have linked amygdala connectivity to prior trauma exposure and stress (Patel et al., 2012), with enhanced functional coupling of the amygdala with regions of the insula and anterior cingulate cortex (Brown et al., 2014; Sripada et al., 2012; Van Marle et al., 2010). Cocaine use disorder (CUD) patients also evidence "heightened coupling" of RSFC signatures, with the amygdala exhibiting stronger connectivity with nodes of the motivational circuitry including the caudate, putamen, nucleus accumbens, and insula (Contreras-Rodríguez et al., 2016; Gu et al., 2010; Konova et al., 2015). Though RSFC has promise for characterizing dysfunctional neural circuitry in addiction, the findings across CUD studies are not always consistent (Ma et al., 2015). Some of the inconsistences may be due to important historical variables such as trauma exposure, a relatively understudied variable in the context of brain imaging in CUD. Given the high frequency of trauma exposure among those with CUD, we plan to test RSFC in CUD patients with and without trauma. We hypothesize that CUD patients with prior trauma (versus those without) will evidence increased RSFC between the amygdala and nodes of the mesolimbic motivational circuitry (i.e., amygdala, caudate nucleus, putamen, pallidum, and insula). To our knowledge, this has not been previously examined.

2. Methods

2.1. Participants

Participants were 34 treatment-seeking, cocaine-dependent men, between 34 and 60 years of age, who met DSM-IV criteria for cocaine dependence, described smoking as their primary route of cocaine-crack administration, and reported using cocaine on at least 8 of the 30 days before screening (See Table 1 for demographics). Participants were recruited through advertisements in local media and were part of a larger study examining brain and behavioral vulnerabilities associated with addiction. After completing a detailed telephone screen, participants provided informed consent, were medically screened, and completed psychological assessment measures.

Exclusion criteria included: contraindications for fMRI (e.g., metal in the body, claustrophobia), use of medications affecting central dopaminergic neurotransmission, history of psychosis, seizures, or organic brain syndrome unrelated to cocaine use, clinically significant cardiovascular, hematologic, hepatic, renal, neurological, or endocrine abnormalities, history of head trauma or loss of consciousness for more than 3 min. Psychiatric diagnoses were based on the *Mini International Neuropsychiatric Interview* (MINI; Sheehan et al., 1998) and those diagnosed with comorbid Axis I disorders were excluded, with exception for dependence on nicotine, marijuana, or alcohol not requiring medical detoxification. Participants meeting diagnostic criteria for depression were not excluded if their diagnosis was linked solely to periods of cocaine use/cessation. This study adhered to the Declaration of Helsinki and was approved by the University of Pennsylvania Institutional Review Board.

Table 1
Demographics and Clinical Measures.

Characteristics	Entire Sample Value	Trauma Value	No-Trauma Value	Differences
Age (year), *n*	34	18	16	ns.
Mean (SD)	47.20(6.70)	47.38	47.00	
Range	34–60	34–60	34–59	
Years of Education, *n*	34	18	16	ns.
Mean (SD)	12.87 (1.86)	12.78 (2.13)	12.96 (1.57)	
Range	8.0–16.0	8.0–16.0	10–16	
Race/ethnicity, *n* (%)	34	18	16	ns.
White non-Hispanic	2 (5.9%)	0 (0%)	2 (12.5%	
African American	32 (94.1%)	18 (100%)	14 (87.5%)	
Psychiatric Diagnosis, *n* (%)	34	18	16	
MDD, Current	6 (17.6%)	6 (33.3%)	0 (0%)	*
MDD, Recurrent	4 (11.8%)	4 (22.2%)	0 (0%)	*
MDD, Recurrent Remitted	2 (5.9%)	1 (5.6%)	1 (6.3%)	ns.
Cannabis Dependence	4 (11.8%)	2 (11.1%)	2 (12.5%)	ns.
Years of Lifetime Use, *n*	34	18	16	ns.
Mean (SD)	19.36 (9.76)	21.72 (9.58)	16.72 (9.56)	
Range	2.0–38.0	5.0–38.0	2.0–30.0	
Days Used (in past 30), *n*	34	18	16	ns.
Mean (SD)	18.80 (7.92)	20.91 (5.63)	16.44 (9.52)	
Range	1.5–30	10.0–30.0	1.5–29.0	
Days Since Last Use, *n*	31	16	15	ns.
Mean (SD)	4.03 (3.96)	2.88 (1.85)	5.27 (5.17)	
Range	1–22	1–6	1–22	
Total PCL-C Score, *n*	34	18	16	**
Mean (SD)	34.29 (16.07)	42.50 (16.11)	25.06 (10.13)	
Range	17–69	17–69	17–48	
Total HAM-D Score, *n*	34	18	16	ns.
Mean (SD)	6.62 (5.87)	8.06 (5.83)	5.00 (5.62)	
Range	0–20	0–20	0–15	
Total BDI Score, *n*	32	16	16	ns.
Mean (SD)	9.72 (9.09)	10.81 (10.55)	8.63 (7.56)	
Range	0–31	0–31	0–23	
Total BAI Score, *n*	32	16	16	ns.
Mean (SD)	4.78 (5.72)	6.63 (6.70)	2.94 (3.95)	
Range	0–27	0–27	0–11	

Note. All group differences were assessed using independent samples T-Tests and Chi-Square.
MDD = Major Depressive Disorder; PCL-C = PTSD symptom checklist; HAM-A = Hamilton Rating Scale for Depression; BDI = Beck Depression Inventory; BAI = Beck Anxiety Inventory.
No group differences were observed for all group comparisons with exception for PCL-C scores, which were expected to differ between groups.
ns. = none significant differences.
*$p < 0.05$.
**$p < 0.01$.

2.2. Study design

Participants were stabilized in a supervised drug-free residential stabilization unit for 7–10 days prior to participating in a one-hour fMRI scanning session involving several experimental tasks including a BOLD resting state scan, which preceded the behavioral tasks. This controlled setting eliminates the impact of cocaine intoxication and minimizes the contribution of cessation symptoms to study measures.

2.3. Measures

Cocaine and other illicit drug use for the past 30 days were assessed with the *Addiction Severity Index* (ASI; McLellan et al., 1992) and the *Timeline Followback interview* (TLFB; Sobell and Sobell, 1992). Presence of psychiatric diagnosis was based on results from the MINI (Sheehan et al., 1998). To assess for recent anxiety and depression, additional measures included the *Beck Anxiety Inventory* (BAI; Leyfer et al., 2006), the Beck et al., 1996 Beck Depression Inventory (BDI; Beck, Steer, and Brown, 1996), and the clinician administered, *Hamilton Rating Scale for Depression* (HAM-D; Miller et al., 1985). The PTSD Checklist for Civilians (PCL-C; Weathers et al., 1993) was also administered to characterize symptoms that may accompany trauma exposure as a potential clinical validator for the Trauma subgroup. Participants completed measures during their initial screening assessment (PCL-C, MINI, ASI) and their baseline visit (BAI, BDI, HAM-D, TLFB).

2.4. fMRI acquisition

Functional MR imaging was conducted on a 3-T whole-body scanner (Siemens Tim Trio, Erlangen, Germany). High-resolution structural images were acquired for spatial brain normalization using a 3D magnetization prepared rapid gradient echo (MPRAGE) sequence (TR/TE/TI = 1620/3/950 ms). Images for the resting-scan were acquired during a 6-min scan using a gradient-echo-planar-imaging sequence (TR/TE = 2s/30 ms, FOV = 220 × 220 mm^2, matrix = 64 × 64, slice thickness = 4.5 mm, 150 images were acquired). Participants were asked to remain still with their eyes open and to not think about anything in particular during this scan.

Data preprocessing was carried out using Data Processing Assistant for Resting-State fMRI Basic Edition (DPARSF) and Data Processing and Analysis of Brain Imaging (REST) toolbox, based on SPM8 (http://www.fil.ion.ucl.ac.uk/spm) run under Matlab R2015 environment. In this paper, we followed the standard preprocessing pipeline still accounting for motion related artifacts. Each participants' images were slice-time corrected, realigned, coregistered to high-resolution structural images, and subsequently normalized to MNI standard space and smoothed with the FWHM kernel of 6 mm. Summary motion statistics for each subject were examined and confirmed the motion was below 2 mm in both directions. In addressing the head motion concerns, we regressed out Friston 24 head motion parameters which includes six head motion estimates from current time point (R_t = [X Y Z pitch roll

yaw]), six head motion parameters from immediately preceding time point (R_{t-1}) and their corresponding squares(R_t^2, R_{t-1}^2; Yan et al., 2013a,b). Given the concerns of the field (Power et al., 2012; Van Dijk et al., 2012; Satterthwaite et al., 2012; Yan et al., 2013a,b) about the impact of micro motion (as small as 0.2 mm) on resting functional connectivity, we additionally calculated mean Frame-by-Frame head displacement (FD; Power et al., 2012) to compare the two groups and for subsequent use as a nuisance covariate at the second level analysis (see below). Images were then detrended to remove linear trends due to scanner drift; band-pass filtered (0.01-0.1 Hz) to remove scanner and cardio-respiratory noise. Tissue based signals such as white matter, CSF and global signal were used as nuisance regressors to remove the sources of spurious variance and their temporal derivatives were also removed from the data through linear regression. Smoothed normalized images were entered into seed-based region of interest (ROI) analysis with amygdalae as seeds. A cross-correlation map was constructed by doing voxel-wise correlation between the temporal signals from both the right and left amygdala and each voxel in the brain. The right and left amygdalae were selected as ROIs (AAL atlas; Maldjian et al., 2003, 2004) based on prior work implicating their involvement in the pathophysiology of stress, trauma exposure, and addiction. We examined connectivity for each side of the amygdala separately, as the human literature has documented differences in anatomical connections for the left and right amygdala. The resulting correlation map from each participant was converted to Z map using Fisher's *r*-to-*z* transformation in order to improve the normality of the correlation coefficients (Press et al., 1992; Lowe et al., 1998). The Z maps were then analyzed in a random-effects model in SPM8 to reveal any differences in RSFC between the Trauma and No-Trauma subgroups (see below for trauma-status determination). In all the group analysis, mean FD was entered as a nuisance variable to control for participants' head motion.

Based on prior work (Regier et al., 2016), we further constrained the voxels that we queried in relation to the amygdala, based on a mask that includes mesolimbic regions (amygdala, ventral tegmental area/midbrain, ventral striatum, caudal orbitofrontal cortex), and three other addiction-relevant regions including the insula (Naqvi and Bechara, 2010), dorsal striatum (Everitt and Robbins, 2013), and thalamus (Asensio et al., 2010). The mask including our *a priori* ROIs, was created using Harvard-Oxford Cortical Structural Atlas (FMRI of the Brain [FMRIB] Software Library, Oxford Centre for FMIRB) with a probability threshold ranging between 10 and 25%. For the purposes of the current paper, this limbic mask is treated as the unit of analysis (a single region of interest). Individual sub-group maps were thresholded at FWE corrected, $p < 0.05$, and the group contrast maps are cluster corrected at $p < 0.05$ with 425 contiguous voxels based on the recently debugged version of 3dClustSim using autocorrelation function (ACF) option in AFNI_17.2.05. ACF was calculated by running 3dFWHMx on the residual image at group level.

2.5. Trauma versus No-Trauma subgroups

Of the 34 participants, 18 were designated to the "Trauma" group while 16 were designated as the "No-Trauma" group. Determination of trauma status was based on participants' response to two measures. The first was the ASI supplement − PTSD questionnaire (McLellan et al., 1992), which probes whether one has 'ever experienced something so frightening, horrible, or upsetting that others rarely go through'. Prior studies have used the ASI to measure trauma exposure (Najavits et al., 1998; Ouimette et al., 2000; Rosen et al., 2002; Pirard et al., 2005; Charney et al., 2007). Trauma status was further queried by participants' responses to the clinician administered MINI (Sheehan et al., 1998), which assesses for trauma exposure as a preliminary criterion for PTSD diagnosis. All participants in the Trauma group endorsed trauma exposure on both the MINI and ASI. It is worth noting that, while the parent study excluded Axis-I diagnosis including PTSD, Trauma participants in this study endorsed trauma exposure but did not meet criteria for PTSD.

3. Results

3.1. Group comparisons: behavioral assessments

3.1.1. Corroboration of trauma status

Importantly, individuals' PTSD symptom severity, assessed with PCL-C scores, was also examined for a potential corroboration of the trauma split. The Trauma group endorsed prior trauma and had elevated scores on the PCL-C ($M = 42.50$, $SD = 16.11$), relative to the No-Trauma group ($M = 25.06$, $SD = 10.13$; $(t(32) = -3.72$, $p = 0.001)$, as would be expected (see Table 1). Scores on the PCL-C range from 17 to 85 with higher scores reflecting increased PTSD symptom severity.

3.1.2. Demographic comparisons

Trauma and No-Trauma groups did not differ on any demographic measures, clinician administered measures, self-report measures, or substance use severity measures, with exception for diagnosis of Major Depressive Disorder (MDD). Significant group differences were observed for diagnosis of MDD, Current ($\chi(1) = 6.476$, $p = 0.011$) and Recurrent ($\chi(1) = 4.030$, $p = 0.045$) with the trauma group evidencing greater prevalence of MDD diagnoses.

3.2. Group comparisons: resting-State functional connectivity (RSFC)

Our analyses focused on an intralimbic mask in order to limit our observations to interconnected nodes within our *a priori* limbic-striatal hypotheses. While both the No-Trauma and Trauma groups exhibited positive connectivity between amygdala and interconnected nodes within our limbic-striatal mask (See Fig. 1, top panel), formal statistical comparison revealed significant differences in connectivity between the groups (See Fig. 1, bottom panel). As shown, the Trauma group evidenced significantly greater positive connectivity between the amygdala and limbic-striatal regions (threshold as detailed above in Methods). For the left amygdala, peaks within the limbic-striatal mask (See Fig. 1, bottom panel and Table 2) included amygdala, putamen, caudate, pallidum, insula, hippocampus, and brain stem (not shown). For the right amygdala, peaks within the limbic-striatal mask included these same regions (See Fig. 1, bottom panel and Table 2) with exception for the brain stem and the addition of thalamus and parahippocampus. There was an absence of inverse connectivity patterns between the amygdala and any regions included in the limbic-striatal mask.

4. Discussion

4.1. Summary of findings

RSFC maps of the Trauma and No-Trauma groups evidenced similar overall patterns of amygdala connectivity with limbic-striatal regions. However, our findings indicate that CUD patients with trauma, relative to no trauma, evidenced enhanced amygdala RSFC with limbic-striatal regions. To our knowledge, this study is the first to examine RSFC among those with CUD and trauma history. Data presented here may help to identify a vulnerability phenotype, as trauma-exposed SUD patients have a heightened communication among interconnected motivational nodes that is observable, even at rest. This heightened state of intra-limbic connectivity might predispose one to being more easily triggered by drug-related cues, thus leading to relapse.

The current results, finding differences within CUD patients (i.e., between Trauma and No-Trauma subgroups) complement the literature examining amygdala RSFC and SUDs. For example, amygdala RSFC has shown the ability to distinguish heroin dependent patients (Ma et al., 2010) and CUD patients (Gu et al., 2010) from healthy controls. Further, amygdala RSFC has shown, within CUD patients, the ability to

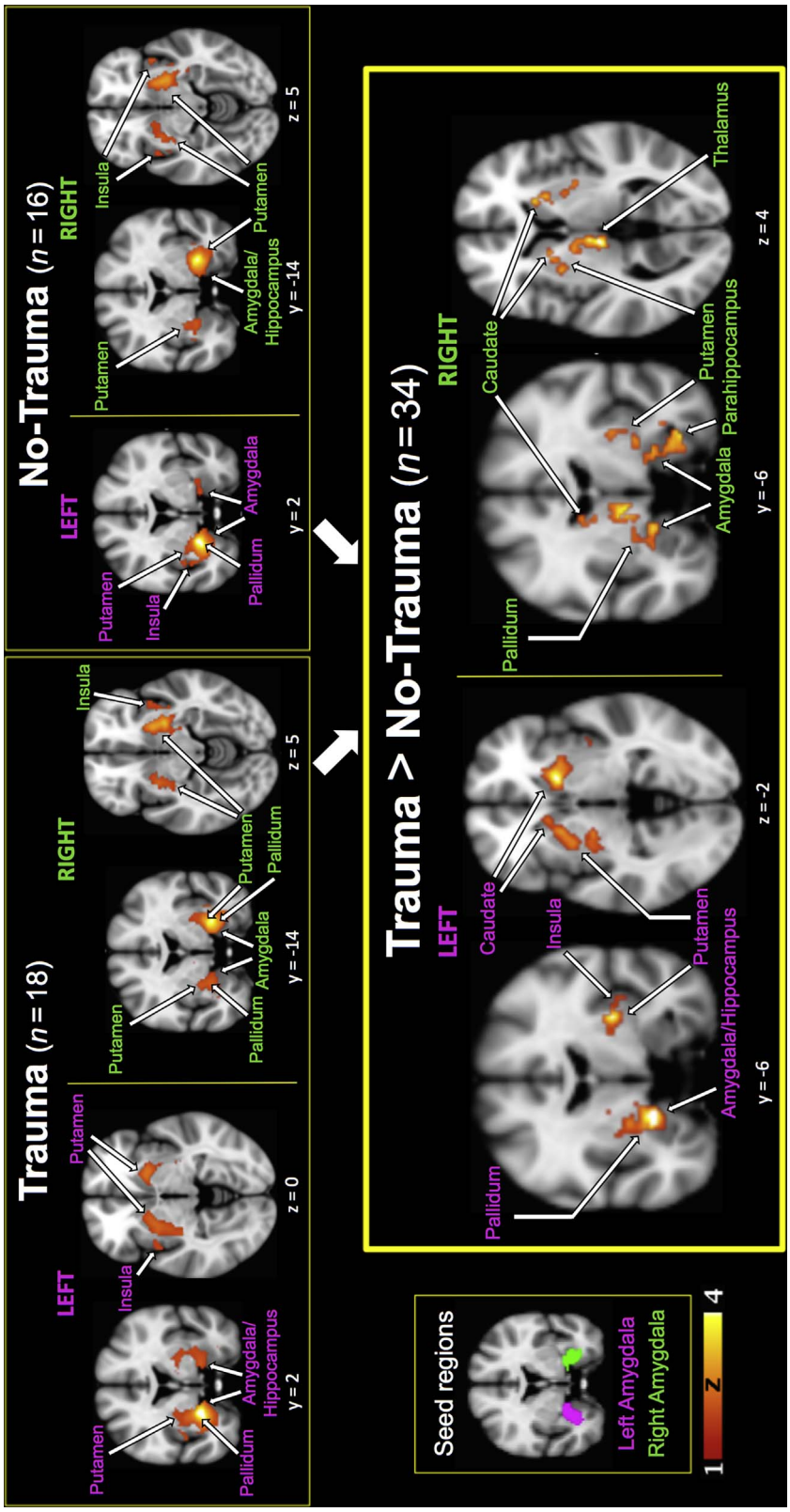

Fig. 1. Seed based connectivity between the left and right amygdala and the *a priori* limbic-striatal mask for the Trauma and No-Trauma groups.

Top panel depicts left and right amygdala connectivity for Trauma and No-Trauma groups (FWE corrected at $p < 0.05$ with k = 20 for each group).

Bottom panel depicts the Trauma > No-Trauma contrast (cluster corrected at $p > 0.05$ with k = 347). Peaks within the statistically significant limbic-striatal mask included the amygdala, putamen, pallidum, caudate, thalamus, insula, hippocampus/parahippocampus, and brain stem (not shown). Images displayed in neurologic convention (left = left) with corresponding MNI coordinates.

distinguish CUD patients with recent cocaine use (i.e., past 3–4 days verified with urine drug screen) compared to those without recent use (Gu et al., 2010), and to distinguish those who relapse from those who do not within the first 30 days following treatment (McHugh et al., 2014). These several results demonstrate the potential sensitivity of RSFC both for detecting differences *between* patients and healthy controls, and for distinguishing clinically important subgroups. Our results reveal further within-group heterogeneity: amygdala-intralimbic RSFC can distinguish CUD patients with prior trauma from those without a trauma history.

Table 2

Seed Region	Cluster (C)	Brain nodes within a priori mask	Hemisphere	Peak T	P value	Coordinates		
						x	y	z
Left Amygdala								
	C1 (875 voxels)	Amygdala	Left	5.89	0	−18	−6	−16
		Putamen	Left	3.38	0.001	−26	4	6
		Pallidum	Left	2.86	0.004	−22	−8	−4
		Brain stem	Left	2.51	0.009	−6	−20	−20
		Caudate	Left	2.39	0.012	−10	18	−2
		Hippocampus	Left	2.18	0.018	−28	−22	−14
	C2 (558 voxels)	Putamen	Right	4.33	0	18	16	−4
		Caudate	Right	2.75	0.005	16	12	6
		Insula	Right	2.65	0.006	38	−10	4
Right Amygdala								
	C3 (632 voxels)	Thalamus	Left	3.68	0	−8	−22	6
		Pallidum	Left	3.44	0.001	−20	−10	−4
		Caudate	Left	3.13	0.002	−20	16	12
		Putamen	Left	2.66	0.006	−26	4	2
		Amygdala	Left	2.64	0.006	−18	−6	−16
	C4 (421 voxels)	Parahippocampus	Right	2.91	0.003	32	−4	−30
		Putamen	Right	2.63	0.007	22	6	−8
		Caudate	Right	2.50	0.009	20	20	4
		Amygdala	Right	2.34	0.013	22	−6	−16

Note. Trauma and No-Trauma cocaine patient sub-groups differed in amygdala connectivity within an *a priori* limbic-striatal mask (cluster threshold $p < 0.05$). Shown above are peaks within the significant clusters with right and left amygdala as seed regions.
C = Cluster.

4.2. Interpretation of findings

Increased connectivity between the amygdala and limbic-striatal structures in the resting state likely reflects an underlying dysfunction that may also manifest during tasks that make demands on these same circuits. Indeed, recent data from our lab (Regier et al., 2016), suggests that CUD individuals with prior adversity (e.g., prior sexual, emotional, and physical abuse) have an enhanced response to evocative cues (i.e., cocaine, sexual, and aversive) in mesolimbic motivational brain circuitry. Parallel results have been documented in aversively-motivated disorders (i.e., PTSD, generalized anxiety), in which there is enhanced amygdala reactivity to evocative cues (Patel et al., 2012; Shin and Liberzon, 2010). The impact of prior adversity (trauma or abuse) on *both* resting connectivity and task-related measures underscores the potential relevance of these brain measures as biomarkers of clinical vulnerability.

As with any human studies examining the impact of trauma history, the current findings are correlational. However, whether the current results reflect predisposing factors, the impact of prior trauma, or very likely, an interaction, they have both theoretical and practical value, underscoring the importance of within group heterogeneity on the neural substrates associated with addiction.

4.3. Limitations and future directions

One strength of this study is the demonstration of differences in amygdala-based RSFC observed *in the absence of* clinically-significant comorbid psychiatric diagnosis, as our population was intentionally truncated on psychiatric severity. These observations, in a truncated sample, are robust and suggest, if anything, a continuum wherein studies including a full range of psychiatric severity (e.g., co-occurring PTSD, depression) could be stronger. As with any set of new findings, certain limitations were present that may help to guide future research. First, this study focused exclusively on male cocaine patients. Future studies may wish to include female participants and other SUDs to determine the generalizability of our results. Second, our seed-based analysis considered the amygdala as a singular unit. Future studies will benefit by examining the independent functions of connectivity within amygdala subdivisions (laterobasal, centromedial, and superficial) that may play unique roles in addiction (Roy et al., 2009; Pitkänen et al., 2000; Russchen et al., 1985; Davis, 2006). Future studies with a larger sample size would increase sensitivity for detection of differences, enabling examinations of amygdala sub-regions.

For this initial study of RSFC in cocaine patients with and without trauma, we used a single ROI (limbic-striatal mask) and a cluster corrected threshold of $p < 0.05$ in the group comparison. Our hypotheses and discussions are thus intentionally limited to circuit-level, rather than the several interconnected nodes within the mask. This initial study lays the foundation for future studies with sample sizes that will enable statistical examination of connectivity with multiple individual brain regions.

4.4. Concluding remarks

Our results suggest that amygdala-connected neural circuits, assessed with RSFC, may offer a sensitive biomarker of prior trauma for those with CUD. To our knowledge, this is the first study to demonstrate enhanced intralimbic connectivity among those with trauma history, within a sample of CUD patients. This finding has potential clinical relevance as trauma-exposed SUD individuals' have greater relapse rates (Farley et al., 2004; Gil-Rivas et al., 2009; Ouimette et al., 1998), underscoring the need for treatments to address the special needs of this population. Our ongoing studies will test whether this biomarker of enhanced RSFC intralimbic connectivity can predict clinical outcomes, including drug craving and relapse. Indeed, our findings may serve to identify who is at greater risk for stress-related relapse − encouraging development of therapeutic interventions (behavioral or pharmacological) that address these critical brain vulnerabilities.

Conflicts of interest

No conflicts declared

Contributors

All authors contributed to the design of the study, and interpretation of the data. MG, ARC, and KJ led the data analysis for the manuscript and MG and ARC wrote the first draft. All authors contributed to writing and editing subsequent drafts of the manuscript.

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