Published in final edited form as:

Psychiatry Res. 2015 August 30; 233(2): 212–217. doi:10.1016/j.psychres.2015.07.013.

Self-reported impulsivity is negatively correlated with amygdalar volumes in cocaine dependence

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Abstract

Although impulsivity has been associated with cocaine dependence and other addictive behaviors, the biological factors underlying impulsivity have yet to be precisely determined. This study aimed to examine relationships between impulsivity and volumes of the amygdala and hippocampus in cocaine-dependent and healthy comparison individuals. The Barratt Impulsiveness Scale (BIS-11) was used to assess impulsivity. FreeSurfer was used to assess amygdalar and hippocampal volumes from high-resolution structural magnetic resonance images. Relative to healthy comparison subjects, cocaine-dependent individuals scored higher on all three subscales of BIS-11 but did not differ from healthy comparison subjects in amygdalar or hippocampal volumes. Cocaine-dependent individuals showed significant negative correlations between amygdalar volumes and scores on the BIS-11 Attentional subscale, and this relationship differed significantly from the non-significant relationship in healthy comparison subjects. As individual differences in amygdalar structure may contribute to the high impulsivity observed in cocaine-dependent individuals, the findings suggest that future studies should assess the extent to

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ClinicalTrials.gov Identifier: NCT00350870

All authors declare no conflict of interest with the content of this manuscript.

Disclosure: Dr. Potenza has consulted for Lundbeck, Ironwood, Shire and INSYS pharmaceuticals and RiverMend, LLC; received research support from Pfizer, Mohegan Sun Casino and the National Center for Responsible Gaming; has participated in surveys, mailings, or telephone consultations related to drug addiction, impulse-control disorders, or other health topics; has consulted for gambling, legal and governmental entities on issues related to addictions or impulse-control disorders; has provided clinical care in the Connecticut Department of Mental Health and Addiction Services Problem Gambling Services Program; has performed grant reviews for the NIH and other agencies; has guest edited journal sections; has given academic lectures in grand rounds, Continuing Medical Education events, and other clinical or scientific venues; and has generated books or book chapters for publishers of mental health texts.

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which therapies that target impulsivity in cocaine dependence may operate through the amygdala or alter its structure or function.

Keywords

addiction; neuroimaging; brain volume; amygdala; hippocampus; substance use disorder; MRI;
BIS-11

1. Introduction

Impulsivity, characterized by tendencies to act rapidly and rashly without considerable forethought, represents an important intermediate phenotype relating to cocaine dependence and other addictions (Fineberg et al., 2014). Individuals with addiction to cocaine or other drugs often show elevated impulsivity (Bechara, 2005; Garavan and Hester, 2007). As elevated impulsivity has been associated with greater addiction severity and poorer treatment outcome (Helmus et al., 2001; Moeller et al., 2001; Krishnan-Sarin et al., 2007; Poling et al., 2007), impulsivity may represent an important treatment target for addictions (Helmus et al., 2001; Moeller et al., 2001). Thus, understanding the neural correlates of impulsivity may help guide treatment development strategies for addictions. In this regard, neuroimaging has been used to assess the integrity of brain structures in cocaine-dependent individuals and the relationships between these structures and impulsivity. Reduced gray-matter volumes in extensive brain regions including the frontal cortex, cingulate gyrus, insula, and temporoparietal junction have been observed in cocaine-dependent patients, and a significant negative correlation between trait impulsivity and volumes of gray matter in some of these regions, including the orbitofrontal cortex and insula, has been reported (Ersche et al., 2011; Moreno-López et al., 2012; Crunelle et al., 2014)

Data suggest that the amygdala and hippocampus may contribute to self-reported or “trait” impulsivity. For example, genetic factors have been linked to impulsive/aggressive tendencies, which in turn are linked to reduced volumes of the amygdala and hippocampus and to their increased functional response to emotional/motivational stimuli (Pavlov et al., 2012). Healthy individuals have shown positive correlations between impulsivity and activity in the bilateral amygdala while viewing images of emotional faces or appetizing foods (Beaver et al., 2006; Brown et al., 2006) and negative correlations between aggression and volumes of the amygdala (Matthies et al., 2012; Pardini et al., 2014). Veterans with comorbid posttraumatic stress (PTSD) and mild traumatic brain injury (mTBI) have shown reduced volume of the amygdala relative to veterans without PTSD and/or mTBI, and the extent of this reduction correlated with trait impulsivity (Depue et al., 2014). Neuropsychiatric disorders with increased impulsivity and/or aggression, such as psychopathy and borderline personality, are associated with reduced amygdalar and hippocampal volumes (Zetsche et al., 2007; Huebner et al., 2008; Soloff et al., 2008; Sala et al., 2011) and exaggerated amygdalar reactivity when viewing emotional stimuli. One study reported that after co-varying with impulsivity measures, the difference in amygdalar and hippocampal volumes between individuals with and without borderline personality disorder was no longer significant, suggesting that the reduced volumes may relate to increased impulsivity (Soloff et al., 2008).

Findings of previous studies investigating amygdalar and hippocampal volumes in cocaine-dependent patients appear inconsistent. One study reported increased amygdalar volume (Ersche et al., 2012), several studies reported reduced volume in at least one of the two structures (Makris et al., 2004; Alia-Klein et al., 2011; Barrós-Loscertales et al., 2011; Moreno-López et al., 2012; Rando et al., 2013), and several studies did not find volumetric differences (Jacobsen et al., 2001; Sim et al., 2007; Narayana et al., 2010; Mackey and Paulus, 2013). We are not aware of studies specifically assessing relationships between impulsivity and amygdalar and hippocampal volumes in cocaine-dependent individuals. To examine further amygdalar and hippocampal volumes in cocaine-dependent individuals and their possible relationships with impulsivity, we assessed impulsivity as measured by the Barratt Impulsiveness Scale (BIS-11) (Patton and Stanford, 1995) and examined relationships with amygdalar and hippocampal volumes in cocaine-dependent and healthy comparison subjects. We hypothesized that: 1) cocaine-dependent as compared with healthy comparison subjects would show reduced amygdalar and hippocampal volumes; and 2) BIS-11 scores would correlate inversely with amygdalar and hippocampal volumes in cocaine-dependent individuals.

2. Methods

2.1. Subjects

This study included 34 cocaine-dependent patients and 41 healthy subjects for comparison. Participants were recruited by media advertisements. Some were treatment-seeking cocaine-dependent individuals participating in outpatient randomized clinical trials (Mitchell et al., 2013). They provided written informed consent for participation in the study approved by the Yale School of Medicine Human Investigations Committee. Cocaine-dependent individuals were assessed using the Structured Clinical Interview (SCID) (First et al., 1996; First et al., 1997). They met DSM-IV criteria for current cocaine dependence. Participants were excluded if they had not used cocaine within the past 28 days, less than a 3rd-grade reading level, metal in their body, or any acute or unstable illness including untreated psychotic disorders or current use of prescribed psychotropic medications or were pregnant, breast feeding, color-blind, or left-handed.

Healthy participants were recruited by media advertisements. Urine samples were assessed for recent use of cocaine, opioids, stimulants, marijuana and benzodiazepines. Healthy individuals were excluded if urine samples were positive for any substance. Other exclusionary criteria included left-handedness, pregnancy, current psychiatric diagnoses, or unstable medical conditions.

2.2. Impulsivity Assessment

The BIS-11 is a reliable, valid and widely used 30-item questionnaire measuring self-reported impulsivity and yields Attentional, Motor, and Non-planning subscales (Patton and Stanford, 1995). The Attentional subscale measures the capacity for concentration, the Motor subscale measures the propensity of acting without thinking, and the Non-planning subscale measures the propensity of focusing on present events without considering future events (Patton and Stanford, 1995).

2.3. Image acquisition and processing

High-resolution T1-weighted anatomical images were acquired using a 3-T scanner (Siemens Trio) with the following parameters: TR=1,500 ms, TE=2.83 ms, flip angle=7°, FOV=256×256 mm², matrix=256×256, 1 mm³ isotropic voxels, 176 slices. The hippocampus and amygdala were automatically segmented using FreeSurfer version 5.1.0 (<http://www.surfer.nmr.mgh.harvard.edu>) (Dale et al., 1999; Fischl and Dale, 2000; Fischl et al., 2001). Automated segmentation with the FreeSurfer package has been found to be highly valid and reliable (Morey et al., 2009; Doring et al., 2011). Segmentation of subcortical structures is based on a probabilistic atlas provided by FreeSurfer. The atlas is created by the Center for Morphometric Analysis from 20 unrelated, randomly selected healthy people. The detailed procedure has been described previously (Fischl et al., 2002). In brief, FreeSurfer scripts autorecon 1, 2 and 3 were run in sequence on all imaging data. Processing consisted of removal of non-brain tissue, Talairach transformation, segmentation of subcortical volumetric structures including the hippocampus and amygdala, intensity normalization, tessellation of the gray-matter/white-matter boundary, and labeling of each voxel based on previous probabilistic information. Intracranial volume (ICV) was generated during this processing.

2.4. Data analyses

SPSS Version 19 was used in analyses of the volumetric and clinical data. General-linear-model (GLM) univariate analysis was used to assess between-group differences in scores on BIS-11 and in amygdalar and hippocampal volumes where diagnostic group (cocaine-dependent versus healthy comparison) was included as a between-subject factor and age and gender were included as covariates. ICV was also included as a covariate for comparing volumes between groups. GLM for repeated measure was used to assess potential two-way interactions between group and hemisphere with respect to amygdalar and hippocampal volumes. Partial correlations were used, separately for cocaine-dependent and comparison subjects, to assess the relationships between scores on BIS-11 subscales and volumes of amygdala and hippocampus, controlling for ICV and age. These correlations were compared between cocaine-dependent and comparison individuals using multiple regression (Preacher, 2002). A false-discovery-rate (FDR) approach was used to correct for multiple comparisons (Genovese et al., 2002). The algorithm described in Benjamini & Hochberg was used to perform FDR (Benjamini & Hochberg 1995), and the Q value was set at 0.05. Since the BIS-11 has three subscales, we corrected for three comparisons when assessing group differences in these subscales. We corrected for 12 comparisons when assessing the correlations between the three subscales and four brain structures ($3 \times 4 = 12$). We also explored potential effects of demographic information and comorbidities on differences in BIS-11 scores and volumes of amygdala and hippocampus between patients and comparisons. These exploratory analyses were performed after controlling for demographic information and comorbidities differently. Their results were presented in supplementary materials.

3. Results

3.1. Demographic measures

Demographic information from cocaine-dependent and healthy comparison subjects is presented in Table 1. Cocaine-dependent individuals were older ($t=-4.5$, $df=73$, $p<0.001$) and had received fewer years of education ($t=5.3$, $df=73$, $p<0.001$) relative to healthy comparison subjects. Table 2 presents the employment and clinical characteristics of the cocaine-dependent subjects.

3.2. Impulsivity scores and amygdalar and hippocampal volumes and their correlations

Relative to healthy comparison subjects, cocaine-dependent individuals scored higher on each BIS-11 subscale (Table 3). These group differences were statistically significant after corrections for 3 comparisons (i.e., one for each subscale). However, cocaine-dependent and healthy comparison subjects did not show significant group differences in the volumes of amygdala and hippocampus, with the possible exception that the left amygdala showed a tendency of smaller volume in patients relative to controls. No significant group-by-hemisphere interactions were identified with respect to the volumes of the two structures.

Table 4 shows the correlations between BIS-11 scores and hippocampal and amygdalar volumes. Cocaine-dependent individuals showed significant negative correlations between scores on the Attentional subscale and left ($df=30$, $p=0.006$) and right ($df=30$, $p=0.002$) amygdalar volumes (Fig. 1). These p values were 0.02 and 0.04, respectively, after correction for 12 comparisons. Healthy controls did not show significant correlations between BIS-11 scores and amygdalar and hippocampal volumes. Cocaine-dependent and comparison subjects showed significant differences in correlations between scores on the Attentional subscale and volumes of the left ($z=2.9$, $p=0.004$) and right ($z=2.7$, $p=0.008$) amygdala (Fig. 1). Both p values were 0.045 after correction for 12 comparisons. Among cocaine-dependent patients, years of cocaine use and age of first use of cocaine did not show significant correlations with any scores on the BIS-11 and volumes of the amygdala and hippocampus.

4. Discussion

Consistent with our prediction and previous findings (Gerard Moeller et al., 2002; Patkar et al., 2004; Meda et al., 2009; Ersche et al., 2011), cocaine-dependent individuals scored higher on the BIS-11 relative to healthy comparison subjects. The current cocaine-dependent patients showed a tendency for smaller left amygdala relative to control subjects, but the two groups did not show significant differences in amygdalar and hippocampal volumes. This finding does not support our prediction but is consistent with previous findings of similar volumes of these structures in cocaine-dependent and healthy comparison subjects (Jacobsen et al., 2001; Sim et al., 2007; Narayana et al., 2010; Mackey and Paulus, 2013.). On the other hand, several other studies reported reduced gray-matter volumes in the hippocampus and/or amygdala in cocaine-dependent individuals relative to healthy comparison subjects (Makris et al., 2004; Alia-Klein et al., 2011; Moreno-López et al., 2012; Rando et al., 2013). One possible explanation for these variable findings from different studies may involve

small effect sizes of chronic cocaine use on the volumes of the hippocampus and amygdala, although individual differences may also contribute.

Consistent with our prediction, cocaine-dependent patients showed negative correlations between scores on the BIS-11 Attentional subscale and amygdalar volumes. However, they did not show significant correlations between scores on the BIS-11 Motor and Non-planning subscales and volumes of amygdala and hippocampus. The correlations between scores on BIS-11 Attentional subscale and amygdala volumes in the cocaine-dependent group were significantly different from the corresponding correlations exhibited by healthy comparison subjects. Lower amygdalar volumes have been associated with psychiatric conditions with high aggression and impulsiveness such as psychopathy, conduct disorder, and borderline personality disorder (Yang Y, 2009; Fairchild et al., 2011; Jia et al., 2011; Ermer et al., 2012; Bobes et al., 2013). The amygdala can be divided into basolateral (BLA) and central-medial (CMA) divisions. It has been suggested that the BLA is related to calculated behavior while the CMA related to emotional/impulsive behavior (Balleine and Killcross, 2006; Terburg et al., 2012; van Honk et al., 2013). Furthermore, it has been demonstrated that the BLA regulates the activity of the CMA (Tye et al., 2011; Terburg et al., 2012), and selective damage to the BLA can result in impulsive behavioral tendencies (van Honk et al., 2013). The current study cannot determine whether the finding of a tendency of smaller left amygdalar volumes reflects impaired BLA function, and whether impaired BLA function may contribute to increased impulsivity in cocaine-dependent patients. Therefore, future studies should specifically assess whether reduced amygdalar volumes and elevated impulsivity in cocaine-dependent individuals may relate to structural and functional alterations in the BLA and/or CMA and whether these relationships predate or are a consequence of chronic cocaine use.

The current finding of negative correlations between amygdalar volumes and impulsivity does not imply that the amygdala is the only, or even the primary, brain structure related to impulsivity. It has been reported that chronic cocaine use is associated with reduced volumes in extensive brain regions including the medial and lateral prefrontal cortex (Ersche et al., 2011; Hanlon and Canterberry, 2012), orbitofrontal cortex, insula, cingulate, and temporoparietal cortex. Subcortical structures such as the amygdala and hippocampus are regulated by top-down executive control from the frontoparietal cortex (Corbetta et al., 2008; Banich et al., 2009; Hollmann et al., 2012). It has been proposed that these subcortical structures may exert a greater influence on human behavior if the top-down executive control is reduced due to frontoparietal cortical impairment (Everitt and Robbins, 2005; Volkow et al., 2011). As discussed above, chronic cocaine abuse impairs extensive brain regions including the frontoparietal cortex. Therefore, impaired frontoparietal cortex and reduced top-down executive control might contribute to the current finding of negative correlations between impulsivity measures and amygdalar volumes, although this possibility presently remains speculative.

A limitation of this study is that it assessed only amygdalar and hippocampal volumes. This approach was driven by our hypotheses and the relevance of these structures to cocaine dependence and impulsivity (Volkow et al., 2004; Volkow et al., 2011; Pavlov et al., 2012).

Future studies should assess relationships between impulsivity and volumetric measures of other brain regions.

In summary, this study observed in cocaine-dependent individuals relative to healthy comparison participants an increased impulsivity as measured by the BIS-11 Attentional subscale and altered relationship between scores on the BIS-11 Attentional subscale and amygdalar volumes. The findings suggest that future studies should further investigate impulsivity as related to the development of and remission from cocaine dependence, and whether interventions targeting amygdalar structure and/or function may reduce impulsivity and cocaine use in cocaine-dependent patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: This study was funded by the following grants: National Institute on Drug Abuse (NIDA) grants K01 DA027750, P50 DA09241, R01 DA020908, P20DA027844, and R01 DA035058.

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Highlights

1. Cocaine dependent patients reported a greater score on each of BIS-11 subscale than controls.
2. Patients showed negative correlations between amygdalar volumes and impulsivity measures.
3. Patients and healthy controls showed significant differences in this correlation.

Fig. 1. Correlations between impulsivity measures and amygdalar volumes. Scatter plots show correlations between scores on the attentional subscale of the BIS-11 and volumes of the left and right amygdala.

Table 1

Demographic information of cocaine-dependent and healthy comparison subjects

Demographics	Cocaine Dependent (n=34)		Healthy Comparison (n=41)		t/χ^2	df	p
	mean	%	mean	%			
Age: years (SD)	39.3 (7.7)		29.7 (10.1)		4.5	73	0.00
Education: years (SD)	12.2 (1.8)		15.3 (3.0)		5.3	73	0.00
Female	9	26.5	17	41.5	1.9	1	0.17
Race					5.0	3	0.17
Caucasian	12	35.3	23	56.1			
African-American	16	47.1	14	34.1			
Hispanic	4	11.8	1	2.4			
Multiracial	2	5.9	3	7.3			

Table 2

Demographic and clinical characteristics of cocaine-dependent subjects

Cocaine Dependent (n=34)		
Employment and Clinical Characteristics	mean	%
Employment Status		
Full-time (35 or more hours per week)	3	8.8
Part-time (less than 35 hours per week)	8	23.5
Unemployed less than one month	6	17.6
Unemployed greater than one month	14	41.2
Not in labor force (student, housewife)	3	8.8
Clinical Characteristics		
Lifetime cocaine use: years (SD)	7.9 (5.7)	
Substance use: Days out of 28 days before treatment (SD)		
Cocaine	15.2 (6.9)	
Cigarettes	22.0 (11.3)	
Heroin	0.35 (1.7)	
Alcohol	7.1 (8.9)	
Marijuana	2.1 (4.9)	
Comorbid Diagnosis		
Lifetime Depressive Disorder	7	20.6
Lifetime Alcohol Dependence/Abuse	24	70.6
Lifetime Marijuana Dependence/Abuse	17	50
Lifetime Substance-induced Mood Disorder	6	17.6
Lifetime Anti-social Personality Disorder	2	5.9
Current Depressive Disorder	0	0
Current Alcohol Dependence/Abuse	6	17.6
Current Marijuana Dependence/Abuse	6	17.6
Current Substance-induced Mood Disorder	2	5.9

Table 3

BIS-11 scores and volumes (mm^3) of the amygdala and hippocampus

	Cocaine-Dependent		Healthy Comparison		<i>f</i>	<i>df</i>	<i>p</i> [*]	Effect Size (<i>d</i>)
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>				
BIS-11 Total	68.19	10.67	55.44	8.93	20.1	1, 71	0.00	4.04
Attentional	15.59	3.63	13.2	3.34	4.9	1, 71	0.004 (0.004)	1.25
Motor	23.53	4.92	20.76	3.67	8.7	1, 71	0.002 (0.003)	1.31
Non-planning	28.82	4.88	20.66	4.86	22.2	1, 71	0.000 (0.000)	3.24
Volumes								
Left amygdala	1621.2	209.9	1734.2	288.9	3.3	1, 71	0.07	
Right amygdala	1765.0	230.5	1817.3	263.6	1.4	1, 71	0.24	
Left hippocampus	3997.6	424.2	4065.4	565.7	0.5	1, 71	0.49	
Right hippocampus	4109.4	438.1	4184.4	493.4	0.7	1, 71	0.41	

* number in parentheses are *p* values after correction for multiple comparisons (i.e., 3 comparisons) using FDR algorithm.

Table 4
Correlations between BIS-11 scores and volumes of the amygdala and hippocampus

		BIS-11		
		Total	Atten	Mot Nonpl
Cocaine-Dependent (n=34)				
Amygdala	L	-0.35	-0.48*	-0.23 -0.21
	R	-0.42	-0.52*	-0.29 -0.26
Hippocampus	L	0.09	0.03	0.16 0.02
	R	0.02	0.01	0.10 -0.04
Healthy Comparison (n=41)				
Amygdala	L	0.10	0.17	-0.06 0.13
	R	0.08	0.07	0.03 0.08
Hippocampus	L	-0.07	0.05	-0.03 -0.14
	R	-0.14	-0.01	-0.27 -0.07

* p<0.05, after correction for 12 comparisons. The highlighted cells indicate significant differences in corresponding correlations between cocaine-dependent and healthy comparison.

Abbreviations: Atten: Attentional; Fun: fun-seeking; L: left; Mot: motor; Nonpl: non-planning; R: right; RR: reward responsiveness