Neural Correlates of Affect Processing and Aggression in Methamphetamine Dependence

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Context: Methamphetamine abuse is associated with high rates of aggression but few studies have addressed the contributing neurobiological factors.

Objective: To quantify aggression, investigate function of the amygdala and prefrontal cortex, and assess relationships between brain function and behavior in methamphetamine-dependent individuals.

Design: In a case-control study, aggression and brain activation were compared between methamphetamine-dependent and control participants.

Setting: Participants were recruited from the general community to an academic research center.

Participants: Thirty-nine methamphetamine-dependent volunteers (16 women) who were abstinent for 7 to 10 days and 37 drug-free control volunteers (18 women) participated in the study; subsets completed self-report and behavioral measures. Functional magnetic resonance imaging (fMRI) was performed on 25 methamphetamine-dependent and 23 control participants.

Main Outcome Measures: We measured self-reported and perpetrated aggression and self-reported alexithymia. Brain activation was assessed using fMRI during visual processing of facial affect (affect matching) and symbolic processing (affect labeling), the latter representing an incidental form of emotion regulation.

Results: Methamphetamine-dependent participants self-reported more aggression and alexithymia than control participants and escalated perpetrated aggression more often following provocation. Alexithymia scores correlated with measures of aggression. During affect matching, fMRI showed no differences between groups in amygdala activation but found lower activation in methamphetamine-dependent than control participants in the bilateral ventral inferior frontal gyrus. During affect labeling, participants recruited the dorsal inferior frontal gyrus and exhibited decreased amygdala activity, consistent with successful emotion regulation; there was no group difference in this effect. The magnitude of decrease in amygdala activity during affect labeling correlated inversely with self-reported aggression in control participants and perpetrated aggression in all participants. Ventral inferior frontal gyrus activation correlated inversely with alexithymia in control participants.

Conclusions: Contrary to the hypotheses, methamphetamine-dependent individuals may successfully regulate emotions through incidental means (affect labeling). Instead, low ventral inferior frontal gyrus activity may contribute to heightened aggression by limiting emotional insight.

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deployed if sufficient cognitive resources are available. As such, both cognitive capacity and emotional insight are necessary to produce a thoughtful outcome, while failure of either faculty can result in aggression.

Both faculties have been investigated in MA-dependent individuals. Studies of cognitive capacity have suggested deficits in attentional control, response inhibition, cognitive flexibility, and decision making. Similarly, studies of emotional insight have described poor self-awareness and difficulty with facial affect recognition and theory of mind. Disturbances in either capacity described by the General Aggression Model could therefore contribute to MA-related aggression but these links have not been tested directly.

Neurobiologically, aggression is associated with emotion processing circuitry, particularly the amygdala and prefrontal cortex (PFC). Whereas the amygdala mediates rapid, automatic responses to social stimuli, especially emotional facial expressions, the PFC mediates the more deliberative aspects of emotion processing, with its ventral sectors implicated in semantic processing and integration of emotional information as well as response selection and behavior control. The PFC can modulate amygdala activity through direct and indirect connections, and aggressive behavior relies on the integrity of this connectivity. Low PFC activity, high amygdala activity, and disruption of their connections have been linked to aggressive behavior in violent and psychiatric populations. Low PFC activity, high amygdala activity, and lowered markers of physiological arousal and subjective distress have consistently demonstrated involvement of the inferior frontal gyrus (IFG), often on the right side, which contributes to inhibitory control.

Individuals who abuse methamphetamine show abnormalities in this circuitry, suggesting a link between neurobiological deficits and their propensity for aggression. In PFC (particularly IFG), numerous structural, neurochemical, and metabolic differences have been identified, and functional magnetic resonance imaging (fMRI) has uncovered deficits in PFC activation during cognitive and socioemotional tasks. Examination of subcortical regions has also uncovered MA-related neurochemical and metabolic abnormalities in the amygdala. These neurobiological differences have been linked to mood, psychiatric states, and personality traits that can influence aggression and, and, in one study, related to aggression itself. However, no study has directly linked functional differences to emotion processing and aggression.

To address this issue, we previously conducted an fMRI study investigating neural responses to emotional facial expressions in MA-dependent individuals. Surprisingly, the study found no difference between MA-dependent and control participants in amygdala response but revealed activation differences in the right IFG. Because one of the roles ascribed to the right IFG is inhibition control, including control over emotional responses, we reasoned that the IFG finding may relate to emotion dysregulation in the MA group. However, because the task did not assess emotion regulation directly, it was not possible to test this hypothesis. The study presented here, therefore, extended the task to include such a condition.

The added task condition (affect labeling) involves verbal labeling of emotional facial expressions, which, unlike the previously used visual matching condition (affect matching), requires symbolic representation of affect. In healthy individuals, affect labeling produces neural activation patterns that are consistent with emotion regulation and is accompanied by decreased markers of negative emotion. “Putting feelings into words,” therefore, incidentally recruits PFC resources whose activity can influence the amygdala, thereby regulating those feelings.

This study used fMRI to investigate the integrity of the PFC-amygdala circuit in MA-dependent and control participants and used self-reported and behavioral measures to relate brain function to aggression and associated traits. Specific objectives of the study were to (1) quantify and compare aggression in MA-dependent and control participants, (2) determine whether the previously observed difference in right IFG activation reflects a deficit in emotion regulation, and (3) investigate how these activation patterns relate to aggression.

METHODS

PARTICIPANTS AND STUDY PROCEDURE

All procedures were approved by the UCLA Office for the Protection of Research Subjects. Individuals who used MA but were not seeking treatment (MA group) and healthy control individuals (control group) between the ages of 18 and 35 years were recruited using radio, internet, and newspaper advertisements. Following an explanation of the study, participants gave written informed consent and were screened for eligibility using questionnaires, psychiatric diagnostic interviewing (Structured Clinical Interview for DSM-IV Axis I Disorders), and a medical examination. Participants in the MA group were required to meet DSM-IV criteria for current MA dependence and to demonstrate recent MA use by providing a urine sample that tested positive. Exclusion criteria for all participants were any current axis I diagnosis other than MA dependence or substance-induced mood or anxiety disorder in the MA group or nicotine abuse/dependence in both groups; use of psychotropic medications or substances, except some marijuana or alcohol (not qualifying for abuse or dependence); central nervous system, cardiovascular, pulmonary, or systemic disease; human immunodeficiency virus, severe hepatic impairment, hematocrit lower than 32, prostatic hypertrophy, or chronic inflammation; pregnancy; lack of English fluency; and MRI contraindications.

Eligible MA-dependent participants were admitted to the UCLA General Clinical Research Center and participated on a residential basis for 15 to 31 days. They were required to abstain from MA for the duration of the study, verified by urine screening, and no testing occurred in the first 4 days to allow residual MA to clear. Measures presented here were collected over the first 15 days, with the order slightly varied for each participant. Control participants visited the laboratory only on test days and were required to provide urine samples on each test day that tested negative for illicit substances. On completion of the study, participants were compensated with cash, gift certificates, and vouchers.

A total of 76 individuals (39 MA-dependent participants, 37 controls) participated in the study. Owing to subject attrition, late addition of measures to the study protocol, and inconsistencies in data collection, not all participants completed all measures.
addition, fMRI runs were discarded for excessive head movement, problems acquiring behavioral data, chance performance on the task, claustrophobic reaction, or missing structural data. Of the participants with acceptable fMRI data, 21 (11 MA-dependent participants, 10 controls) had participated in a previously described study, while 48 (23 MA-dependent participants, 23 controls) performed an updated version of the task (described below).

MEASURES

Task Paired With fMRI

The Affect Matching/Labeling Task is a visual match-to-sample task using face stimuli and is designed to elicit characteristic PFC and amygdala activation patterns during each of the three conditions: affect match, affect label, and shape match (Figure 1A).

Out-of-Scanner Aggression Task

Competitive Reaction Time Task. The Competitive Reaction Time Task (CRT) is a measure of perpetrated aggression, operationalized as the amount of aversive noise to which a participant is willing to expose another person. It captures one of the hallmark features of aggression: delivery of a noxious stimulus to a victim with the intent and expectation of harming the victim. External, convergent, discriminant, and construct validity of the task have been established in previous studies.

In this task (Figure 1B), participants believed they were competing against another person in a reaction time game (pressing a button faster than their opponent following a “go” cue) and that the loser of each trial would be subjected to a noise blast selected by the winner of the trial. In reality, opponent responses were computer controlled. Noise settings selected by the participant for delivery to the opponent on each trial were the outcome measure. Participants were debriefed immediately following completion of the task.

Aggression Questionnaire. For this 34-item paper-and-pencil questionnaire, participants indicated how much each item reflected their behavior on a 5-point scale.

State Trait Anger Expression Inventory. For the paper-and-pencil State Trait Anger Expression Inventory (STAXI), composed of 3 scales (state anger, 15 items; trait anger, 10 items; anger expression, 20 items), participants indicated agreement with each item on a 4-point scale.

Toronto Alexithymia Scale. For the 20-item, paper-and-pencil Toronto Alexithymia Scale (TAS), participants rated their agreement with each item on a 5-point scale, yielding 3 measures: difficulty identifying feelings, difficulty describing feelings, and externally oriented thinking.

MA Abstinence Measures

Methamphetamine Withdrawal Questionnaire. This 30-item, rater-scored questionnaire, described in detail elsewhere, is an adaptation of the Amphetamine Withdrawal Questionnaire. Participants in the MA group indicated the severity of functional, emotional, and physical withdrawal symptoms on a 4-point scale.

Visual Analog Scale for Craving. Participants in the MA group completed this measure daily, indicating current levels of MA craving on a 15-cm line marked from 0 to 100 in 10-point increments.

APPARATUS

Functional MRI was performed on a 3.0 Tesla Siemens Allegra (Erlangen, Germany) using a single-channel head coil. Functional images were acquired using a standard T2*-weighted gradient-echo-planar imaging pulse sequence to collect blood oxygen level–dependent signal. Acquisition parameters were time to repetition, 2500 milliseconds; echo time, 28 milliseconds; flip angle, 80°; and matrix, 64 × 64. Each volume consisted of 36 interleaved slices, parallel to the anterior commissure–posterior commissure line, with slice thickness of 2.3 mm and a 23.5% distance factor. Each of 2 functional runs resulted in 210 volumes. T2-weighted and high-resolution T1-weighted (magnetization-prepared rapid-acquisition gradient-echo) structural scans were also acquired.

Stimulus displays for the affect matching/labeling task were generated using MacStim software on an Apple MacBook computer (Cupertino, California) and presented through magnet-
DATA ANALYSIS

Imaging Data

Preprocessing. Functional MRI data were processed using SPM5. To correct for head motion (within 3-mm translation or 5° rotation; movement beyond these parameters was exclusionary), functional images were spatially realigned to the mean image of the time series, using a least squares approach and 6-parameter rigid body spatial transformation. Images were then coregistered to individual structural templates to allow for localization of activation and subsequent spatial normalization.

Amygdala Region-of-Interest Analysis. Amygdala regions of interest (ROIs) were drawn on individual magnetization-prepared rapid-acquisition gradient-echo images using FSL FIRST software. Functional scans were smoothed with a 5-mm Gaussian kernel and masked with the ROIs. Using the MarsBar toolbox, a general linear model was applied at each voxel within the ROIs, containing a regressor for each condition of the task (affect match, shape match, and affect label for the subset completing this condition), and fixation as an implicit baseline. Condition blocks were modeled as boxcar functions, convolved with a hemodynamic response function provided by SPM. After fitting the general linear model, parameter estimates were averaged across all voxels in the ROI, and the resulting values exported for further analysis.

Whole-Brain Analysis

For individual whole-brain analyses, functional images were smoothed with an 8-mm Gaussian kernel, and the general linear model described above was applied at each voxel across the brain. After fitting the model for each participant, the resulting maps of parameter estimates were spatially normalized to a standard template provided by SPM using a 12-parameter affine transformation and passed to a group-level random-effects analysis. The group-level model combined the previously described and added sample, group, and sex as factors and age and education as covariates of no interest to account for any potentially confounding effects.

Imaging Data

Effective connectivity between IFG and the amygdala was assessed using the psychophysiological interaction function in SPM5. Psychophysiological interaction analysis uses a multiple regression approach to isolate regions showing a differential response to different conditions of the affect matching/labeling task as the manipulated variable, a linear contrast was specified for a greater inverse relationship with the amygdala during the affect label than affect label condition. The resulting statistical maps were spatially normalized to the standard SPM template and passed to a group

### Table 1. Demographic and Methamphetamine Use Characteristics of Participants

<table>
<thead>
<tr>
<th>Mean (SD) by Group</th>
<th>MA (n=39)</th>
<th>Control (n=37)</th>
<th>Test for Group Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Measures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men/women, No.</td>
<td>23/16</td>
<td>19/18</td>
<td>$\chi^2 &lt; .01$</td>
</tr>
<tr>
<td>Age, y</td>
<td>34.1 (8.7)</td>
<td>30.0 (8.6)</td>
<td>$t_{a} = 2.06^{b}$</td>
</tr>
<tr>
<td>Education, y</td>
<td>12.6 (1.8)</td>
<td>14.7 (1.9)</td>
<td>$t_{b} = 4.74^{c}$</td>
</tr>
<tr>
<td>Cigarette smokers/ nonsmokers, No.</td>
<td>13/26</td>
<td>19/21</td>
<td>$\chi^2 = 21.15^{c}$</td>
</tr>
<tr>
<td>Participants who do/do not drink alcohol regularly, No.</td>
<td>20 (8)</td>
<td>29 (8)</td>
<td>$\chi^2 = 1$</td>
</tr>
<tr>
<td>Alcoholic drinks per wk, No.</td>
<td>2.65 (2.68)</td>
<td>3.50 (2.62)</td>
<td>$t_{a} = 1.07$</td>
</tr>
<tr>
<td>MA use measures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at onset of MA, y</td>
<td>22.6 (7.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of MA use, y</td>
<td>11.4 (7.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MA used, g/wk</td>
<td>3.53 (5.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MA used, d/mo.</td>
<td>22.2 (8.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: MA, methamphetamine.

*The sample contained no participants with current psychiatric diagnoses other than MA dependence, tobacco abuse/dependence, or substance-induced mood disorder (n=21). However, a review of lifetime medical histories revealed alcohol abuse/dependence histories in 2 control and 21 MA-dependent participants, anxiety/dependence histories for other substances in 1 control and 22 MA-dependent participants, and histories of mood/anxiety disorders in 1 control and 10 MA-dependent participants. Mann-Whitney U tests showed no effect of these histories on outcome measures.

Mann-Whitney U tests found no differences in outcome measures between smoking and nonsmoking participants.

Mann-Whitney U tests found no differences in outcome measures between drinking and nondrinking controls but found higher competitive reaction time task scores in drinking (n=5) than nondrinking (n=7) MA-dependent participants (z=2.16; P=.039); no other outcome measures differed by drinking status in the MA group.

Use of MA measures did not relate to outcome measures except for a trend correlation between days of MA use in the past month and difficulty identifying feelings on the Toronto Alexithymia Scale (r=.35; P=.06).

level random effects analysis, with group and sex as factors and age and education as covariates of no interest.

All whole-brain group analyses were assessed at a statistical threshold of $P < .005$ with a cluster criterion of at least 30 contiguous voxels, offering a good balance between type I and type II error.

Brain Structure

To account for potentially confounding structural differences, we examined volumetric information from individual FIRST-generated amygdala ROIs and IFG gray matter volume using voxel-based morphometry. For the voxel-based morphometry analysis, individual magnetization-prepared rapid-acquisition gradient-echo images were manually aligned to the anterior commissure–posterior commissure line, segmented into 3 tissue types, spatially normalized to a standard template, modulated to adjust for nonlinear warping, and smoothed using a 12-mm full-width at half-maximum Gaussian kernel. Signal intensity values, representing an index of regional gray matter volume, were then extracted from voxels of interest for further analysis.

Behavioral and ROI Data

The remaining data were analyzed in SPSS 16.0 (SPSS Inc, Chicago, Illinois), using analysis of variance (ANOVA) and regres-
Table 2. Outcome Measures by Subsample

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Mean (SD) by Group</th>
<th>Test for Group Difference</th>
<th>Significant Covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MA</td>
<td>Control</td>
<td></td>
</tr>
<tr>
<td>Subsample Who Completed the AQ and STAXI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample, No.</td>
<td>24</td>
<td>20</td>
<td>F_{32}=9.98b</td>
</tr>
<tr>
<td>Aggression questionnaire score</td>
<td>292.7 (68.3)</td>
<td>230.2 (48.0)</td>
<td>F_{32}=21.74b</td>
</tr>
<tr>
<td>STAXI trait anger score</td>
<td>17.0 (5.2)</td>
<td>14.7 (3.5)</td>
<td>F_{32}=11.70c</td>
</tr>
<tr>
<td>STAXI anger expression score</td>
<td>36.7 (9.4)</td>
<td>26.8 (13.9)</td>
<td>F_{32}=9.09f</td>
</tr>
<tr>
<td>Subsample Who Completed the CRT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample, No.</td>
<td>12</td>
<td>15</td>
<td>See Figure 2</td>
</tr>
<tr>
<td>CRT scores</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subsample Who Completed the TAS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample, No.</td>
<td>31</td>
<td>27</td>
<td>F_{32}=2.17c</td>
</tr>
<tr>
<td>TAS difficulty identifying feelingsd</td>
<td>12.5 (5.6)</td>
<td>8.48 (1.83)</td>
<td>F_{32}=1.10</td>
</tr>
<tr>
<td>TAS externally oriented thinking</td>
<td>10.7 (5.2)</td>
<td>8.96 (3.72)</td>
<td>None</td>
</tr>
<tr>
<td>Age, sex</td>
<td>18.4 (5.0)</td>
<td>16.3 (4.4)</td>
<td>None</td>
</tr>
<tr>
<td>Subsample Who Completed the fMRI and Affect Matching</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample, No.</td>
<td>36</td>
<td>33</td>
<td>F_{64}&lt;1</td>
</tr>
<tr>
<td>Amygdala activation, affect match &gt; shape match parameter estimate</td>
<td>0.423 (0.412)</td>
<td>0.574 (0.378)</td>
<td>None</td>
</tr>
<tr>
<td>Ventral IFG activation, affect match &gt; shape match parameter estimate</td>
<td>0.108 (0.356)</td>
<td>0.432 (0.323)</td>
<td>F_{64}=4.06c</td>
</tr>
<tr>
<td>Subsample Who Completed the fMRI and Affect Matching/Labeling</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample, No.</td>
<td>25</td>
<td>23</td>
<td>See Figure 3B</td>
</tr>
<tr>
<td>Amygdala activation, affect match, affect label, shape match parameter estimates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effective connectivity between amygdala and IFG</td>
<td></td>
<td></td>
<td>See Figure 3C</td>
</tr>
</tbody>
</table>

Abbreviations: AQ, aggression questionnaire; CRT, Competitive Reaction Time task; fMRI, functional magnetic resonance imaging; IFG, inferior frontal gyrus; MA, methamphetamine; NA, not applicable; STAXI, State Trait Anger Expression Inventory; TAS, Toronto Alexithymia Scale.

Tests adjust for demographic variables (age, sex, education). Demographic characteristics of each subsample are detailed in eTable 1.

Toronto Alexithymia Scale difficulty identifying feelings was the only measure on which the 2 participants with substance-induced mood disorder differed from the remaining participants. Removing the participants from the analysis did not change the group difference.

Participants were unable to match the groups for age and education, and aggression and associated neurocircuitry vary with age and sex. Demographic variables were entered into all analyses as covariates of no interest.

RESULTS

PARTICIPANT CHARACTERISTICS

Demographic measures are detailed in Table 1 and eTable 1 (www.archgenpsychiatry.com). The MA and control groups did not differ in sex composition but, on average, MA-dependent participants were older than controls and had completed fewer years of education. Almost all MA-dependent participants but only about half of the controls smoked cigarettes; however, the number of cigarettes per day did not differ between groups among those who smoked. Current alcohol use was low across participants and did not differ between groups. Methamphetamine use characteristics indicated moderately heavy use in the present sample (Table 1). Withdrawal symptoms and cravings tended to decrease between intake and test days but not all differences reached statistical significance (Table 2 and Table 3). Neither MA use nor abstinence measures correlated with outcome measures.

AGGRESSION AND TRAIT CHARACTERISTICS

To compare self-reported aggression between groups, we performed univariate ANOVAs on Aggression Questionnaire, STAXI trait anger, and STAXI anger expression scores, with group as a between-subjects factor, and demographic variables as covariates of no interest. All tests showed significant differences between groups, with higher scores in MA-dependent than control participants (Tables 2 and 3).

To compare perpetrated aggression between groups, we examined CRT performance. Noise intensity and duration settings correlated during all blocks (all r > 0.66; all P < .001) and were summed to form a composite score. Repeated-measures ANOVA of these scores, with group as a between-subjects factor and block as a within-subjects factor, showed a significant block × group interaction. Follow-up tests revealed higher scores in MA-dependent than control participants during block 4 (peak provocation) but no significant group differences for trial 1, block 2, or block 3 (Figure 2).

To evaluate group differences in alexithymia, we performed univariate ANOVAs on TAS subscales, with group as a between-subjects factor and demographic variables as covariates. The MA-dependent participants reported more difficulty identifying feelings than controls but no differ-
ences in describing feelings or externally oriented thinking (Tables 2 and 3). Across control participants, TAS difficulty identifying feelings correlated with STAXI trait anger (r = 0.57; P = .009) and anger expression (r = 0.47; both P< .01). Across MA-dependent participants, TAS total scores correlated with STAXI anger expression (r = 0.42; P = .04).

**FUNCTIONAL MRI**

**Affect Matching**

Across all participants, the affect match compared with shape match contrast showed widespread activation consistent with the neural system for face processing, including in the bilateral amygdala and IFG (Table 4). Within these regions, t tests comparing groups revealed lower activation in MA-dependent than control participants in bilateral ventral IFG, predominantly on the right (Figure 3A; Table 4). No regions showed greater activation in MA-dependent than control participants.

To account for potential volumetric differences between groups, we examined individual gray matter concentration in these ventral IFG clusters using voxel-based

### Table 3. Methamphetamine Abstinence Measures by Subsample<sup>a</sup>

<table>
<thead>
<tr>
<th>Abstinence Measure&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Intake Day</th>
<th>Test Day</th>
<th>Test for Difference Between Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abstinence from MA, d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical withdrawal symptoms (range, 0-21)</td>
<td>1.53 (2.34)</td>
<td>.84 (1.34)</td>
<td></td>
</tr>
<tr>
<td>Emotional withdrawal symptoms (range, 0-27)</td>
<td>2.95 (2.59)</td>
<td>2.74 (3.70)</td>
<td>t&lt;sub&gt;25&lt;/sub&gt; = &lt;0.14</td>
</tr>
<tr>
<td>Functional withdrawal symptoms (range, 0-18)</td>
<td>2.95 (2.92)</td>
<td>2.63 (2.41)</td>
<td>t&lt;sub&gt;25&lt;/sub&gt; = &lt;0.14</td>
</tr>
<tr>
<td>MA craving (range, 0-100)</td>
<td>60.5 (26.6)</td>
<td>31.4 (30.4)</td>
<td>b&lt;sub&gt;25&lt;/sub&gt; = 4.11&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Subsample Who Completed the AQ and STAXI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abstinence from MA, d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical withdrawal symptoms (range, 0-21)</td>
<td>1.00 (1.27)</td>
<td>.91 (1.58)</td>
<td>t&lt;sub&gt;25&lt;/sub&gt; = &lt;0.14</td>
</tr>
<tr>
<td>Emotional withdrawal symptoms (range, 0-27)</td>
<td>2.91 (4.28)</td>
<td>3.55 (3.21)</td>
<td>t&lt;sub&gt;25&lt;/sub&gt; = &lt;0.14</td>
</tr>
<tr>
<td>Functional withdrawal symptoms (range, 0-18)</td>
<td>2.73 (3.50)</td>
<td>1.64 (1.50)</td>
<td>t&lt;sub&gt;25&lt;/sub&gt; = 1.24</td>
</tr>
<tr>
<td>MA craving (range, 0-100)</td>
<td>46.4 (22.7)</td>
<td>27.3 (32.3)</td>
<td>t&lt;sub&gt;25&lt;/sub&gt; = 1.90; P = .09</td>
</tr>
<tr>
<td>Subsample Who Completed the CRT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abstinence from MA, d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical withdrawal symptoms (range, 0-21)</td>
<td>9.11 (4.57)</td>
<td>9.91 (4.57)</td>
<td>NA</td>
</tr>
<tr>
<td>Emotional withdrawal symptoms (range, 0-27)</td>
<td>1.39 (2.31)</td>
<td>1.64 (1.50)</td>
<td>t&lt;sub&gt;25&lt;/sub&gt; = &lt;0.14</td>
</tr>
<tr>
<td>Functional withdrawal symptoms (range, 0-18)</td>
<td>1.00 (1.27)</td>
<td>.91 (1.58)</td>
<td>t&lt;sub&gt;25&lt;/sub&gt; = &lt;0.14</td>
</tr>
<tr>
<td>MA craving (range, 0-100)</td>
<td>53.8 (29.7)</td>
<td>31.1 (34.3)</td>
<td>b&lt;sub&gt;25&lt;/sub&gt; = 1.84</td>
</tr>
<tr>
<td>Subsample Who Completed the TAS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abstinence from MA, d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical withdrawal symptoms (range, 0-21)</td>
<td>1.13 (1.97)</td>
<td>0.64 (1.22)</td>
<td>b&lt;sub&gt;25&lt;/sub&gt; = 1.84</td>
</tr>
<tr>
<td>Emotional withdrawal symptoms (range, 0-27)</td>
<td>3.90 (2.31)</td>
<td>3.14 (3.36)</td>
<td>t&lt;sub&gt;25&lt;/sub&gt; = &lt;0.14</td>
</tr>
<tr>
<td>Functional withdrawal symptoms (range, 0-18)</td>
<td>3.52 (2.90)</td>
<td>2.07 (1.85)</td>
<td>t&lt;sub&gt;25&lt;/sub&gt; = 2.56&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>MA craving (range, 0-100)</td>
<td>53.8 (29.7)</td>
<td>31.1 (34.3)</td>
<td>b&lt;sub&gt;25&lt;/sub&gt; = 3.15&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Abbreviations:** AQ, Aggression Questionnaire; CRT, Competitive Reaction Time task; IMRI, functional magnetic resonance imaging; IFG, inferior frontal gyrus; MA, methamphetamine; NA, not applicable; STAXI, State Trait Anger Expression Inventory; TAS, Toronto Alexithymia Scale.

<sup>a</sup>Tests adjust for demographic variables (age, sex, education). Demographic characteristics of each subsample are detailed in eTable 1.

<sup>b</sup>Abstinence measures did not correlate with any outcome measure.

<sup>c</sup>P<.001.

<sup>d</sup>P<.05.

Figure 2. Perpetrated aggression across competitive reaction time task (CRT) blocks. Repeated-measures analysis of variance showed a significant block × group interaction (F<sub>2,33</sub> = 2.88; P<.04). Follow-up t tests revealed that methamphetamine-dependent (MA) and control participants did not differ in aggressive responding during trial 1 (t<sub>20</sub> = 1.18, block 2 (t<sub>20</sub> = 1.38), or block 3 (t<sub>20</sub> = 1.34; all P>.18) but MA-dependent participants scored significantly higher than controls during block 4 (t<sub>20</sub> = 2.36; P<.03). Owing to the small sample size, it was not possible to include demographic covariates; however, entering each covariate separately in follow-up analyses did not change the block × group interaction.
morphometry. An ANOVA testing voxel-based morphometry values for group differences showed a trend toward lower gray matter concentration in the MA group ($F_{1,54}=2.86; P=.10$) (in addition to effects of age and sex). To test whether local gray matter concentration influenced task-related ventral IFG activation, we entered gray
tivation values from left and right amygdala ROIs correlated with one another across ROI voxels) correlated with one another (all r > 0.61; all P < .001) and were combined by calculating their average. An ANOVA of these values, with group as a factor and ROI volume as a covariate, revealed no effect of volume or group difference in activation (Tables 2 and 3).

Affect Labeling

To test the hypothesis that, owing to IFG dysfunction, MA-dependent participants would fail to lower amygdala activity during affect labeling, we performed a repeated-measures ANOVA on amygdala activation values, with group as a between-subjects factor and condition (affect match, affect label, shape match) as a within-subjects factor. Activation values from left and right amygdala ROIs correlated during all task conditions (all r > 0.75; all P < .001), and were combined by calculating the average. The ANOVA showed a significant effect of condition, and follow-up tests revealed that, as predicted, amygdala activity during the affect label condition was lower than during the affect match condition. Activation during the shape match condition was lower than during both conditions involving faces. Contrary to prediction, however, we found no group difference or group \times condition interaction (Figure 3B).

To identify brain regions associated with this reduction in amygdala activity, we tested voxels across IFG for a greater inverse relationship with amygdala activity (ie, greater functional connectivity) during affect label than affect match using psychophysiological interaction analysis. Dorsal IFG showed the expected pattern of connectivity, predominantly on the right (Figure 3C, Table 4). The clusters did not overlap with the ventral IFG clusters that showed a group difference during affect matching. Within the dorsal IFG clusters, no voxels differed between MA-dependent and control participants, suggesting successful IFG recruitment and subsequent amygdala regulation in both groups.

BEHAVIORAL CORRELATES OF DECREASED AMYGDALE ACTIVITY

Individual decreases in amygdala activity were calculated as the difference in activation between affect match and affect label conditions. To determine the functional significance of this decrease, values were entered as independent variables into linear regression models, with aggression scores as the outcome variables and demographic measures as covariates of no interest. Self-reported aggression scores were intercorrelated (all r > 0.47; all P < .01) and were combined into a composite score by calculating their average.

The model examining these scores showed a relationship between decreased amygdala activity and self-reported aggression in control but not MA-dependent participants (Figure 4A). However, MA-dependent participants showed a relationship between decreased amygdala activity and CRT scores (Figure 4B). Control participants showed a similar relationship (Figure 4B) that did not reach statistical signifi-
did not survive Holm-Bonferroni correction for multiple comparisons. However, the model estimates in left and right ventral IFG clusters (Figure 3A). However, the model did not relate to scores on the difficulty identifying feelings subscale of the Toronto Alexithymia Scale (TAS) (β = −0.42; t = 2.16; P = .04). Individual ventral IFG activation values were calculated as the cluster-weighted average of parameter estimates in left and right ventral IFG clusters (Figure 3A). However, the model did not survive Holm-Bonferroni correction for multiple comparisons.

BEHAVIORAL CORRELATES OF VENTRAL IFG ACTIVITY

Because low ventral IFG activity in the MA group (Figure 3A) did not significantly relate to aggression, decreased amygdala activity, controlling for group, showed a significant inverse relationship with CRT performance (r = −0.43; P = .03).

The results are consistent with the view that emotional insight, in addition to emotion regulation, contributes to aggression, and that this capacity involves ventral IFG. Low ventral IFG activity and associated alexithymia in MA-dependent individuals may therefore precipitate aggression despite successful emotion regulation. Because results were found in early abstinence and did not relate to MA use history or withdrawal, they also suggest that at least some proportion of MA-related aggression is mediated by personality characteristics rather than acute intoxication, withdrawal, or MA use history.

In this study, MA-dependent participants self-reported higher aggression than controls, replicating previous findings and confirming descriptions from community samples. The MA-dependent participants also perpetrated more aggression on the CRT, where, despite similar initial behavior to controls, they escalated aggression more steeply following provocation. These results provide the first laboratory description of MA-related aggression patterns and suggest that aggression occurs as an increasingly disproportionate response to interpersonal interaction, rather than a preemptive attack.

According to the General Aggression Model, failure of either emotion regulation or emotional insight can account for such a pattern. Despite our hypotheses' focus on emotion regulation, however, we found no deficit in this capacity in MA-dependent participants, as affect labeling resulted in dorsal IFG recruitment and lowered amygdala activity across participants. These activation patterns related to self-reported aggression in controls and perpetrated aggression in all participants, suggesting that they represent a neural signature for successful emotion regulation and that this capacity is relevant to the restraint of aggression in both groups.

Instead, poor emotional insight may underlie MA-related aggression. The General Aggression Model states that even in the presence of sufficient cognitive capacity (ie, emotion regulation), behavior can be aggressive if assessment of internal states is unsuccessful. Alexithymia scores in the MA sample support this view, showing greater difficulty identifying feelings, which, in turn, related to self-reported aggression. This finding is consistent with evidence of impaired introspection and social comprehension in drug addiction and confirming descriptions from community samples. The MA-dependent participants also perpetrated more aggression on the CRT, where, despite similar initial behavior to controls, they escalated aggression more steeply following provocation. These results provide the first laboratory description of MA-related aggression patterns and suggest that aggression occurs as an increasingly disproportionate response to interpersonal interaction, rather than a preemptive attack.

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reporting observed among MA-dependent participants. The finding that in the MA group, decreased amygdala activity related to perpetrated aggression but not self-report of this aggression suggests that, owing to limited insight, objective tasks characterize their behavior more reliably than subjective self-report.

Together, the data are consistent with theoretical and neurocognitive models of aggression and suggest that a deficit in the evaluation of internal states rather than insufficient cognitive capacity precipitates MA-related aggression. Amygdala activation during affect matching suggests appropriate immediate responses, and successful amygdala regulation by dorsal IFG during affect labeling suggests sufficient cognitive capacity; however, low ventral IFG activation and associated alexithymia suggest limited evaluation of internal states, thus favoring aggressive outcomes.

Several limitations of the study should be noted. First, we were unable to match MA-dependent and control participants for age, education, psychiatric history, and smoking status, potentially confounding group differences. Although we included demographic covariates in analyses and performed follow-up tests, we recognize that MA-dependent and control participants likely differ in ways other than MA exposure and that these factors need to be distinguished in future studies. Second, MA-related abnormalities in neurovascular coupling or hemodynamic response could have influenced fMRI results. To minimize such effects, the study used a blocked design but this decreased temporal resolution. The surprising lack of a group difference in amygdala activation during affect labeling suggests sufficient cognitive capacity; however, low ventral IFG activation and associated alexithymia suggest limited evaluation of internal states, thus favoring aggressive outcomes.

These limitations notwithstanding, the study adds important neurobiological components to the examination of aggression in MA dependence. The findings suggest that emotion regulation, at least when elicited incidentally, can be successful in MA-dependent individuals but that dysfunction of ventral IFG contributes to heightened aggression by limiting emotional insight. In the continued pursuit of intervention strategies focused on stress-related relapse prevention and improved personal and social function, future studies may therefore benefit from taking these socioemotional considerations into account.

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