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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 in 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 sym-

bolic 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 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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METHAMPHETAMINE (MA) abuse is associated with a propensity for irritability, hostility, and aggression, resulting in high rates of interpersonal violence, emergency department/trauma center visits, assault, weapons charges,¹⁻⁹ and, ultimately, public health and safety burdens.^{10,11} Despite the frequent co-occurrence of aggression with MA abuse,¹²⁻¹⁴ however, the nature of their relationship remains debated.¹⁵⁻¹⁷ Few laboratory studies have evaluated socioemotional function in MA-dependent individuals,^{18,19} and only 1 has directly assessed aggression.²⁰ The aim of this study, therefore, was to delineate possible relationships between brain func-

tion, emotion processing, and aggression in individuals who abuse MA.

Aggression (particularly impulsive aggression) is defined as any action toward another person that is elicited by provocation, driven by anger, and intended to cause harm. Its generation is conceptualized by the General Aggression Model,²¹ in which internal states are translated into either impulsive aggression or thoughtful action, depending on the success of appraisal and decision processes. These processes require introspection (ie, appraisal and evaluation of one's internal state) but they are only 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^{22,23} have suggested deficits in attentional control,²⁴ response inhibition,^{25,26} cognitive flexibility,²⁷ and decision making.²⁸⁻³⁰ Similarly, studies of emotional insight^{31,32} have described poor self-awareness³³ and difficulty with facial affect recognition and theory of mind.¹⁹ 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).³⁴ Whereas the amygdala mediates rapid, automatic responses to social stimuli,^{35,36} especially emotional facial expressions,^{37,38} the PFC mediates the more deliberative aspects of emotion processing,³⁹ with its ventral sectors implicated in semantic processing and integration of emotional information⁴⁰⁻⁴² as well as response selection and behavior control.⁴³ The PFC can modulate amygdala activity through direct and indirect connections,⁴⁴⁻⁴⁶ 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,⁴⁷⁻⁵³ and healthy individuals performing emotion regulation tasks including restraint from aggression⁵⁴ exhibit PFC activation, reduced amygdala activity,⁵⁵⁻⁶¹ and lowered markers of physiological arousal and subjective distress.⁶²⁻⁶⁴ These studies have consistently demonstrated involvement of the inferior frontal gyrus (IFG), often on the right side,^{55,65,66} which contributes to inhibitory control.⁶⁷

Individuals who abuse methamphetamine show abnormalities in this circuitry, suggesting a link between neurobiological deficits and their propensity for aggression. In the PFC (particularly the IFG⁶⁸), numerous structural, neurochemical, and metabolic differences have been identified,^{69,70} and functional magnetic resonance imaging (fMRI) has uncovered deficits in PFC activation during cognitive^{27,29,71,72} and socioemotional tasks.^{18,73} Examination of subcortical regions has also uncovered MA-related neurochemical and metabolic abnormalities in the amygdala.^{20,74,75} These neurobiological differences have been linked to moods, psychiatric states, and personality traits that can influence aggression^{70,74-78} and, in one study, related to aggression itself.²⁰ 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.¹⁸ 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 inhibitory control, including control over emotional responses,⁷⁹ 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 (ie, increased right IFG and lowered amygdala activity⁵⁵⁻⁵⁷) and is accompanied by decreased markers of negative emotion.^{57,80} "Putting feelings into words," therefore, incidentally recruits PFC resources whose activity can influence the amygdala, thereby regulating those feelings.⁸¹

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-sided IFG activation¹⁸ 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 55 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 Disorders⁸²), 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. In addition, fMRI runs were discarded for excessive head movement, problems acquiring behavioral data, chance performance

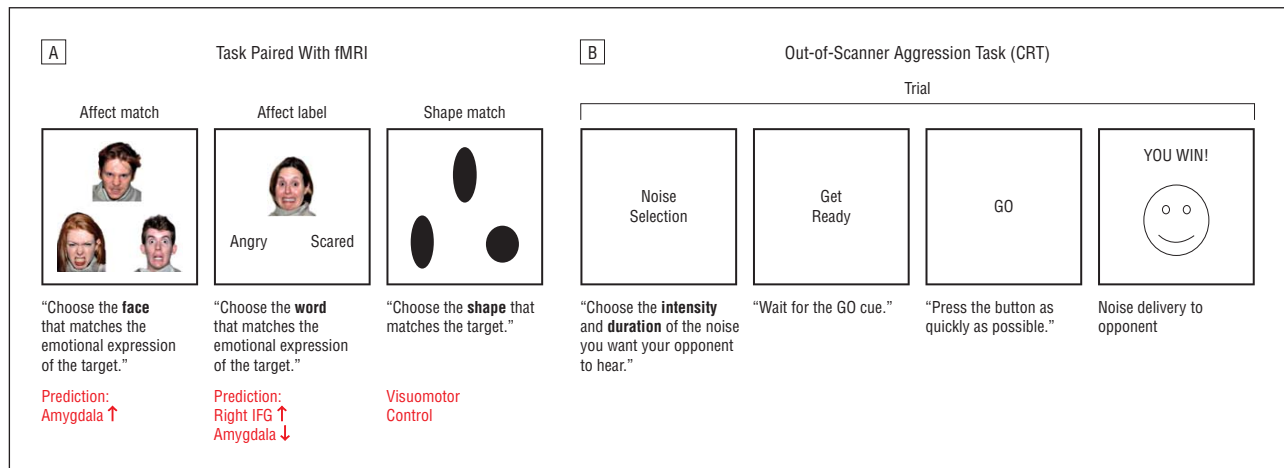


Figure 1. Sample stimuli from the Affect Matching/Labeling task and Competitive Reaction Time Task (CRT). A, On all trials, participants chose the item on the bottom of the display that matched the target item at the top of the display. Target faces were 50% female, and facial expressions were fearful or angry on 80% of trials and happy or surprised on the remaining 20%. Trials were grouped by task condition and presented as blocks. Each block contained five 5-second trials and was preceded by a 2-second instruction cue and followed by 16-second of fixation. Participants completed 4 blocks of each condition over 2 sequential functional runs, counterbalanced across participants. Each functional run lasted 8 minutes, 36 seconds. Predictions regarding activation are based on previous studies.^{55,56} B, Noise intensity settings available to the participant on each trial ranged from 0 to 10, with 0 being no noise, level 1 calibrated to 60 dB, and level 10 calibrated to 110 dB. Duration settings ranged from 1 to 5 seconds in 0.5-second increments. The task consisted of 25 trials divided into 4 blocks: trial 1, measuring unprovoked aggression, and three 8-trial blocks that gradually increased opponent noise settings (means, 3.5, 6.0, and 8.5 during blocks 2, 3, and 4, respectively). Participants were predetermined to win 50% of the trials, selected at random. IFG indicates inferior frontal gyrus; fMRI, functional magnetic resonance imaging.

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,¹⁸ while 48 (25 MA-dependent participants, 23 controls) performed an updated version of the task (described below).

MEASURES

Task Paired With fMRI

The Affect Matching/Labeling Task^{55,56} is a visual match-to-sample task using face stimuli⁸³ and is designed to elicit characteristic PFC and amygdala activation patterns during each of 3 conditions: affect match, affect label, and shape match (**Figure 1A**).

Out-of-Scanner Measures

Competitive Reaction Time Task. The Competitive Reaction Time Task (CRT⁸⁴) is a measure of perpetrated aggression, operationalized as the amount of aversive noise to which a participant is willing to subject 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.⁸⁵ External, convergent, discriminant, and construct validity of the task have been established in previous studies.⁸⁵⁻⁸⁷

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,⁸⁸ 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),⁸⁹ composed of 3 scales (state anger, 15 items; trait anger, 10 items; anger expression, 32 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),⁹⁰ 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,⁹¹ is an adaptation of the Amphetamine Withdrawal Questionnaire.⁹² 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 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 2.5 mm and a 25% 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 software⁹³ on an Apple MacBook com-

Table 1. Demographic and Methamphetamine Use Characteristics of Participants^a

Demographic Measures	Mean (SD) by Group		Test for Group Difference
	MA (n=39)	Control (n=37)	
Men/women, No.	23/16	19/18	$\chi^2_1 < 1$
Age, y	34.1 (8.7)	30.0 (8.6)	$t_{74} = 2.06^b$
Education, y	12.6 (1.8)	14.7 (1.9)	$t_{73} = 4.74^c$
Cigarette smokers/nonsmokers, No. ^d	36/3	16/21	$\chi^2_1 = 21.15^c$
Cigarettes smoked per d, No.	13.9 (10.7)	12.2 (8.3)	$t_{50} < 1$
Participants who do/do not drink alcohol regularly, No. ^e	20/19	25/12	$\chi^2_1 = 2.19$
Alcoholic drinks per wk, No.	2.65 (2.68)	3.50 (2.62)	$t_{43} = 1.07$
MA use measures ^f			
Age at onset of MA use, y	22.6 (7.5)		
Duration of MA use, y	11.4 (7.8)		
MA used, g/wk	3.53 (5.05)		
MA used, d/mo	22.2 (8.5)		

Abbreviation: MA, methamphetamine.

^aThe sample contained no participants with current psychiatric diagnoses (other than MA dependence, tobacco abuse/dependence, or substance-induced mood disorder [$n=2$]). However, a review of lifetime medical histories revealed alcohol abuse/dependence histories in 2 control and 21 MA-dependent participants, abuse/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.

^b $P < .05$.

^c $P < .001$.

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

^eMann-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 ($z=2.16$; $P=.03$); no other outcome measures differed by drinking status in the MA group.

^fUse 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 ($r=0.35$; $P=.06$).

puter (Cupertino, California) and presented through magnet-compatible video goggles.⁹⁴ Responses were registered using a magnet-compatible button box.⁹⁴ The CRT was performed using the HyperCard version of the program on an Apple MacBook computer, with noise blasts delivered through TDK headphones (Uniondale, New York).

DATA ANALYSIS

Imaging Data

Preprocessing. Functional MRI data were processed using SPM5.⁹⁵ 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.⁹⁶ Functional scans were smoothed with a 5-mm Gaussian kernel and masked with the ROIs. Using the MarsBaR toolbox,⁹⁷ 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 described¹⁸ and added sample, and included sample, group, and sex as factors and age and education as covariates of no interest to account for any potentially confounding effects.

Psychophysiological Interaction Analysis. 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 relationship with a target region depending on psychological context and can be interpreted as the context-specific influence one brain region exerts over another.^{98,99} In the present study, individual FIRST-generated amygdala ROIs served as the target, conditions of the affect matching/labeling task as the manipulated context, and IFG as a potential source region for connectivity.

For each participant, regressors that modeled amygdala activity, task conditions, and the amygdala \times condition interaction were entered into whole-brain multiple regression analysis. Given our a priori hypotheses,^{55,56} analyses were restricted to IFG using the PickAtlas toolbox.¹⁰⁰ After estimating the model for each participant, a linear contrast was specified for a greater inverse relationship with the amygdala during the affect label than affect match condition. The resulting statistical maps were spatially normalized to the standard SPM template and passed to a group-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.¹⁰¹

Brain Structure

To account for potentially confounding structural differences,⁶⁸ we examined volumetric information from individual FIRST-generated amygdala ROIs and IFG gray matter volume using voxel-based morphometry.¹⁰² 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 regression models. Because we were unable to match the groups for

Table 2. Methamphetamine Abstinence Measures by Subsample

Abstinence Measure ^a	Intake Day	Test Day	Test for Difference Between Days
Subsample Who Completed the AQ and STAXI			
Abstinence from MA, d		7.82 (2.82)	NA
Physical withdrawal symptoms (range, 0-21)	1.53 (2.34)	.84 (1.34)	$t_{18} = 1.43$
Emotional withdrawal symptoms (range, 0-27)	2.95 (2.59)	2.74 (3.70)	$t_{18} < 1$
Functional withdrawal symptoms (range, 0-18)	2.95 (2.92)	2.63 (2.41)	$t_{18} < 1$
MA craving (range, 0-100)	60.5 (26.6)	31.4 (30.4)	$t_{20} = 4.11^b$
Subsample Who Completed the CRT			
Abstinence from MA, d		9.91 (4.57)	NA
Physical withdrawal symptoms (range, 0-21)	1.00 (1.27)	0.91 (1.58)	$t_{10} < 1$
Emotional withdrawal symptoms (range, 0-27)	2.91 (4.28)	3.55 (3.21)	$t_{10} < 1$
Functional withdrawal symptoms (range, 0-18)	2.73 (3.50)	1.64 (1.50)	$t_{10} = 1.24$
MA craving (range, 0-100)	46.4 (27.7)	27.3 (32.3)	$t_{10} = 1.90; P = .09$
Subsample Who Completed the TAS			
Abstinence from MA, d		9.23 (3.57)	NA
Physical withdrawal symptoms (range, 0-21)	1.31 (1.97)	0.64 (1.22)	$t_{28} = 1.48$
Emotional withdrawal symptoms (range, 0-27)	3.90 (5.27)	3.14 (3.36)	$t_{28} < 1$
Functional withdrawal symptoms (range, 0-18)	3.52 (2.90)	2.07 (1.85)	$t_{28} = 2.56^c$
MA craving (range, 0-100)	53.8 (29.7)	31.1 (34.3)	$t_{28} = 3.15^c$
Sample Who Completed fMRI and Affect Matching			
Abstinence from MA, d		9.22 (3.56)	NA
Physical withdrawal symptoms (range, 0-21)	1.42 (2.02)	0.65 (1.09)	$t_{25} = 2.00; P = .06$
Emotional withdrawal symptoms (range, 0-27)	3.62 (4.71)	3.23 (3.51)	$t_{25} < 1$
Functional withdrawal symptoms (range, 0-18)	3.69 (2.64)	2.31 (2.19)	$t_{25} = 2.45^c$
MA craving (range, 0-100)	53.5 (32.0)	28.9 (33.5)	$t_{25} = 3.10^c$
Subsample Who Completed fMRI and Affect Matching/Labeling			
Abstinence from MA, d		8.52 (2.89)	NA
Physical withdrawal symptoms (range 0-21)	1.46 (2.09)	0.59 (1.05)	$t_{21} = 2.04; P = .05$
Emotional withdrawal symptoms (range 0-27)	2.77 (2.86)	2.96 (3.44)	$t_{21} < 1$
Functional withdrawal symptoms (range 0-18)	3.50 (2.67)	2.05 (1.59)	$t_{21} = 2.40^c$
MA craving	49.6 (31.2)	30.5 (35.2)	$t_{21} = 2.18^c$

Abbreviations: AQ, Aggression Questionnaire; CRT, Competitive Reaction Time task; fMRI, functional magnetic resonance imaging; MA, methamphetamines; NA, not applicable; STAXI, State Trait Anger Expression Inventory; TAS, Toronto Alexithymia Scale.

^aAbstinence measures did not correlate with any outcome measure.

^b $P < .001$.

^c $P < .05$.

age and education, and aggression and associated neurocircuitry vary with age and sex,¹⁰³ demographic variables were entered into all analyses as covariates of no interest.

RESULTS

PARTICIPANT CHARACTERISTICS

Demographic measures are detailed in the 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 sig-

nificance (Table 2). 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 (Table 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 \times 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).

Table 3. Outcome Measures by Subsample^a

Outcome Measure	Mean (SD) by Group		Omnibus Test	Test for Group Difference	Significant Covariates
	MA	Control			
Subsample Who Completed the AQ and STAXI					
Sample, No.	24	20			
Aggression questionnaire score	292.7 (68.3)	230.2 (48.0)	$F_{4,39}=9.98^b$	$F_{1,39}=21.74^b$	Age, sex
STAXI trait anger score	17.0 (5.2)	14.7 (3.5)	$F_{4,39}=3.79^c$	$F_{1,39}=11.70^c$	Education
STAXI anger expression score	36.7 (9.4)	26.8 (13.9)	$F_{4,39}=4.47^b$	$F_{1,39}=9.09^c$	Age
Subsample Who Completed the CRT					
Sample, No.	12	15			
CRT scores			See Figure 2		
Subsample Who Completed the TAS					
Sample, No.	31	27			
TAS difficulty identifying feelings ^d	12.5 (5.6)	8.48 (1.83)	$F_{4,53}=3.17^c$	$F_{1,53}=8.50^c$	None
TAS difficulty describing feelings	10.7 (5.2)	8.96 (3.72)	$F_{4,53}=1.10$	None	None
TAS externally oriented thinking	18.4 (5.0)	16.3 (4.4)	$F_{4,53}<1$	None	None
Sample Who Completed fMRI and Affect Matching					
Sample, No.	36	33			
Amygdala activation, affect match vs shape match parameter estimate ^e	0.423 (0.412)	0.574 (0.378)	$F_{4,64}<1$	None	None
Ventral IFG activation, affect match vs shape match parameter estimate ^e	0.108 (0.356)	0.432 (0.323)	$F_{4,64}=4.06^c$	$F_{1,64}=9.51^c$	None
Subsample Who Completed fMRI and Affect Matching/Labeling					
Sample, No.	25	23			
Amygdala activation, affect match, affect label, shape match parameter estimates			See Figure 3B		
Effective connectivity between amygdala and IFG			See Figure 3C		

Abbreviations: AQ, Aggression Questionnaire; CRT, Competitive Reaction Time task; fMRI, functional magnetic resonance imaging; IFG, inferior frontal gyrus; MA, methamphetamines; STAXI, State Trait Anger Expression Inventory; TAS, Toronto Alexithymia Scale.

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

^b $P < .001$.

^c $P < .05$.

^dToronto 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.

^eTests additionally adjust for volume.

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 differences in describing feelings or externally oriented thinking (Table 3). Across control participants, TAS difficulty identifying feelings correlated with STAXI trait anger ($r=0.57$; $P=.009$) and anger expression ($r=0.47$; $P=.04$). 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 vs shape match contrast showed widespread activation consistent with the neural system for face processing,^{103,104} 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,⁶⁸ we examined individual gray matter concentration in these ventral IFG clusters using voxel-based 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 matter concentration as a covariate into an ANOVA, comparing activation between groups. Activation values (average parameter estimates in ventral IFG clusters) correlated between left and right clusters ($r=0.57$; $P<.001$) and were combined by calculating a cluster-weighted average. The ANOVA showed no effect of gray matter concentration on these values, while the group difference remained (Table 3).

Finally, we investigated amygdala activation for differences between groups. Volume of amygdala ROIs differed by sex but not group ($F_{1,64}=1.21$; $P=.28$). Left and right amygdala activation values (average parameter estimates across ROI voxels) correlated with one another ($r=0.68$; $P<.001$) 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 $r > 0.61$; 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 activation, 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 AMYGDALA 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 significance, possibly because of low statistical power owing to the small subsample. When the 2 groups were combined to increase statistical power, decreased amygdala activity, controlling for group, showed a significant inverse relationship with CRT performance ($r = -0.45$; $P = .03$).

BEHAVIORAL CORRELATES OF VENTRAL IFG ACTIVITY

Because low ventral IFG activity in the MA group (Figure 3A) did not signify emotion dysregulation, we investigated its functional significance using linear regression. Ventral IFG

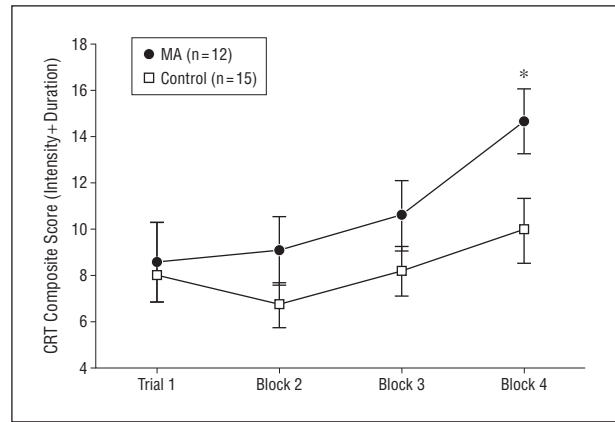


Figure 2. Perpetrated aggression across competitive reaction time task (CRT) blocks. Repeated-measures analysis of variance showed a significant block \times group interaction ($F_{3,75} = 2.88$; $P = .04$). Follow-up t tests revealed that methamphetamine-dependent (MA) and control participants did not differ in aggressive responding during trial 1 ($t_{25} < 1$), block 2 ($t_{25} = 1.38$), or block 3 ($t_{25} = 1.34$; all $P > .18$) but MA-dependent participants scored significantly higher than controls during block 4 ($t_{25} = 2.36$; $P = .03$). 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 \times group interaction.

activation (cluster-weighted average of left and right clusters) was entered as the independent variable, with behavioral measures as outcomes and demographic measures as covariates. In controls, ventral IFG activation did not directly relate to aggression but showed a significant inverse relationship with scores on the difficulty identifying feelings subscale of the TAS (Figure 5), suggesting that ventral IFG contributes to emotional insight. In MA-dependent participants, ventral IFG activation did not relate to TAS scores, suggesting a decoupling owing to their functional deficit in this region.

COMMENT

The results are consistent with the view that emotional insight, in addition to emotion regulation, contributes to aggression,²¹ and that this capacity involves the ventral IFG.¹⁰⁵⁻¹⁰⁷ 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 findings²⁰ and confirming descriptions from community samples.¹⁻⁹ 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,²¹ failure of either emotion regulation or emotional insight can ac-

Table 4. Functional MRI Clusters During Affect Matching/Labeling Task Performance^a

Region by Contrast	MNI Coordinates of Peak Voxel, mm			t	Cluster Size, Voxels
	x	y	z		
Affect match vs shape match					
All participants					
Left amygdala, parahippocampus	-22	-4	-14	4.01	192
Right amygdala, parahippocampus, putamen	22	-4	-14	5.01	964
Right inferior/middle frontal gyrus	52	22	26	7.79	6294
Left middle frontal gyrus	-40	16	28	6.92	6235
Left orbitofrontal cortex	-28	22	-24	3.62	73
Paracingulate gyrus	6	18	48	5.02	620
Left occipital cortex	-32	-86	18	7.43	702
Left inferior temporal gyrus	-38	-40	-22	6.43	4975
Right inferior temporal gyrus	40	-44	-20	6.17	
Left temporoparietal junction	-30	-54	42	5.91	728
Right temporoparietal junction	36	-56	44	6.22	
Left middle temporal gyrus	-54	-52	10	2.97	102
Right precuneus	6	-70	44	4.15	358
Right thalamus	10	-8	6	3.72	139
Left thalamus	-16	4	10	2.99	66
Control > MA					
Right ventral inferior frontal gyrus	42	48	-8	3.91	117
Left ventral inferior frontal gyrus	-40	58	-10	4.49	39
MA vs control					
None					
PPI with amygdala					
All participants					
Right dorsal inferior frontal gyrus	42	8	28	5.52	1105
Left dorsal inferior frontal gyrus	-36	18	24	3.84	375
Control > MA					
None					
MA vs control					
None					

Abbreviations: MA, methamphetamine; MNI, Montreal Neurological Institute; MRI, magnetic resonance imaging; PPI, psychophysiological interaction.
^aAll analyses adjusted for age, sex, and education.

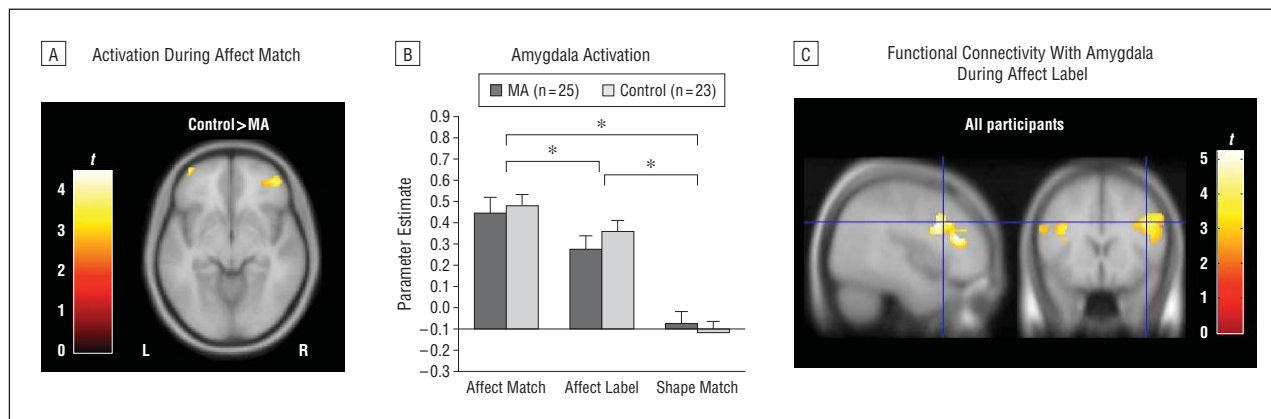


Figure 3. Inferior frontal gyrus (IFG) and amygdala activation patterns during the Affect Matching/Labeling task. A, Methamphetamine-dependent (MA) participants (n=36) showed less bilateral ventral IFG activation than controls (n=33) on the affect match vs shape match contrast (Table 2). Demographic covariates had no effect on activation. Whole-brain statistical maps are overlaid onto a structural template provided by SPM. B, Repeated-measures analysis of variance of amygdala region-of-interest values showed a significant effect of condition ($F_{2,92}=55.12$; $P<.001$) but no effect of group ($F_{1,46} < 1$; $P=.65$) or group \times condition interaction ($F_{2,92} < 1$; $P=.54$). Across participants, amygdala activation was lower during the affect label than affect match condition ($t_{47}=2.69$; $P=.01$) and lower than both affect match and affect label during the shape match condition ($t_{47}=10.09$; $t_{47}=7.50$; both $P<.001$). Demographic variables had no effect on the magnitude of decrease between conditions. C, Psychophysiological interaction analysis investigating the prefrontal cortex for regions that showed a greater inverse relationship with the amygdala during the affect label than affect match condition, identified dorsal IFG, predominantly on the right (Table 2). There was no difference between MA and control participants within these regions. Demographic variables did not influence connectivity. Statistical maps are overlaid onto a structural template provided by SPM. Orientation is neurological. Clusters in A and C did not overlap.

count 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 perpe-

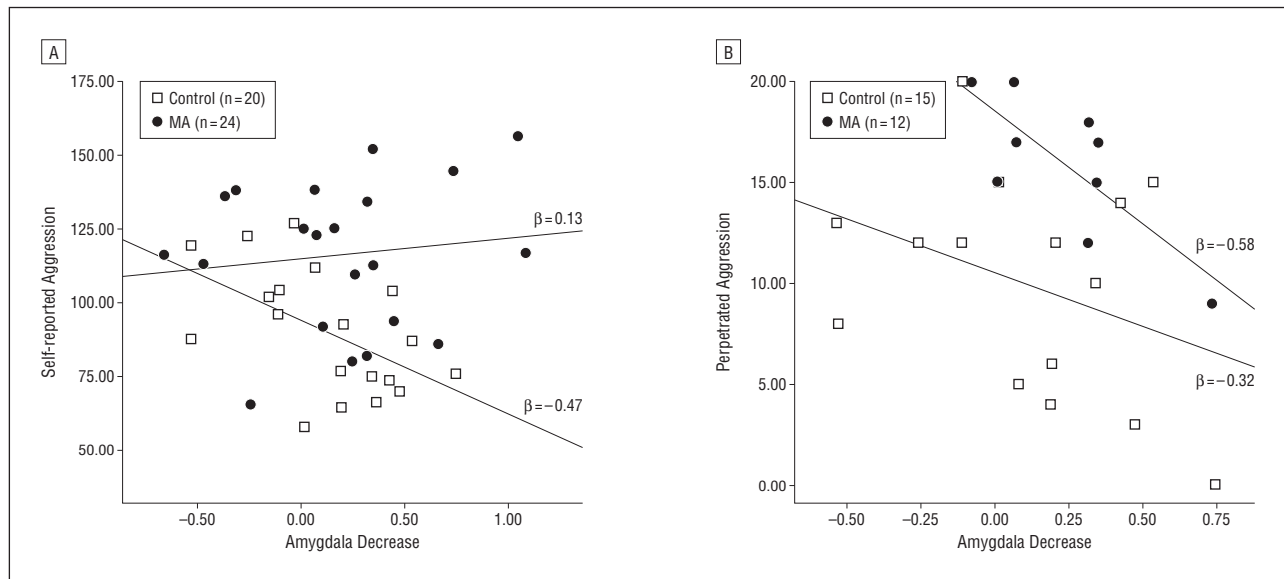


Figure 4. Relationships between decreased amygdala activity and aggression. Amygdala decrease denotes the magnitude of decrease in amygdala activation between affect match and affect label conditions, calculated as the difference between amygdala region-of-interest values (left and right combined) during each condition. A, Linear regression analysis showed that amygdala decrease inversely related to self-reported aggression (calculated as a composite of Aggression Questionnaire and State Trait Anger Expression Inventory trait anger and anger expression scores) in controls ($\beta = -0.47$; $t = 2.42$; $P = .03$) but not methamphetamine-dependent (MA) participants ($\beta = 0.13$; $t < 1$; $P = .56$). Age also showed a significant effect. B, Decreased amygdala activation inversely related to perpetrated aggression (competitive reaction time task [CRT] score at peak aggression [block 4]) in both groups. This effect was statistically significant in methamphetamine-dependent participants ($\beta = -0.58$; $t = 4.47$; $P = .01$) but not controls ($\beta = -0.32$; $t = 1.10$; $P = .30$). Sex also showed a significant effect in the analysis. All significant regression models survived Holm-Bonferroni correction for multiple comparisons.

trated aggression in all participants, suggesting that they represent a neural signature for successful emotion regulation^{55,57} 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^{31,32} and evidence that MA-related hostility results in part from misinterpretation of the world as a hostile and threatening place.¹⁰⁸

Importantly, our imaging data suggest that emotional insight relies on the ventral IFG, a region showing dysfunction in MA-dependent participants. During facial affect matching, MA-dependent participants showed low activity in bilateral ventral IFG (not overlapping with the dorsal IFG region implicated in amygdala regulation), while amygdala activation did not differ between groups. These results replicate and extend our previous findings¹⁸ and suggest that, while amygdala-dependent automatic reactions to socioemotional cues are comparable with those of healthy individuals, IFG-dependent deliberative processing is compromised. Ventral IFG is implicated in the recognition, representation, and comprehension of emotionally salient information, including the mental and emotional states of oneself and others,^{40-42,109} and neurocognitive models suggest that its activity can influence behavioral outcomes by modulating hypothalamic fight-or-flight responses following comprehension of socioemotional cues.^{110,111} The in-

verse correlation between ventral IFG activity and alexithymia observed in the controls is consistent with this evidence and suggests that low ventral IFG activity (as exhibited by MA-dependent participants) reflects a limited capacity to identify feelings. In line with a previously described relationship between ventral IFG function and harm avoidance/fear in MA-dependent individuals,⁷⁶ this deficit could diminish the motivation to temper maladaptive interpersonal behavior, thus escalating aggression.

Beyond increasing the likelihood of aggression, the same deficit could also contribute to the unreliable self-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 theoretical²¹ and neurocognitive¹¹¹ 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

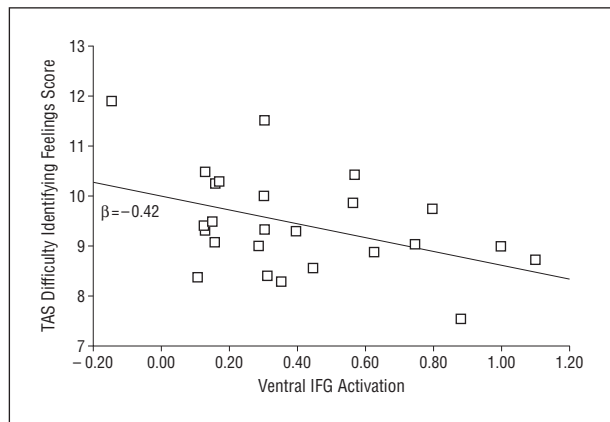


Figure 5. Relationship between ventral inferior frontal gyrus (IFG) activation and emotional insight. Linear regression analysis showed that across control participants ($n=25$), ventral IFG activation during affect matching was inversely related to scores on the difficulty identifying feelings subscale of the Toronto Alexithymia Scale (TAS) ($\beta=-0.42$; $t=2.16$; $P=.04$). 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.

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 activity or regulation could therefore reflect the low temporal resolution of the design (or the low spatial resolution of fMRI) rather than true equivalence in function. Further, amygdala and ventral PFC are susceptible to signal dropout, potentially obscuring the data. Third, decreased amygdala activation between affect match and label conditions could have resulted from factors other than inhibitory control processes such as differences in stimulus parameters or attention. However, Lieberman et al⁵⁵ have shown that amygdala activity decreases with affect labeling but not perceptual and attentional control conditions, and other studies^{57,80} have shown associated decreases in subjective measures of emotion, making incidental emotion regulation a plausible interpretation. Finally, although our data suggest that alexithymia is a crucial contributor to MA-related aggression, the possibility that additional trait characteristics (eg, impulsivity, volatile temper, sensation-seeking) mediate this relationship cannot be excluded.

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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