Dysfunctional Amygdala Activation and Connectivity With the Prefrontal Cortex in Current Cocaine Users

Cleo L. Crunelle,1,2* Anne Marije Kaag,3 Hanna E. van den Munkhof,4
Liesbeth Reneman,3 Judith R. Homberg,5 Bernard Sabbe,6
Wim van den Brink,1 and Guido van Wingen1

1Department of Psychiatry, Academic Medical Center, University of Amsterdam, Amsterdam,
The Netherlands
2Toxicological Center, University of Antwerp, Antwerp, Belgium
3Department of Radiology, Academic Medical Center, University of Amsterdam, Amsterdam,
The Netherlands
4Department of Neurochemistry and Neuropharmacology, Institute of Biomedical Sciences of
Barcelona, Barcelona, Spain
5Department of Cognitive Neuroscience, Donders Institute for Brain, Cognition, and
Behaviour, Centre for Neuroscience Radboud University Medical Centre, Nijmegen,
The Netherlands
6Collaborative Antwerp Psychiatric Research Institute, University of Antwerp, Antwerp,
Belgium

Abstract: Objectives: Stimulant use is associated with increased anxiety and a single administration of
dexamphetamine increases amygdala activation to biologically salient stimuli in healthy individuals.
Here, we investigate how current cocaine use affects amygdala activity and amygdala connectivity
with the prefrontal cortex in response to biologically salient stimuli in an emotional face matching task
(EIFMT). Experimental design: Amygdala activity and amygdala connectivity during the EFMT were
assessed in 51 cocaine using males and 32 non-drug-using healthy males using functional magnetic
resonance imaging (fMRI). Within the cocaine use group, we explored whether amygdala activation
was associated with age of first use of cocaine and duration of cocaine use to distinguish between
amygdala activation alterations as a cause or a consequence of cocaine use. Principal observations: We
observed hyperactivity of the amygdala, thalamus, and hippocampus and reduced amygdala connec-
tivity with the anterior cingulate gyrus in response to angry and fearful facial expressions in current
cocaine users compared to controls. Increased amygdala activation was independently associated
with earlier age of first cocaine use and with longer exposure to cocaine. Conclusions: Our findings

Conflict of interest: Dr. van den Brink has no conflicts of interest with regard to the present report. However, he has received hon-
oraria from Lundbeck, Merck Serono, Schering-Plough, Reckitt Benckiser, Pfizer and Eli Lilly; has received investigator-initiated
industry grants from Alkermes, and Neurotech; has been a con-
sultant to Lundbeck, Merck Serono, and Schering-Plough; and has
given paid expert testimony for Schering-Plough. None of the
other authors have a potential conflict of interest.
Cleo L. Crunelle and Anne Marije Kaag contributed equally to
this work.

Contract grant sponsor: Netherlands Organisation for Scientific
Research; Contract grant number: 40-00812-98-11002.
*Correspondence to: C. L. Crunelle, Toxicological Center, Univer-
sity of Antwerp, Universiteitsplein 1, CDE R.328, 2610 Antwerp,
Belgium. E-mail: cleo.crunelle@gmail.com
Received for publication 3 September 2014; Revised 10 July 2015;
Accepted 15 July 2015.
DOI: 10.1002/hbm.22913
Published online 28 July 2015 in Wiley Online Library
(wileyonlinelibrary.com).

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suggest that amygdala hyperactivity to biologically salient stimuli may represent a risk factor for 
an early onset of cocaine use and that prolonged cocaine use may further sensitize amygdala 
activation. High amygdala activation to emotional face processing in current cocaine users may result 
from low prefrontal control of the amygdala response to such stimuli. *Hum Brain Mapp* 36:4222–4230, 
2015. © 2015 Wiley Periodicals, Inc.

**Key words:** cocaine dependence; amygdala; drug abuse; emotion; magnetic resonance imaging; fMRI

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**INTRODUCTION**

The amygdala is a brain structure involved in emotional responses and fear recognition [Morris et al., 1996; Whalen et al., 1998]. While fear recognition is impaired in cocaine users [Kemmis et al., 2007; Morgan and Marshall, 2013], studies investigating the relation between cocaine use and amygdala function in response to emotional stimuli are lacking. Stimulants can induce fear and anxiety and withdrawal from repeated cocaine administration leads to increased anxiety responses [Angrist and Gershon, 1970; Blanchard and Blanchard, 1999; Hall et al., 1988; Murphy et al., 2001]. In healthy individuals, a single administration of the stimulant dextroamphetamine resulted in elevated amygdala activation while viewing angry and fearful facial expressions [Hariri et al., 2002]. During a reward and loss processing task, Patel et al. [2013] observed reduced amygdala activation during loss prospect and proposes that this reflects emotional/motivational abnormalities in cocaine users, thus referring to a pre-existent problem. In contrast, in abstinent methamphetamine-dependent patients (abstinent between 5 and 30 days), amygdala activation upon emotional stimuli was similar to non-drug using control subjects [Kim et al., 2011; Payer et al., 2008]. This latter finding suggests that either the effects of repeated stimulant use on the amygdala are reversible or that chronic stimulant use has no effect on amygdala activation in humans.

Thus far, no data are available on amygdala activation to emotional stimuli in active cocaine users. Amphetamines and cocaine are strong stimulant drugs that affect brain dopamine, serotonin, and norepinephrine systems, however, by blocking reuptake (cocaine) and by promoting monoamine release (amphetamine) [Cagniard et al., 2014; Silvia et al., 1997]. As such, observed findings from methamphetamine studies cannot directly be extrapolated to cocaine users. Furthermore, it is not clear whether possible differences in amygdala activation are a cause or a consequence of cocaine use, because there is no information on the relation between amygdala activation and age of first use of cocaine and duration of cocaine use.

The amygdala is part of a larger emotion circuitry that includes the anterior cingulate cortex (ACC). The ACC is part of the medial prefrontal cortex and plays an important role in emotion-based decision making. The ACC is known to be hypoactive in cocaine users during emotionally salient tasks, and this effect appears to be proportional to drug use severity [Goldstein et al., 2009]. Amygdala connections to (prefrontal brain regions have been described earlier [Davis and Whalen, 2002; Price, 2003] and relate to the suppression of a response to negative emotions and seem to be instrumental in the choice of appropriate behaviors [Quirk and Beer, 2006]. Moreover, prenatal cocaine exposure has been shown to alter amygdala activity and its functional and structural connectivity with prefrontal brain regions [Li et al., 2013]. Reduced connectivity between the amygdala and ACC in cocaine users could represent reduced capacity to choose appropriate behavior upon biologically salient stimuli. However, it is unknown whether functional connectivity between the amygdala and the ACC is affected in current cocaine users.

Here, we compare amygdala activation to fearful and angry faces and amygdala-ACC connectivity between current cocaine users and non-drug using healthy controls. We hypothesize that cocaine users show higher amygdala activation during an emotional face matching task (EFMT) and reduced connectivity between the amygdala and ACC. In addition, we explore the association between amygdala activation with age of first use of cocaine and with the duration of cocaine use in current cocaine users.

**METHODS AND MATERIALS**

**Subjects**

Male healthy non-drug using controls (HC) and male current cocaine users (COC) of 22–50 years old were recruited through local advertisement. Cocaine users were included when using at least 1 g of cocaine during at least two occasions per week for the last six consecutive months prior to inclusion. With the exception of heroin, other drug use was allowed. Cocaine users were instructed not to use any drug (except nicotine) at least 10 h before scanning. Cocaine has a half-life of only 1 h, and no acute effects of cocaine are expected 10 h after last consumption. HCs were non-drug users (with the exception of alcohol use) and were instructed not to use alcohol at least 10 h before scanning. Participants were excluded if having a psychotic or bipolar disorder, currently taking medication, if ever being treated for a prior psychiatric or neurological disorder, if having prior head trauma, or if having metal in their body.
The study was approved by the Ethical Review Board of the Academic Medical Center of the University of Amsterdam, The Netherlands. Participants gave written informed consent.

**Clinical Assessments**

Psychiatric disorders were assessed using the Mini International Neuropsychiatric Interview [MINI; Sheehan et al., 1998]. Premorbid intellectual functioning (IQ) was estimated using the Dutch version of the National Adult Reading Test [DART; Schmand et al., 1991]. Smoking behavior and nicotine dependence were assessed using the Fagerström Test for Nicotine Dependence [FTND; Heatherton et al., 1991]. Drug and alcohol use was assessed during a personal interview with separate questions about recreational and regular drug and alcohol use, detailed by dose, time, and frequency of use. Depressive symptoms and individual levels of impulsivity were assessed using the Beck Depression Inventory [BDI; Beck and Steer, 1987] and the Barratt Impulsivity Scale [BIS; Patton et al., 1995], respectively.

**Magnetic Resonance Imaging**

Data were collected on a 3.0-T Intera full-body scanner (Philips Medical Systems, Best, The Netherlands) using a 32-channel SENSE head coil. Echo planar images (EPIs) were acquired covering the whole brain, with a total of 37 ascending axial slices (3 mm × 3 mm × 3 mm voxel size; slice gap 3 mm; Repetition Time (TR)/Echo Time (TE) 2,000 ms/28 ms; matrix 80 × 80). A T1-3D high resolution anatomical scan (TR/TE 8.3/3.8; matrix 240 × 187; 1 × 1 × 1 voxel; transverse slices) was acquired for coregistration with the T1-weighted EPIs. None of the subjects showed head movement larger than the voxel size (<3 mm) in any direction. Mean and standard deviation of motion during scanning were 0.7 mm ± 0.4 mm in any direction and 0.2 ± 0.1 mm from scan-to-scan.

**Emotional Face Matching Task**

The EFMT [adapted from Hariri et al., 2002; van Marle et al., 2011] was used, including two blocks of an emotional (faces) condition interleaved with three blocks of a non-emotional control condition (ellipses) (see Fig. 1). The emotional condition consisted of three faces projected on the screen, from which participants had to select one of two faces (bottom row) that corresponded to the emotion presented on the face in the upper row. The presented faces were from different individuals and represented angry or fearful male and female individuals, presented for 5 s each [Hariri et al., 2002]. The non-emotional control condition presented ellipses depicted horizontally or vertically, and participants were again required to select one of
two ellipses presented horizontally or vertically (bottom row) to match the ellipse presented in the upper row [Hariri et al., 2002]. Each block consisted of six trials each, resulting in 30 s blocks. The total task duration was 2.5 min.

Task stimuli were generated with E-Prime and projected on a 61 cm × 36 cm projection screen. Task stimuli were visible through a mirror (17 cm × 10 cm) fixated on the head-coil (distance mirror-eyes 8 cm; distance projection-screen-mirror: 113 cm). Participants responded by pressing a button on right and left button boxes (4-button box HHSC-2x4-C). The head was stabilized with foam for minimal head movement.

Behavioral Data Analysis

Normality of all data was assessed with Shapiro–Wilk tests. Differences between groups in clinical assessments (IQ, age, FTND scores, BDI, BIS, proportion of alcohol, nicotine and illicit drug users) were analyzed using independent sample t-tests, non-parametric Mann–Whitney U tests, or Chi-square tests where appropriate.

Performance on the EFMT was analyzed using independent sample t-test (for between group effects) and paired sample t-tests (for between condition effects). Non-parametric Mann–Whitney U tests were used for accuracy data. Data were analyzed using SPSS version 20 (Statistical Package for the Social Sciences) and are presented as mean ± standard deviation (SD) for normally distributed data and as median ± interquartile range (IQR) for non-parametric data. P-values < 0.05 were considered significant.

fMRI Data Analysis

Image analysis was performed in SPM8 (Statistical Parametric Mapping; Welcome Department of Cognitive Neurology, London UK). EPIs were slice-time corrected, realigned to correct for head movement, co-registered with the individual anatomical scan, normalized to Montreal Neurological Institute (MNI) space, and spatially smoothed with a 3-D Gaussian kernel of 8 mm at FWHM. Statistical analysis was performed within the framework of the general linear model. The first-level analysis included the two experimental conditions modeled as box-car regressors convolved with the canonical hemodynamic response function of SPM8, the realignment parameters to model potential movement artifacts, and high-pass filtering (cut-off 1/128 Hz). Contrast images comparing the time-course as covariate of interest, and the convolved box-car regressors for the experimental conditions and realignment parameters as covariates of no interest. Time course correlation images were obtained and entered into subsequent random-effects analyses. ANCOVAs were used to identify brain regions with a correlated time-course that differed between groups of cocaine users and healthy controls. Because of our a priori hypothesis regarding the ACC, we corrected the statistical tests for the ACC on the voxel-level for volumes that were based on a previous study that showed reduced ACC activity in cocaine users during an EFMT [x = −28, y = −8, z = −12]. To obtain time-course correlation images irrespective of the experimental conditions, a new statistical model was constructed with the amygdala time-course as covariate of interest, and the convolved box-car regressors for the experimental conditions and realignment parameters as covariates of no interest. Time course correlation images were obtained and entered into subsequent random-effects analyses. ANCOVAs were used to identify brain regions with a correlated time-course that differed between groups of cocaine users and healthy controls. Because of our a priori hypothesis regarding the ACC, we corrected the statistical tests for the ACC on the voxel-level for volumes that were based on a previous study that showed reduced ACC activity in cocaine users during an EFMT [x = −9, y = 48, z = −12, and x = 6, y = 0, z = 45; Goldstein et al., 2009]. For the rest of the brain, we corrected the statistical tests on the cluster-level (P < 0.05) across the whole brain [Friston et al., 1994]. Clusters were defined using an initial height threshold of P < 0.001 uncorrected.

For correlation analyses, we extracted data from the anatomically defined amygdala. We analyzed effects of age of first cocaine use and duration of cocaine use on amygdala activity using multiple linear regression in SPSS. Amygdala activation (left or right) was entered as the dependent variable, BDI and BIS scores were entered as covariates, and age of first use of cocaine and duration of cocaine use were entered as independent variables. Additionally, to investigate a possible interaction between age of first cocaine use and duration of cocaine use, the interaction term “duration of cocaine use × age of first use of cocaine” was entered into the model. Upon non-significance of the interaction term, this term was removed and a model with only main effects of age of first use, years of use, and the covariates BDI and BIS was fitted. The strength of the association between the variables of interest and the outcomes was reported using partial correlation coefficients and the P-values.

RESULTS

A total of 33 HCs and 55 COCs were recruited and all participated. Five participants (1 HC and 4 COCs) had
TABLE I. Clinical characteristics of cocaine dependent individuals (COC) and non-drug using healthy controls (HC)

<table>
<thead>
<tr>
<th></th>
<th>COC (n = 51)</th>
<th>HC (n = 32)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>32 ± 8</td>
<td>33 ± 9</td>
<td>0.410</td>
</tr>
<tr>
<td>IQ</td>
<td>102 ± 9</td>
<td>105 ± 10</td>
<td>0.084</td>
</tr>
<tr>
<td>BDI</td>
<td>9.1 ± 5.6</td>
<td>3.3 ± 3.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BIS total</td>
<td>72.2 ± 9.7</td>
<td>59.8 ± 8.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cocaine use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Users (%)</td>
<td>100%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Age of first use</td>
<td>20.3 ± 5.2</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Years of regular use</td>
<td>7.5 ± 5.3</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Grams per session</td>
<td>1.2 ± 0.8</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Days of use last month</td>
<td>11.3 ± 6.8</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Route of administration</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>9.4%</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Snorting (%)</td>
<td>90.6%</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Nicotine use</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>73.6%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>FTND</td>
<td>5.1 ± 2.1</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Alcohol use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drinkers (%)</td>
<td>96.2%</td>
<td>86.7%</td>
<td>0.106</td>
</tr>
<tr>
<td>Units per week (10 g units)</td>
<td>19 ± 8</td>
<td>12 ± 11</td>
<td>0.084</td>
</tr>
<tr>
<td>Cannabis use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Users (%)</td>
<td>46.2%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Use per week (g)</td>
<td>4.2 ± 5.1</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Ecstasy use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Users (%)</td>
<td>38.5%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Use in last 6 months (pills)</td>
<td>8.3 ± 8.0</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Speed use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amount of users (%)</td>
<td>26.9%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Use in last 6 months (g)</td>
<td>3.4 ± 5.5</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Sedative use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amount of users (%)</td>
<td>13.5%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Use in last 6 months (pills)</td>
<td>24.2 ± 29.8</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Comorbid psychiatric disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression (%)</td>
<td>3.9%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Dysphoric (%)</td>
<td>0%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Manic (%)</td>
<td>0%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Panic (%)</td>
<td>0%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>PTSD (%)</td>
<td>0%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Obsessive compulsive (%)</td>
<td>0%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Antisocial personality disorder (%)</td>
<td>21.6%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Adult ADHD (%)</td>
<td>3.9%</td>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>

FTND, Fagerström test of nicotine dependence; BDI, Beck Depression Inventory; BIS, Barratt Impulsivity Scale; PTSD, post-traumatic stress disorder; ADHD, Attention Deficit/Hyperactivity Disorder. Data are presented as means ± standard deviation or as median ± interquartile range (for BDI scores). A P-value < 0.05 is considered statistically significant.

many more (>66%) omissions (no response) during the EFMT than all other participants and were excluded from all further analyses. Analyses were thus performed on data from 32 HCs and 51 COCs.

**Clinical Characteristics**

With the exception of self-reported depression scores (BDI), all data were normally distributed (all Shapiro–Wilks P > 0.204; NS). Groups did not differ in age and premorbid intellectual functioning. However, there was a significant difference between groups on BDI depression scores and on total BIS trait impulsivity scores (Table I). Table I also shows that the vast majority of the COC group snorted cocaine and that there was extensive polydrug use in this group, including the use of tobacco, cannabis, ecstasy, speed, and sedatives. In the COC group, 82% of included participants met the diagnosis of DSM-IV cocaine dependence: 14 (27%) cocaine abuse and 28 (55%) cocaine dependence. Comorbid psychiatric disorders are also presented in Table I.
Emotional Faces Task

Behavioral data

Reaction times (RTs) were normally distributed (Shapiro–Wilk P > 0.071), but accuracy was not normally distributed (Shapiro–Wilk P < 0.001). RTs on emotional faces and geometrical control stimuli were similar for both groups (see Table II). Also, no between group differences were observed in accuracy on the EFMT or on the control task, suggesting that conditions were similar in difficulty for both groups.

fMRI task activation

Consistent with previous findings [Hariri et al., 2002; Kim et al., 2011], a significant main effect of task (faces > ellipse stimuli) was present in a cluster (coordinates: x = 42, y = −52, z = −18; voxel size = 45,522; Z > 8; P(FWE) < 0.001) encompassing the right and left fusiform gyrus (coordinates x = 42, y = −52, z = −18 and x = −40, y = −46, z = −20), the left and the right amygdala (coordinates x = 23, y = −8, z = −12 and x = −20, y = −8, z = −12), the right calcarine

TABLE II. Performance data of the emotional processing task for cocaine dependent individuals (COC) and non-drug using healthy controls (HC)

<table>
<thead>
<tr>
<th>Emotional faces task performance</th>
<th>COC (n = 51)</th>
<th>HC (n = 32)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT emotional (s)</td>
<td>2.15 ± 0.49</td>
<td>2.16 ± 0.63</td>
<td>0.916</td>
</tr>
<tr>
<td>RT control (s)</td>
<td>1.29 ± 0.54</td>
<td>1.22 ± 0.58</td>
<td>0.590</td>
</tr>
<tr>
<td>Accuracy emotional (%)</td>
<td>100.00 ± 8.33</td>
<td>100.00 ± 14.60</td>
<td>0.809</td>
</tr>
<tr>
<td>Accuracy control (%)</td>
<td>94.44 ± 11.11</td>
<td>100.00 ± 5.60</td>
<td>0.645</td>
</tr>
</tbody>
</table>

RT, reaction times. Data are presented as mean ± standard deviation (RT) and as median ± interquartile range (Accuracy). A P value < 0.05 indicates statistical significance.

Figure 2.
Cocaine-dependent individuals showing significantly increased activation during an EFMT in the left amygdala (A) and in the hippocampus and thalamus region (B). Results are depicted with a threshold of P < 0.005 uncorrected to show the extent of activation. The color bar represents the corresponding T values. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]
Cocaine-dependent individuals show significantly reduced functional connectivity between the amygdala and anterior cingulate gyrus (A). Results are depicted with a threshold of $P < 0.005$ uncorrected to show the extent of activation. The color bar represents the corresponding $T$ values. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

**Correlation analyses**

To study the effect of age of first cocaine use and duration of cocaine use on amygdala activation, a multiple linear regression analysis was performed for the COC group. The analysis was adjusted for the known effects of BDI and BIS. All data were normally distributed (Shapiro–Wilk all $P > 0.130$). First, we tested whether the effects of years of use was influenced by the age of first use of cocaine. Regression analysis showed no significant interaction between these two variables (left amygdala: $P = 0.924$; right amygdala $P = 0.799$), indicating that the effect of the duration of cocaine use is not influenced by the age of first use of cocaine and vice versa.

The unique effects of the independent variables "age of first cocaine use" and "duration of cocaine use" on left and right amygdala activation were estimated using multiple linear regression, whereby the effect of one independent variable was corrected for the effect of the other independent variable and for the covariates BDI and BIS.

Age of first cocaine use was negatively associated with amygdala activation (left amygdala: $r = -0.36$, $P = 0.012$; right amygdala $r = -0.32$, $P = 0.026$), i.e., individuals with a relatively early age of first use of cocaine showed higher amygdala activation. Years of cocaine use was positively associated with amygdala activation (left amygdala: $r = 0.36$, $P = 0.013$; right amygdala: $r = 0.32$, $P = 0.028$), i.e., individuals with a longer duration of cocaine use showed higher amygdala activation.

**Sensitivity analyses**

In an additional sensitivity analysis, we included comorbid drug use (i.e., use of nicotine, alcohol, cannabis, ...
The suppression of a response to negative emotions and EFMT has not been studied previously in current cocaine users. The studies in methamphetamine-dependent individuals were performed in abstinent methamphetamine-dependent patients, while the current study focuses on emotional processing without a reward or loss component. The present finding that cocaine-dependent individuals display increased amygdala activity during an EFMT is in correspondence with the statement by Patel et al. [2013] that cocaine users show emotional abnormalities, based on their findings of altered (however reduced) amygdala activation during the prospect of loss [Patel et al., 2013]. The differences regarding hypo- vs. hyperactivation of the amygdala in cocaine users between our study and the study by Patel et al., [2013] may be due to differences in the tasks used; a monetary incentive delay task addresses reward and loss prospect, anticipation, and outcome [Patel et al., 2013], while the EFMT as used in this study focuses on emotional processing without a reward or loss component. Also, our findings differ from the observation that abstinent methamphetamine-dependent patients do not show amygdala hyperactivity compared to non-stimulant users [Kim et al., 2011; Payer et al., 2008]. This could be due to inherent differences between cocaine and amphetamines regarding half-life, working mechanism, and involved neurotransmitter systems, but could also be due to the studied population: the studies in methamphetamine-dependent individuals were performed in abstinent treatment-seeking stimulant users (with abstinence ranging between 5 and 30 days), whereas our sample consists of non-treatment-seeking current cocaine users who were abstinent only for about 10 h.

Functional connectivity between the amygdala and prefrontal cortex as well as amygdala activation during the EFMT has not been studied previously in current cocaine users. The prefrontal cortex is thought to be involved in the suppression of a response to negative emotions and seems to be instrumental in the choice of appropriate behaviors [Quirk and Beer, 2006]. Altered amygdala–prefrontal cortex connectivity may be of crucial importance in both the initiation and continuation of cocaine use. In this respect, the reduced connectivity between the amygdala and the ACC in COCs compared to HCs may represent a reduced capacity to regulate the amygdala in the presence of biologically salient (negative) stimuli, including drug-related stimuli and related processes of reward and relief craving. Also, our findings imply that the amygdala is dysfunctional in current cocaine users. More specifically, the positive association of amygdala hyperactivity in response to biologically salient stimuli in the EFMT with age of first use of cocaine and with duration of cocaine use proposes that amygdala hyperactivity may be both cause and consequence of cocaine use.

This study is the first to investigate amygdala activation during an EFMT in a large sample of current cocaine users. Previous studies have shown amygdala neuronal firing upon cocaine administration in drug dependent animals [Carelli et al., 2003]. Yet, this was never translated to amygdala activity and activation during an EFMT in humans, for which this study provides the first evidence. One limitation of this study is its cross-sectional design, which limits causal inference and the direction of causality. However, longitudinal and randomized studies on the development of drug addiction are non-existing for reasons of logistics and ethics. Nevertheless, analyses that simultaneously take into account the effects of several time-related variables (years of drug use; duration of use) can dissect the relationships of these time-dependent variables on the outcome (amygdala hyperactivity). This approach allows us to make a tentative distinction between the causal and consequential effects of drug use. Another limitation is that connectivity analyses do not show the direction of the connectivity (to or from) the ACC, which should be investigated in future studies. For future studies, we also propose to include a group of non-cocaine drug users and a group of cocaine abusers in remission. Finally, most current cocaine users were poly-drug users and it cannot be excluded that part of the observed relations between brain activation and cocaine use are due to the use of nicotine, alcohol, or illicit drugs other than cocaine. However, cocaine was the primary substance of abuse in all subjects and our findings were very similar after we controlled for the use of other drugs.

CONCLUSIONS

In summary, this is the first study showing increased amygdala activation during an EFMT and decreased connectivity between the amygdala and the ACC in current cocaine users compared to non-drug-using healthy controls. Moreover, amygdala hyperactivity was independently associated with early age of first use of cocaine and longer duration of cocaine use, suggesting that high
amygdala activation to emotional stimuli is both a risk factor for the early onset of cocaine use and a consequence of prolonged cocaine use.

REFERENCES


