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Posterior Hippocampal Regional Cerebral Blood Flow Predicts Abstinence: A Replication Study

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Abstract

The posterior hippocampus (pHp) plays a major role in the processing and storage of drug-related cues and is linked to striatal-limbic brain circuits involved with craving and drug salience. We have recently reported that increased basal regional cerebral blood flow (rCBF) in a pHp loci, as measured by pseudo-continuous arterial spin labeling magnetic resonance imaging (MRI), predicted days to cocaine relapse following residential treatment. In this secondary analysis, we explored whether rCBF in this same pHp region would successfully predict 30-day point prevalence abstinence 60 days following residential treatment in an independent group of participants with cocaine dependence previously studied. rCBF was assessed with single photon emission computerized tomography (SPECT) during a saline infusion in 21 cocaine dependence and 22 healthy control participants. pHp rCBF was significantly higher in those endorsing cocaine use (n=10) relative to both abstinent (n=11) ($p<0.001$) and control ($p<0.05$) participants. There were no significant differences in measured demographic or clinical variables between the actively using and non-using participants. This replicative finding suggests that heightened pHp activation is a significant predictor of substance use in cocaine dependent individuals, possibly reflecting a neural susceptibility to continued drug cues.

Keywords

cocaine dependence; SPECT; regional cerebral blood flow; hippocampus; limbic system; relapse

INTRODUCTION

The subjective desire for drug use, or craving, is commonly experienced during abstinence following the chronic use of substances and has recently been added as a diagnostic criteria

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Authors Contribution

BA was responsible for study concept and design. TSH obtained all study data and conducted all analyses. HG, in consultation with EAS and BA, developed the mask. BA drafted the manuscript. HG and EAS provided critical revision of the manuscript for important intellectual content. All authors critically reviewed content and approved final version for publication.

for Substance Use Disorder in the Diagnostic Statistical Manual 5 (Association, 2013). Importantly, the experience of craving is associated with heightened cocaine use in cocaine-dependent individuals (Epstein et al., 2010; Preston et al., 2009) and its presumed preclinical analogue, re-instatement, induces increased responding to conditioned cocaine cues in rodent models of addiction (Kalivas and McFarland, 2003; Shaham et al., 2003). Craving-induced striatal-limbic activation is evident in substance-dependent individuals in response to gustatory (Myrick et al., 2008), visual (Childress et al., 1999; Garavan et al., 2000), tactile (Filbey et al., 2009) and emotional (Sinha et al., 2005) cues and the intensity of this neural response is predictive of subsequent cocaine use (Bell et al., 2014; Prisciandaro et al., 2013).

Empirical studies of craving in the laboratory setting typically utilize the presentation of isolated and discrete cues. This approach, in both individuals with substance use disorders and non-human models of addiction, induces marked amygdalar activation (Childress et al., 1999; Kilts et al., 2001; Marchant et al., 2014). However, the ecological relevance of this approach is limited given the multiple personal triggers associated with drug use in the addicted individual or, in 12-step parlance, the “people, places and things” associated with substance use. The complex integrated environments associated with substance use form contextual (or associative) memories, in which the time, place, person, situation, and/or internal emotional and physiological states associated with substance use form strengthened neural pathways that, over time, result in powerfully engrained memories (Hyman et al., 2006). These contextual memories are critical to the development and persistence of addictive disorders. Contextual cues, in fact, induce greater psychomotor sensitization to stimulants in rodent studies than discrete cues (i.e. drug-associated light, tone, or odor) (Crombag et al., 2000).

The posterior hippocampus (pHp) is critical for the formation and storage of contextual memories (Crombag et al., 2008). Stimulation of metabotropic glutamate receptors 1 (mGluR1s) in rodent dorsal hippocampus [which is considered analogous to the primate posterior hippocampus] (Sasaki et al., 2004), for example, is necessary for context-induced cocaine-seeking behavior (Xie et al., 2010) and lesions of the dorsal hippocampus disrupt both the acquisition and expression of cocaine conditioned place preference (Meyers et al., 2006). Inactivation of the dorsal hippocampus and basolateral amygdala also selectively decreases cocaine-seeking behavior in rats (Fuchs et al., 2007) and the basolateral amygdala and dorsal hippocampus interact to regulate cocaine-related memory reconsolidation (Wells et al., 2011). Dorsal hippocampus inhibition also decreases both the acquisition and expression of cocaine conditioned place preference (Meyers et al., 2006; Otis et al., 2014). In clinical translation studies, cocaine dependent men show pHp activation when read a personalized narrative of a high craving environment incorporating multiple cues (rather than isolated cues) (Potenza et al., 2012).

pHp activity may, therefore, be relevant to drug relapse. Indeed, in a recent study, we found that pHp regional cerebral blood flow (rCBF), as assessed by pseudo-continuous Arterial Spin Labeling, was higher in cocaine dependent individuals who subsequently relapsed soon (< 30 days) after residential treatment relative to those who remained abstinent during this period and to healthy controls (Adinoff et al., 2015). The pHp region identified in this rCBF analysis also predicted days to relapse in the cocaine dependent cohort. In the present

manuscript, we sought to determine whether these findings could be generalized to an independent cocaine dependent cohort. Using a cohort of previously studied cocaine dependent and healthy control individuals (Adinoff et al., 2010; Adinoff et al., 2014), we asked whether basal rCBF in the previously identified pHp significantly differed between those cocaine dependent participants who endorsed 30-day point prevalence substance use at 60 days following residential treatment relative to those who did not use substances during this period. In our previous study (Adinoff et al., 2015), we also observed a significant correlation between left pHp rCBF and left hippocampal volume in control, but not in cocaine dependent, participants. Thus, we explored whether these two measures were significantly correlated in this independent cohort.

METHODS

Twenty-one (11 male) cocaine dependent and 22 (12 male) healthy control subjects were studied. Cocaine-addicted subjects had a primary Diagnostic Statistical Manual (DSM)-IV diagnosis of cocaine dependence and cocaine was their lifetime drug of choice. They were one to six weeks abstinent [range 8–39 days; 27.5 (SD 7.5)], which offered a relatively circumscribed period of abstinence, acclimation to the residential unit, and adequate time for the most marked effects of cocaine withdrawal to subside. Cocaine dependent subjects were recruited from patients requesting treatment for cocaine dependence at the Veteran's Administration Medical Center, Homeward Bound, Inc., and Nexus Recovery Center in Dallas, Texas. Addicted subjects were hospitalized as soon as possible after their last reported use of cocaine, and remained in a structured, residential unit until the study was completed. Exclusion criteria included a substance use disorder (other than cocaine or nicotine) within the previous six months, present use of any central nervous system active medications (including all psychotropics), or a lifetime history for Affective, Anxiety, or Schizophrenic Disorder, or Organic Brain Syndrome experienced prior to the onset of a substance use diagnosis or following a period of at least three months abstinence. Exclusion criteria for healthy controls included the criteria as noted for the cocaine-addicted subjects, as well as a lifetime history of any other Axis I disorder (except nicotine dependence) or a first-degree relative with an addictive disorder (other than nicotine).

After providing a complete description of the study to the subjects, written informed consent was obtained. Subjects were financially compensated for their participation. Approval for the study was obtained from the Institutional Review Board of the University of Texas Southwestern Medical Center and the VA North Texas Health Care System. Subjects underwent a medical history and physical examination, DSM-IV Structured Clinical Interview, clinical laboratory tests, urine drug screen, electrocardiogram, and clinical MRI. Lifetime cocaine and other substance use history, including age of first use, was obtained from cocaine-dependent subjects using the Time Line Follow Back.

SPECT Study Sessions

Study sessions took place at the Clinical Trials Office at the University of Texas

Southwestern Medical Center. Subjects underwent four study sessions over a ten-day period. For one session, only a saline placebo was administered; for the other sessions, subjects

received either ondansetron, physostigmine, or scopolamine [pharmacological data has previously been reported; (Adinoff et al., 2010; Adinoff et al., 2014)]. Sessions were separated by at least 48 hours to allow time for decay of ^{99m}Tc hexamethylpropyleneamine oxime (HMPAO), which has a half-life of approximately six hours. In addition, the half-lives of scopolamine (8 hours), physostigmine (40 minutes), and ondansetron (6 hours) are sufficiently short to assure drug clearance prior to the subsequent scan. The four scans were administered in a pseudo-random order (i.e. randomization was assigned at study initiation to assure that infusion order was balanced within each group). Only the scan obtained following the placebo infusion was utilized for the present analysis.

Nicotine-dependent subjects were allowed a cigarette approximately two hours prior to radioligand administration). This timing was long enough to avoid acute effects of nicotine while short enough to avoid the onset of nicotine withdrawal. Subjects were placed supine in a recliner, at rest, with eyes open, and ears unplugged. An intravenous catheter was inserted at approximately 2:00 PM ($T=-30$ min) and a continuous infusion of saline was given throughout the study (except when medication was being administered). Infusions were administered through the intravenous line that was hidden behind a curtain, and all participants and the study coordinator were blinded to study drug. Following drug or saline infusion, 20 mCi of the SPECT rCBF tracer ^{99m}Tc HMPAO (GE Healthcare, Princeton, New Jersey) was administered over 30 sec and followed by a 10 ml saline flush over 30 sec. SPECT scans were obtained 90 minutes following ^{99m}Tc HMPAO administration to allow time for tracer activity to clear from blood and non-brain tissues. Only data from the saline scan is considered in the present analysis.

SPECT and MRI Imaging

SPECT images were acquired on a PRISM 3000S 3-headed SPECT camera (Picker International, Cleveland, OH) using ultra-high-resolution fan-beam collimators (reconstructed resolution of 6.5mm) in a 128x128 matrix in three-degree increments. For our system, voxels in reconstructed images were 1.9mm^3 . Reconstructed images were smoothed with a 6th-order Butterworth three-dimensional filter, and attenuation corrected using a Chang first-order method with ellipse size adjusted for each slice. MRI acquisition was performed on a Philips Gyroscan NT Intera 1.5 T magnetic resonance scanner (Philips Medical Systems, Best, The Netherlands). There were 100 transverse slices, voxel size $0.78\times0.78\times1.80$ mm, FOV $200\times200\times180$ mm, flip angle 35° , and TE/TR = 9.92/3.98 ms.

Assessment of Relapse

Outcome was assessed as a dichotomous measure: whether cocaine was used (yes/no) during days 31–60 at 60 days following discharge from residential treatment (30-day point prevalence at 60 days post-discharge). As both Homeward Bound and Nexus Recover Center receive substantial funding from the Texas state-funded NorthSTAR Behavioral Health Organization, these programs were required to contact participants or reliable contact (e.g., family member, probation officer, etc.) 60 days following discharge and “In the past 30 days, has the client been abstinent (no use) from alcohol and drug use? Yes/No?”. Participants were noted to be abstinent or non-abstinent during this period. Participants recruited from the Veterans Administration site were assessed for abstinence during days 31–60 following

discharge. Only participants in whom contact information was successfully obtained from participant or contact (Nexus, Homeward Bound) or chart (Veterans Administration) were included.

Posterior Hippocampal Mask

A pHp mask was obtained from our previous study examining arterial spin labeling rCBF differences in a group of 60 individuals (20 healthy controls, 22 cocaine-dependent participants who relapsed prior to 30 days following discharge from a residential program, and 18 cocaine dependent participants who did not relapse prior to 30 days following discharge from a residential program) (Adinoff et al., 2015). Cocaine-dependent participants met the same criteria as participants in this secondary analysis (although cocaine dependent participants in the parent study were not excluded if secondary substance use disorders were present) and participants were recruited from the same three residential programs. Scanning was obtained between 2 and 4 weeks abstinence. Brain regions where basal rCBF showed group main effects were identified using a voxel-wise linear mixed-effects model within the gray matter. The only region that significantly predicted relapse was in the left pHp [Montreal Neurologic Institute (MNI) coordinates $-29, -38, -4; 729 \text{ mm}^3$] (Fig. 1).

Statistical Analysis

Demographic and Clinical Data—Demographic, clinical characteristics, personality, pHp rCBF, and hippocampal volume measures were compared using analysis of variance (ANOVA) F or χ^2 tests, as appropriate. Tukey analyses were used for post-hoc comparisons.

Image Analysis—SPECT images were resliced to 2mm^3 voxels, co-registered to MNI space using each participant's MNI T1 MRI template, smoothed to a final resolution of 10mm and normalized to whole brain counts (to correct for individual variability in global cerebral blood flow). This approach provides only relative, not absolute, rCBF values. The accuracy of normalization in our data is about 2–4mm, and the anatomic designations assigned to observed rCBF effects are constrained by these limitations, as well as by the spatial resolution and partial volume effects. Left hippocampal gray matter volumes were extracted from the T1 data based on segmentation in FreeSurfer and were normalized to individual total subcortical gray matter volume to account for individual differences in brain size (Dale et al., 1999). Left pHp rCBF and hippocampal volume measures were compared using ANOVA F tests. Relationships between left pHp rCBF and hippocampal volume were assessed with Pearson correlation.

RESULTS

10 cocaine dependent participants were abstinent for the second month following treatment discharge; 11 were not. There were no significant differences in age, gender or race between the abstinent, non-abstinent, and control ($n=22$) groups (Table 1). Controls participants had higher education and smoked less than either cocaine dependent group. The two cocaine dependent subgroups did not differ in 90 day or lifetime cocaine use, cigarettes smoked per day, or time from admission to treatment and the scanning session (approximate time from last use).

Posterior hippocampal rCBF significantly differed between groups ($F=7.58$, $df=40$, $p=0.002$) (Fig. 2). Non-abstinent participants had greater pHp rCBF relative to both abstinent ($p<0.001$) and control ($p=0.043$) participants. Abstinent and control participants did not significantly differ from one another.

Left hippocampal volume did not differ between the three groups ($F=2.28$, $df=40$, $p=0.12$). There was no significant relationship between pHp rCBF and hippocampal volume in any group (all $r<0.21$, $p>0.5$).

DISCUSSION

Exploiting neuronal activity in a pHp region derived using a different methodology and independent participant group, we replicated our earlier finding that basal pHp rCBF was heightened in cocaine dependent participants relapsing soon after treatment discharge relative to participants who remained abstinent and to healthy controls. In addition, whereas the parent study utilized a whole brain, exploratory approach, the present study approached the analysis with a single *a priori* defined cluster. These findings further support the relevance of pHp activity to the pathophysiology of cocaine relapse. However, we did not observe a significant correlation between pHp rCBF and hippocampal volume in healthy controls, as reported previously, and which was absent in the cocaine cohort (Adinoff et al., 2015).

The pHp (or dorsal hippocampus in rodents) plays a critical role in reward processes (Meyers et al., 2006) and is essential for the consolidation of craving memories. Luo et al. (Luo et al., 2011) has posited a transsynaptic link from the dorsal hippocampus to the ventral tegmental area, using the lateral septum as a relay, by which environmental context regulates goal-directed behavior. We hypothesize that heightened pHp neuronal activity, as reflected by increased rCBF, reflect a sensitized system that is more easily provoked by environmental drug cues post-discharge. These provocations induce hippocampal-cortico-striatal activation, producing heightened drug cravings and relapse (Collier and Routtenberg, 1984; Meyers et al., 2006; Ursin et al., 1966). Persistent neurobiological cocaine-induced alterations, as evidenced by increased pHp rCBF, may thereby produce heightened susceptibility to cocaine-related memories and ensuing use. Similar pHp rCBF in the abstinent and control groups may reflect lower intensity of ruminative cocaine-related memories in the abstinent group relative to the cocaine using group, consistent with a diminished risk of relapse or cocaine use.

Both task-related blood oxygen level dependent (BOLD) response and resting state functional connectivity studies have implicated striatal, amygdalar, insular, thalamic, anterior and posterior cingulate, and ventromedial prefrontal cortical regions as well as subcortical limbic network as predictors of time to cocaine relapse or relapse severity (Brewer et al., 2008; Luo et al., 2013; McHugh et al., 2013; McHugh et al., 2014; Worhunsky et al., 2013). While these studies typically hypothesize general regions or networks will be predictive of relapse risk, to our knowledge a specific identified brain region has not been replicated in a second cohort. Although our present study suggests that the pHp region is associated with relapse, these findings await replication in a prospective study and the necessary association with relevant clinical measures. Since the role of the

pHp in reward and craving would be expected to be similar for all abused substances, it is anticipated that heightened pHp activity would also be observed in other addicted patients at heightened risk of relapse. This, too, merits confirmation in future studies.

Our measure of pHp rCBF was assessed during a saline infusion. However, the $^{99m}\text{TcHMPAO}$ was administered 90 minutes prior to imaging. During this 90 min period, participants were at rest in a quiet room. As previously reported (Adinoff et al., 2010), cognitive, sensory, and affective symptoms (as assessed by the Brief Symptom Inventory (Derogatis and Melisaratos, 1983)) were minimal and did not significantly change during this 90 minute period in either the cocaine dependence or control group. In addition, participants were in a protected, cue-free environment and actively engaged in residential treatment. Thus, we believe our rCBF measure reflected a basal state relatively free of craving. As participants received no instructions during this resting period, this state presumably consisted of “mind-wandering”, a phase that occupies up to 15% of our waking hours (Sayette et al., 2009).

The primary strength of our approach was the use of an *a priori* defined ROI, initially described using a whole brain predictive search of relapsed and non-relapsed cocaine dependent and control participants, to explore whether this finding would persist in a different group of cocaine dependent and control participants. Demographic and clinical similarities between cocaine dependent groups suggests that the success of pHp rCBF in predicting cocaine use was not associated with other factors often associated with cocaine use (e.g., basal differences in disease severity, previous cocaine use). Limitations included a secondary analysis approach, in that the study was not designed to explore the question posed, there were small numbers of cocaine dependent participants in each group, and differing assessment methods, including self-report, were used to determine relapse status. In our previous study, the cocaine using group was defined as cocaine use within 30 days of treatment discharge; in the present analysis, this group was defined as cocaine use between 31 and 60 days following treatment discharge. Point prevalence measures are commonly used to assess smoking cessation treatment outcomes (Services, 2000) and have also been used to assess cocaine treatment outcomes (Higgins et al., 2000).

Identification of the left pHp as a predictor of early cocaine use following treatment suggests particular relevance of personalized, contextual cravings – rather than distinct, isolated cues – to the addictive process. The hippocampus may offer a useful target for pharmacologic and treatment interventions for relapse prevention.

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References

- Adinoff B, Devous MD Sr, Williams MJ, Best SE, Harris TS, Minhajuddin A, Zielinski T, Cullum M. Altered neural cholinergic receptor systems in cocaine-addicted subjects. *Neuropsychopharmacology*. 2010; 35:1485–1499. [PubMed: 20393457]
- Adinoff B, Devous MD, Williams MJ, Harris TS, Best SE, Dong H, Zielinski T. Differences in regional cerebral blood flow response to a 5HT3 antagonist in early- and late-onset cocaine-dependent subjects. *Addict Biol*. 2014; 19:250–261. [PubMed: 22458709]
- Adinoff B, Gu H, Merrick C, McHugh M, Jeon-Slaughter H, Lu H, Yang Y, Stein EA. Basal Hippocampal Activity and Its Functional Connectivity Predicts Cocaine Relapse. *Biol Psychiatry*. 2015
- Association AP. Diagnostic and statistical manual of mental disorders: DSM-5. 5. American Psychiatric Association; Washington, DC: 2013.
- Bell RP, Garavan H, Foxe JJ. Neural correlates of craving and impulsivity in abstinent former cocaine users: Towards biomarkers of relapse risk. *Neuropharmacology*. 2014; 85:461–470. [PubMed: 24951856]
- Brewer JA, Worhunsky PD, Carroll KM, Rounsaville BJ, Potenza MN. Pretreatment brain activation during stroop task is associated with outcomes in cocaine-dependent patients. *Biol Psychiatry*. 2008; 64:998–1004. [PubMed: 18635157]
- Childress AR, Mozley PD, McElgin W, Fitzgerald J, Reivich M, O'Brien CP. Limbic activation during cue-induced cocaine craving. *Am J Psychiatry*. 1999; 156:11–18. [PubMed: 9892292]
- Collier TJ, Routtenberg A. Electrical self-stimulation of dentate gyrus granule cells. *Behav Neural Biol*. 1984; 42:85–90. [PubMed: 6095804]
- Crombag HS, Badiani A, Maren S, Robinson TE. The role of contextual versus discrete drug-associated cues in promoting the induction of psychomotor sensitization to intravenous amphetamine. *Behav Brain Res*. 2000; 116:1–22. [PubMed: 11090882]
- Crombag HS, Bossert JM, Koya E, Shaham Y. Review. Context-induced relapse to drug seeking: a review. *Philos Trans R Soc Lond B Biol Sci*. 2008
- Dale AM, Fischl B, Sereno MI. Cortical surface-based analysis. I. Segmentation and surface reconstruction. *Neuroimage*. 1999; 9:179–194. [PubMed: 9931268]
- Derogatis LR, Melisaratos N. The Brief Symptom Inventory: an introductory report. *Psychol Med*. 1983; 13:595–605. [PubMed: 6622612]
- Epstein DH, Marrone GF, Heishman SJ, Schmittner J, Preston KL. Tobacco, cocaine, and heroin: Craving and use during daily life. *Addict Behav*. 2010; 35:318–324. [PubMed: 19939575]
- Filbey FM, Schacht JP, Myers US, Chavez RS, Hutchison KE. Marijuana craving in the brain. *Proc Natl Acad Sci U S A*. 2009; 106:13016–13021. [PubMed: 19651613]
- Fuchs RA, Eaddy JL, Su ZI, Bell GH. Interactions of the basolateral amygdala with the dorsal hippocampus and dorsomedial prefrontal cortex regulate drug context-induced reinstatement of cocaine-seeking in rats. *Eur J Neurosci*. 2007; 26:487–498. [PubMed: 17650119]
- Garavan H, Pankiewicz J, Bloom A, Cho JK, Sperry L, Ross TJ, Salmeron BJ, Risinger R, Kelley D, Stein EA. Cue-induced cocaine craving: neuroanatomical specificity for drug users and drug stimuli. *Am J Psychiatry*. 2000; 157:1789–1798. [PubMed: 11058476]
- Higgins ST, Wong CJ, Badger GJ, Ogden DE, Dantona RL. Contingent reinforcement increases cocaine abstinence during outpatient treatment and 1 year of follow-up. *J Consult Clin Psychol*. 2000; 68:64–72. [PubMed: 10710841]
- Hyman SE, Malenka RC, Nestler EJ. Neural mechanisms of addiction: the role of reward-related learning and memory. *Annu Rev Neurosci*. 2006; 29:565–598. [PubMed: 16776597]
- Kalivas PW, McFarland K. Brain circuitry and the reinstatement of cocaine-seeking behavior. *Psychopharmacology (Berl)*. 2003; 168:44–56. [PubMed: 12652346]
- Kilts CD, Schweitzer JB, Quinn CK, Gross RE, Faber TL, Muhammad F, Ely TD, Hoffman JM, Drexler KP. Neural activity related to drug craving in cocaine addiction. *Arch Gen Psychiatry*. 2001; 58:334–341. [PubMed: 11296093]

- Luo AH, Tahsili-Fahadan P, Wise RA, Lupica CR, Aston-Jones G. Linking context with reward: a functional circuit from hippocampal CA3 to ventral tegmental area. *Science*. 2011; 333:353–357. [PubMed: 21764750]
- Luo X, Zhang S, Hu S, Bednarski SR, Erdman E, Farr OM, Hong KI, Sinha R, Mazure CM, Li CS. Error processing and gender-shared and -specific neural predictors of relapse in cocaine dependence. *Brain*. 2013; 136:1231–1244. [PubMed: 23485852]
- Marchant NJ, Kaganovsky K, Shaham Y, Bossert JM. Role of corticostriatal circuits in context-induced reinstatement of drug seeking. *Brain Res*. 2014
- McHugh MJ, Demers CH, Braud J, Briggs R, Adinoff B, Stein EA. Striatal-insula circuits in cocaine addiction: implications for impulsivity and relapse risk. *Am J Drug Alcohol Abuse*. 2013; 39:424–432. [PubMed: 24200212]
- McHugh MJ, Demers CH, Salmeron BJ, Devous MD Sr, Stein EA, Adinoff B. Cortico-amygdala coupling as a marker of early relapse risk in cocaine-addicted individuals. *Front Psychiatry*. 2014; 5:16. [PubMed: 24578695]
- Meyers RA, Zavala AR, Speer CM, Neisewander JL. Dorsal hippocampus inhibition disrupts acquisition and expression, but not consolidation, of cocaine conditioned place preference. *Behav Neurosci*. 2006; 120:401–412. [PubMed: 16719704]
- Myrick H, Anton RF, Li X, Henderson S, Randall PK, Voronin K. Effect of naltrexone and ondansetron on alcohol cue-induced activation of the ventral striatum in alcohol-dependent people. *Arch Gen Psychiatry*. 2008; 65:466–475. [PubMed: 18391135]
- Otis JM, Fitzgerald MK, Mueller D. Inhibition of hippocampal beta-adrenergic receptors impairs retrieval but not reconsolidation of cocaine-associated memory and prevents subsequent reinstatement. *Neuropsychopharmacology*. 2014; 39:303–310. [PubMed: 23907403]
- Potenza MN, Hong KI, Lacadie CM, Fulbright RK, Tuit KL, Sinha R. Neural Correlates of Stress-Induced and Cue-Induced Drug Craving: Influences of Sex and Cocaine Dependence. *The American journal of psychiatry*. 2012
- Preston KL, Vahabzadeh M, Schmittner J, Lin JL, Gorelick DA, Epstein DH. Cocaine craving and use during daily life. *Psychopharmacology (Berl)*. 2009; 207:291–301. [PubMed: 19777216]
- Prisciandaro JJ, Myrick H, Henderson S, McRae-Clark AL, Brady KT. Prospective associations between brain activation to cocaine and no-go cues and cocaine relapse. *Drug Alcohol Depend*. 2013; 131:44–49. [PubMed: 23683790]
- Sasaki M, Tohyama K, Matsunaga S, Nakamura M, Tomizawa N, Inoue T, Ogawa H, Ehara S, Ogawa A. MRI identification of dorsal hippocampus homologue in human brain. *Neuroreport*. 2004; 15:2173–2176. [PubMed: 15371727]
- Sayette MA, Reichle ED, Schooler JW. Lost in the sauce: the effects of alcohol on mind wandering. *Psychol Sci*. 2009; 20:747–752. [PubMed: 19422627]
- Services UDoHaH. Service PH. Treating tobacco use and dependence: Clinical practice guidelines. 2000.
- Shaham Y, Shalev U, Lu L, De Wit H, Stewart J. The reinstatement model of drug relapse: history, methodology and major findings. *Psychopharmacology (Berl)*. 2003; 168:3–20. [PubMed: 12402102]
- Sinha R, Lacadie C, Skudlarski P, Fulbright RK, Rounsaville BJ, Kosten TR, Wexler BE. Neural activity associated with stress-induced cocaine craving: a functional magnetic resonance imaging study. *Psychopharmacology (Berl)*. 2005; 183:171–180. [PubMed: 16163517]
- Ursin R, Ursin H, Olds J. Self-stimulation of hippocampus in rats. *J Comp Physiol Psychol*. 1966; 61:353–359. [PubMed: 5938130]
- Wells AM, Lasseter HC, Xie X, Cowhey KE, Reittinger AM, Fuchs RA. Interaction between the basolateral amygdala and dorsal hippocampus is critical for cocaine memory reconsolidation and subsequent drug context-induced cocaine-seeking behavior in rats. *Learn Mem*. 2011; 18:693–702. [PubMed: 22005750]
- Worhunsky PD, Stevens MC, Carroll KM, Rounsaville BJ, Calhoun VD, Pearson GD, Potenza MN. Functional brain networks associated with cognitive control, cocaine dependence, and treatment outcome. *Psychol Addict Behav*. 2013; 27:477–488. [PubMed: 22775772]

Xie X, Ramirez DR, Lasseter HC, Fuchs RA. Effects of mGluR1 antagonism in the dorsal hippocampus on drug context-induced reinstatement of cocaine-seeking behavior in rats. *Psychopharmacology (Berl)*. 2010; 208:1–11. [PubMed: 19847405]

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Figure 1.

Left posterior hippocampal (pHp) mask (black cluster) derived from voxel-wise, whole-brain comparison of regional cerebral flow (rCBF) prospectively obtained from participants with cocaine dependence who used cocaine 30 to 60 days following residential treatment discharge (n=22), cocaine dependent participants abstinent during this period (n=18) and healthy controls (n=20). rCBF was assessed using pseudo-continuous arterial spin labeling (pCASL). The mask was used in the present study to assess whether neuronal activity in this region predicted relapse following residential treatment in a different group of previously studied participants with cocaine dependence. Transverse image: MNI coordinate $z = -4$; sagittal image: $x = -27$.

Figure 2.

Mean $\pm$ standard deviation of regional cerebral flow (rCBF) in the left posterior hippocampus (pHp), as measured by single photon emission computerized tomography (SPECT). rCBF was assessed in the left posterior hippocampus, as described in Figure 1. There was a significant difference between the control (n=22), non-abstinent (n=10), and abstinent groups (n=11) ($F=7.58$, $df=2, 40$, $p=0.002$). Brackets denote post-hoc group comparisons.

Table 1

Demographic and clinical characteristics of healthy controls and relapsed and non-relapsed participants with cocaine use disorder (CocUD) (means $\pm$ SD)*

	Controls (n=22)	Relapsed (n=10)	Non-relapsed (n=11)
Age (years)	34.5 $\pm$ 6.9	37.1 $\pm$ 7.1	36.9 $\pm$ 7.4
Gender *			
Male	12	5	6
Female	10	5	5
Race			
African-American	11	9	6
Caucasian	9	1	5
Hispanic	2	0	0
Education (years) ***	13.1 $\pm$ 5.8	11.25 $\pm$ 1.7 **	12.2 $\pm$ 2.0 **
Nicotine Use			
Cigarettes/day ***	0.3 $\pm$ 0.8	11.5 $\pm$ 7.7 ***	17.0 $\pm$ 11.4 ***
Cocaine Use			
Time from admission to scan		26.0 $\pm$ 8.1	27.2 $\pm$ 6.7
Age of first use (years)		24.4 $\pm$ 5.5	21.4 $\pm$ 7.5
Cocaine Use – previous 90 days (days)		73.0 $\pm$ 27.5	71.0 $\pm$ 26.5
Cocaine Use – Lifetime (\$)		\$234,908 $\pm$ 329,652	\$188,930 $\pm$ 157,087
Year cocaine use		9.1 $\pm$ 6.1	10.8 $\pm$ 6.8

Group difference by ANOVA (1st column):

*
p<0.05,

p 0.005

Group differences by post-hoc Tukey (compared to controls):

**
p<0.005,

p 0.005