Opiate Addicts Lack Error-Dependent Activation of Rostral Anterior Cingulate

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Background: *Healthy individuals performing response suppression tasks activate anterior cingulate cortex with occurrence of false alarm error responses to nontargets. Fundamental questions include whether this error-related activation provides a signal contributing to behavioral control and, given generally poorer performance on such tasks by addicts, whether this signal is disrupted in addiction.*

Methods: *We used rapid, event-related functional magnetic resonance imaging to study 13 individuals with opiate dependence and 26 healthy control individuals performing a Go/NoGo task.*

Results: *Compared with controls, opiate addicts exhibited an attenuated anterior cingulate cortex error signal and significantly poorer task performance. In controls, the individual level of event-related anterior cingulate cortex activation accompanying false alarm error positively predicted task performance, particularly sensitivity in discriminating targets from nontargets.*

Conclusions: *The attenuation of this error signal in anterior cingulate cortex may play a role in loss of control in addiction and other forms of impulsive behavior.*

Key Words: Substance-related disorders, heroin dependence, decision making, choice behavior, impulsivity, personality

Addiction is defined by the loss of control over behavioral impulses, specifically, the impulse to use drugs. Current laboratory measures used to study impulsive responding capture either of two basic dimensions derived from animal models of impulsivity. The first dimension, reward-discounting (RD), is considered an inability to delay rewards or the choice of a small immediate reward over a larger delayed reward (Ainslie 1975; Monterosso and Ainslie 1999). Laboratory measures of this dimension of impulsive responding include delay discounting tasks (Bickel et al 1999; Epstein et al 2003; Kirby et al 1999; Madden et al 1997; Mitchell 1999), the Bechara gambling task (BGT) (Bechara et al 1994), and the Balloon Analogue Risk Task (BART; Lejuez et al 2003). The other dimension of impulsive responding has been termed rapid-response (RR) impulsivity (Swann et al 2002). Tasks in this category include the Go/NoGo and the Immediate Memory/Delayed Memory Task. In such tasks, the occurrence of commission (false alarm [FA]) errors is considered to reflect "inability to conform tasks [responses] to an environmental context" (Swann et al 2002). The majority of research relating laboratory measures of impulsivity to addiction has involved reward-discounting tasks; however, two recent reports (Finn et al 2002; Kaufman et al 2003) link RR impulsivity to addiction.

Surprisingly, little evidence has emerged directly relating loss of behavioral control to the neurophysiology of addiction. As stated, one prominent cognitive feature characteristic of impulsive individuals, including addicts, is increased occurrence of false alarm error responses to nontargets on response suppression tasks (Swann et al 2002). Healthy, nonaddicted individuals performing such tasks have repeatedly shown activation of anterior cingulate cortex (ACC) associated with occurrence of FA errors both in imaging (Braver et al 2001; Kiehl et al 2000; Menon et al 2001; Ullsperger and von Cramon 2001) and electrophysiological (Falkenstein et al 1990; Gehring et al 1990) studies. A fundamental question is whether this error-related activation provides a signal contributing to behavioral control (Carter et al 1998; Gehring et al 1993) and, given generally poorer performance on such cognitive tasks by disinhibited individuals (Newman 1987) including addicts (Finn et al 2002), whether this signal is disrupted in addiction.

Many theories of cognitive control suggest that the ACC plays a key role in regulating behavior, with dorsal regions primarily responsible for cognitive functions, such as response selection, error detection, and response conflict detection, and rostral regions more involved in affective processing such as mood regulation or pain perception (see Bush et al 2000 for a review). In practice, the separation of "cognition" from "affect" may be impossible, e.g., as Damasio (1994) has suggested that "somatic marking" of events is a necessary component of behavioral control. Hence, the precise contributions of specific ACC regions to behavioral control remain to be determined.

The current experiment was designed to test the idea that RR impulsivity in opiate addiction is related to disruptions of ACC functionality. Rapid-response impulsivity can be investigated by applying signal detection theory (SDT) (Green and Swets 1966) on target discrimination tasks. Signal detection theory allows choice behavior to be separated into two component measures. Response bias (β) reflects the amount of perceptual evidence necessary to decide that a stimulus is a target. Discriminative sensitivity (D') is a measure of the extent to which targets are successfully discriminated from nontargets, which accounts for both the number of targets correctly identified as targets and the number of nontargets correctly rejected as nontargets. Elevated false alarm rates have tended to be equated with RR impulsivity; however, either a "liberal" response bias or low sensitivity could produce such elevated rates of false alarms. Thus, SDT allows one to more clearly differentiate the processes underlying traditional measures of impulsive performance, such as false alarm rates, in

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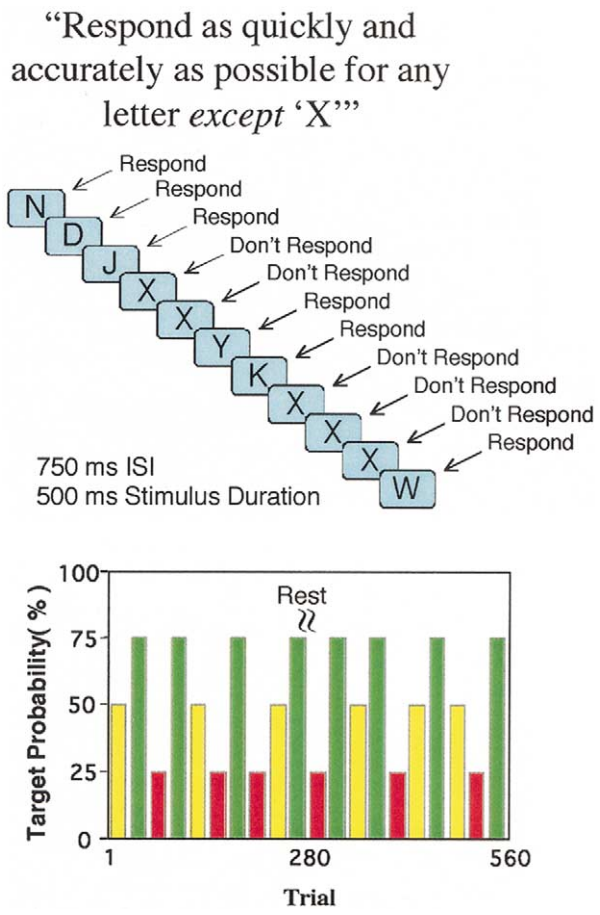

Figure 1. Target probability varying Go/NoGo. The task is explained in the text. ISI, interstimulus interval.

choice reaction tasks. Functional magnetic resonance imaging (fMRI) allows investigation of the extent to which ACC activity is related to performance. Combining fMRI with signal detection analysis allows a fine-grained understanding of how brain activity relates to individual and group differences in performance.

Thus, to investigate the role of the ACC in impulsive responding in opiate addiction, we used a version of a Go/NoGo task in which the probability of a target stimulus occurring at each trial shifted among low, medium, and high likelihood levels every 28 trials (Figure 1). Earlier work (Casey et al 2001) has suggested that varying target probability within-task would prevent participants from establishing a single strategic set for response bias and consequently allow more sensitivity in separating β versus D′ influences on impulsivity within individuals (and across groups). Participants completed this task during assessment of brain activity in the region of the rostral ACC using fMRI.

We hypothesized that 1) opiate addicts would display impaired signal detection on the task; 2) opiate addicts would display disrupted activation in brain areas associated with error responses, namely the ACC; and 3) disrupted ACC activity in opiate addicts would be related to performance on the task. Because our hypotheses involve highly specific predictions about differential effects of brain activation between groups, we chose a two-phase study design. In the first phase, we used one set of healthy control participants to specifically identify ACC regions of interest (ROIs) associated with both differential responsivity to correct and error trials and with task performance. We then performed a confirmatory analysis of brain activity within these ROIs between a group of opiate addicts and an independent, closely demographically matched group of healthy controls.

Methods and Materials

Participants

All 39 participants provided written informed consent to participate in this research according to procedures approved by the VA Pittsburgh Human Studies Subcommittee and the University of Pittsburgh Institutional Review Board (IRB). As part of an ongoing longitudinal study on the cognitive effects of methadone maintenance treatment (MMT), we recruited 13 healthy opiate-addicted participants between the ages of 18 and 55 years at or shortly after intake (mean duration of MMT = 15.5 days, range 0–21 days). A DSM-IV opiate-dependence (OD) diagnosis was established by structured interview (First et al 1996). Exclusion criteria included any active DSM-IV axis I disorder other than substance abuse/dependence, intelligence quotient (IQ) < 85 (by Wechsler Adult Intelligence Scale-Revised [WAIS-R] vocabulary subtest), and any serious neurologic or medical illness (sufficient to preclude magnetic resonance imaging [MRI] or testing).

In addition to the above criteria, any substance abuse/dependence diagnosis was excluded in control participants. Before any analyses, to control for possibly confounding effects of age, gender, ethnicity, and parental education (as a marker for expected socioeconomic status [SES] before onset of addiction), we selected from all control participants those best matched to the opiate-addicted participants on these characteristics (MC, n = 13). One OD and one MC participant each met criteria for past major depression, completely remitted; otherwise, participants had no past history of any DSM-IV axis I disorders.

Control participants not included in the MC group (n = 13) constituted our phase I, ROI identification group (nMC) group. By using an independent sample to identify ACC ROIs, we avoided any selection bias in the choice of voxels sampled for the between-group comparisons of brain activation.

At the time of scanning, five OD participants had not yet received any methadone; the methadone doses for the others were 45 to 80 mg/d. All carried opiate dependence as their primary current substance use diagnosis; seven also carried secondary current substance use disorder diagnoses (4 of 7 cocaine dependence). Saliva testing showed 10 of 10 positive for opiates and 4 of 10 positive for cocaine at time of scanning and 0 of 10 positive for alcohol (3 participants were not tested). No controls tested positive for any illicit substance. With one exception (Objective Opiate Withdrawal Scale [OOWS] = 5) (Handelsman et al 1987), all other OD participants showed minimal or no signs of opiate withdrawal at the time of scanning (mean OOWS = 1.8, range 0–3). Similarly, at time of scanning, no participants exhibited any signs of acute intoxication (as assessed by expert clinicians).

As shown in Table 1, there were no significant differences between the OD and the MC groups on the demographic matching variables, although there was the expected lower current SES for the OD group. Participants in the nMC group were younger and predominantly female. Opiate-dependent participants had a mean (SD) history of 16.3 (11.0) years of opiate use; 12 of 13 OD participants were tobacco smokers; no control subjects smoked. All participants were right-handed and native English-speaking. In this article, we use the terms opiate dependence and opiate addiction interchangeably.

Table 1. Mean (SD) Participant Characteristics

Characteristic	Opiate Addicts	Matched Control	Nonmatched Control
n	13	13	13
Age, y	35.3 (10.2)	34.8 (9.3)	26.7 (8.7)
Gender (women/men)	6/7	6/7	12/1
Ethnicity (African Descent/Caucasian)	2/11	2/11	4/9
Parental Education[a]	4.0 (1.3)	4.8 (.9)	5.0 (1.3)
SES[a]	2.5 (.8)[b]	3.7 (1.1)	4.2 (1.2)
Personality Measures			
Positive affectivity	146 (13)	151 (12)	155 (12)
Negative affectivity	143 (21)[b]	117 (13)	120 (10)
Constraint	161 (13)	171 (14)	165 (15)
Trait Impulsiveness			
BIS total	71.0 (11.9)[b]	57.6 (8.4)	57.4 (10.4)
Performance			
log RT, seconds	−.97 (.13)	−.88 (.20)	−1.00 (.10)
D′	3.75 (.61)[b]	4.38 (.56)	4.30 (.64)
log β	−1.96 (.94)	−1.86 (.99)	−2.29 (.91)

SES, socioeconomic status; BIS, Barratt Impulsiveness Scale; RT, reaction time.
[a]Hollingshead 1965.
[b]Significantly different from Matched Control value ($p < .05$) by Dunnett's test (Dunnett 1955).

Target Probability Varying Go/NoGo

Paradigm presentation and response recording used the CIGAL stimulus presentation environment (Voyvodic 1999). The stimulus set was a pseudorandom sequence of individual uppercase letters presented in a continuous epoch of 280 trials, ITI = 1.25 seconds, stimulus duration = .5 seconds. Participants were instructed to "respond as quickly and accurately as possible to any letter except X." Every 28 trials ("block"), target probability was set to one of three fixed levels (.25, .5, .75) for the next 28 trials in a counterbalanced order. No information was provided to the participant during the course of the task distinguishing one block from the next. Following a 1-minute rest, a similar epoch of 280 trials was presented. Each response (button-press with right index finger) was accompanied by the appearance of a small illuminated dot below the stimuli. This provided immediate visual confirmation to the participant of all button presses without differentiating between correct and incorrect responses (Figure 1).

Measures of Behavioral Performance, Trait Impulsiveness, and Personality

Before analysis, raw accuracy data (e.g., hit rates and false alarm rates) were converted to standard measures of discriminative sensitivity (D′ = Normal Quantile [1-false alarm rate] − Normal Quantile [1-hit rate]), where the Normal Quantile function accepts a probability argument, *p*, and returns the *p*th quantile from the standard normal distribution, and response bias (β = Normal Density [Normal Quantile (1-hit rate)] / Normal Density [Normal Quantile (1-false alarm rate)]), with appropriate adjustment (Davies and Parasuraman 1982) for blocks with perfect performance. β and reaction time (RT) data were natural log transformed to conform to normality assumptions (Nuechterlein 1991). We used the Barratt Impulsiveness Scale (Patton et al 1995) as a trait measure of impulsivity. Individual measures of Positive Affectivity, Negative Affectivity, and Constraint were calculated from responses to the Multidimensional Personality Questionnaire (MPQ) (Tellegen 1982). The MPQ is a 300-item self-report instrument that assesses a wide range of personality characteristics. Its factor-analytically derived scales represent 11 lower-order trait dimensions and 3 higher-order personality traits (e.g., Positive Affectivity, Negative Affectivity, and Constraint). One OD and one MC participant did not complete the questionnaire.

MRI Image Acquisition

Images were acquired with a 1.5T GE Signa scanner with an Advanced NMR Systems (Wilmington, Massachusetts) head coil. Following scout images, a coronal spoiled gradient sequence (time of repetition [TR] = 25 milliseconds, time of echo [TE] = 5 milliseconds, flip angle = 40, 256 × 192 acquisition matrix, field of view [FOV] 24 cm, 124 slice, 1.5 mm) was obtained for precise structural anatomy. A 2-shot spiral scan, gradient echo sequence was used to acquire functional images (TR = 625 milliseconds/shot, TE = 35, flip angle = 35, 64 × 64, FOV 24 cm, 8 oblique coronal slices, 5-mm slice thickness, contiguous). Due to variations in head position between participants, functional imaging coverage was limited to an obliquely canted portion of the frontal cortex encompassing the rostral cingulate (Figure 2A). Two hundred eighty image acquisitions were made for each of the two epochs of behavioral trials for a total of 560 trials per participant. Due to technical malfunction, the scans corresponding to the second epoch of trial presentations were lost for three control participants.

MRI Image Analysis

Phase I (ROI Generation). Following registration to the structural images, the functional images of the nMC participants were resampled into 1 mm^3 isotropic voxels, transformed into standardized atlas space (Talairach and Tournoux 1988), corrected for interacquisition movement, spatially smoothed using an 8-mm full width at half maximum (FWHM) Gaussian filter and linear trends removed. Each voxel time course was submitted to an event-related general linear model (GLM) analysis in which a separate predictor for each participant for each event (false alarm, correct rejection [CR], and miss) was generated by convolving a boxcar function for the trial intervals in question with a standard gamma hemodynamic reference function (Boynton et al 1996) using BrainVoyager v4.6 (BrainInnovation, Maastricht, The Netherlands). Hits were not modeled and thus contributed to the intercept. Time courses were z-transformed to equalize for differences in scan signal intensity and variance across partici-

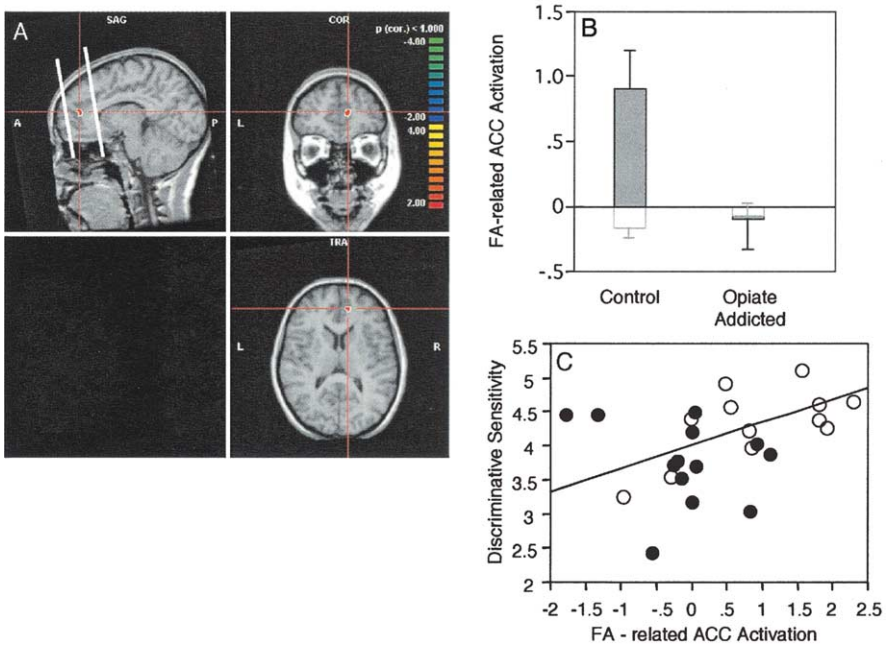

Figure 2. Attenuated FA event-related ACC activation in opiate addicts. **(A)** Region of interest associated with FA error activity. The white lines define the anterior-posterior extent of the region examined. **(B)** Matched control group shows elevated mean levels (+SEM) of event-related ACC activation with FA (gray bars) over that of the OD group—activation averaged across all the voxels in the region of interest for each group (and presented in units of standardized regression coefficient for the respective predictor of the fMRI time course, e.g., FA events or CR events). Neither group showed any event-related ACC activation with CR (open bars). **(C)** Increased FA-related ACC activation is associated with improved discriminative sensitivity in matched controls but not opiate addicts. The line is a plot of linear regression fit to the matched control data ($R^2 = .41$, $p < .03$). Solid circles (Opiate-Addicted), open circles (Matched Control). FA, false alarm; ACC, anterior cingulate cortex; OD, opiate dependence; fMRI, functional magnetic resonance imaging; CR, correct rejection. SAG, sagital; COR, coronal; TRA, transverse.

pants and corrected for serial correlations before generation of statistical parametric maps of the appropriate event contrasts.

Phase II (Confirmatory Analyses of ROI Averaged Data). After using the nMC participants' data to identify appropriately activated clusters as ROIs (see conjunction analysis below), we processed the functional scans of the MC and OD participants identically, except that all the voxels in the ROIs were averaged on a timepoint-by-timepoint basis and subjected to the event-related GLM analysis (as above, except ROI-averaged rather than voxel-based) from which predictor regression weights were derived. These ROI-averaged regression weights for each participant were entered into various analyses as either responses or effects (as further described below) to test for associations with group, personality measures, or performance measures. One matched control participant with perfect performance was eliminated from the individual analysis of FA-related activation. All other participants made at least three FA errors (median = 16, range 3–80) and were included in the analysis. Miss events occurred too infrequently for reliable analysis.

Conjunction Analysis. To selectively identify regions in which activity is both error-associated and performance-associated, we performed a conjunction analysis (Friston et al 1999) across two contrasts on the FA event predictor for the nMC group. In the first contrast, we equally weighted the FA predictor for each participant. This identifies those voxels that are significantly active (2-tailed $\alpha < .05$) with FA error. In the second contrast, we applied a monotonically increasing weighting (−6 to +6 in single step intervals) to the FA predictor for each of the 13 nMC participants, respectively, according to their relative discrimina-tive sensitivity (D′) performance on the Go/NoGo task. This contrast identifies those voxels whose relative FA-related activity tends to parallel the relative level of individual performance. To correct for multiple comparisons, we used a cluster size threshold (Forman et al 1995) of 200 mm^3, with individual voxel α-threshold of .00063, which provided an overall α-level of .1 (Cox 1996). The latter, relatively liberal, threshold was chosen to maximize identification of candidate ROIs for the subsequent confirmatory analysis. Two ROIs exceeding the cluster size threshold were identified as significantly active across both contrasts.

Statistical Analyses

Individual measures of age, gender, ethnicity, parental education, SES, log RT, D′, log β, Trait Impulsiveness, Positive Affectivity, Negative Affectivity and Constraint were compared across groups using univariate analyses of variance (ANOVAs), both to validate our matching procedure (for the matched variables) and to characterize the sample (SES, performance, and personality measures). To test whether addiction, trait impulsiveness, or personality affects performance, we used Group × Trait Impulsiveness or Personality measure analyses of covariance (ANCOVAs) versus measures of performance (e.g., log RT, D′, and log β). To determine whether Opiate Addicts exhibit deficient FA-related ACC activation after statistically controlling for individual differences in performance, we used ANCOVA with Group as main effect and log RT, D′, and log β as covariates. Finally, to test our primary hypothesis of an association between error-related brain activation and task performance, we used two Group × FA-related ACC activation ANCOVAs with log RT as a covariate and D′ and log β as dependent variables. By including log RT as a covariate, we account for correlations among the individual performance components due to cognitive processes such as "speed accuracy trade-off." Note that models involving FA-related activation as either a response or as an effect only compare MC and OD data, as the nMC data were used to generate the ROI tested.

Results

Personality and Trait Impulsiveness Measures

Groups differed significantly in Negative Affectivity [$F(2,34) = 10.3$, $p < .0003$] and Trait Impulsiveness [$F(2,35) = 7.09$, $p < .003$] with opiate-addicted participants having higher scores than MC and nMC participants (Table 1). Groups did not significantly differ in Positive Affectivity [$F(2,34) = 1.79$, NS] or Constraint [$F(2,34) = 1.64$, NS]. None of the three major personality

measures or Trait Impulsiveness significantly predicted any measure of performance (i.e., log RT, D′, or log β) either individually or after covarying out the effect of Group.

Behavioral Data Analysis

Were addicts impaired on signal detection? Opiate-addicted participants showed poorer discriminative sensitivity than MC and nMC participants [$F(2,36) = 4.24$, $p < .02$]. This difference between opiate-addicted participants and controls remains significant, even after excluding the four participants with co-occurring cocaine dependence [$F(2,32) = 4.75$, $p < .02$]. In contrast, groups did not significantly differ in response bias [$F(2,36) = .72$, NS]. Thus, on this task, the larger FA rate (or RR impulsivity) in opiate addicts versus controls appears to result from poorer discriminative sensitivity rather than an excessive tendency to respond (e.g., a "liberal" response bias).

Groups did not significantly differ in overall response latency [$F(2,36) = 2.22$, NS], although consistent with previous work (Braver et al 2001), we found that latency [$F(2,72) = 9.53$, $p < .0002$] decreased with increased target probability across all Groups. In addition, both discriminative sensitivity [$F(2,72) = 14.1$, $p < .0001$] and response bias [$F(2,72) = 182.7$, $p < .0001$] decreased with increased target probability across all groups.

Finally, a Group × log RT ANCOVA model of discriminative sensitivity was significant [$F(5,33) = 4.45$, $p < .003$], with significant Group [$F(2,33) = 6.52$, $p < .004$] and Group × log RT [$F(2,33) = 4.48$, $p < .02$] effects. The Group × log RT ANCOVA model of response bias was also significant [$F(5,33) = 3.34$, $p < .02$], but only the main effect of log RT across all groups was significant [$F(1,33) = 14.45$, $p < .0006$]. Because of the significant effect of log RT on both discriminative sensitivity and response bias, log RT is specifically accounted for as an included covariate in all subsequent models involving these components of performance.

MRI Data Analysis

Did addicts display disrupted ACC activation in brain areas associated with error responses? As described in Methods and Materials, the exploratory conjunction analysis identified two candidate ACC ROIs for confirmatory testing. Region of interest no. 1 (Talairach coordinate 9, 43, 13 at center-of-mass; total volume = 241 mm^3) (Figure 2A) was entirely contained within Brodmann's area 32. Region of interest no. 2 (Talairach coordinate −3, 39, 25 at center-of-mass; total volume = 2701 mm^3) overlies portions of Brodmann's areas 32 and 9. The confirmatory comparison of the ROI-averaged brain activities for FA-related and CR-related events showed significantly greater FA-related activity in the MC group compared with the opiate-addicted group in both ROIs [ROI no. 1: $F(1,23) = 7.52$, $p < .01$] (Figure 2B) and [ROI no. 2: $F(1,23) = 14.54$, $p < .0009$]. This group effect persisted in ROI no. 1 even after statistically controlling for individual differences in performance, trait impulsiveness, and personality by entering log RT, D′, log β, Trait Impulsiveness, Positive Affectivity, Negative Affectivity, and Constraint as simultaneous covariates in an ANCOVA [Group main-effect, $F(1,14) = 4.37$, $p < .05$]. In ROI no. 2, adding the simultaneous covariates weakened the predictive strength of Group for FA-related activation, but the effect was still present at the trend level [Group main-effect, $F(1,14) = 3.72$, $p < .07$]. Separately from Group, none of the performance, trait impulsiveness, or personality measures exhibited any significant predictive strength modeling FA-related activation individually or as simultaneous regressors (in either ROI). Neither group showed any significant difference in event-related ACC activation with correct rejections in either ROI. Finally, the significant Group main effect persisted even after excluding participants with co-occurring cocaine dependence [ROI no. 1: $F(1,19) = 4.14$, $p < .06$ and ROI no. 2: $F(1,19) = 7.80$, $p < .01$].

Thus, opiate addicts both performed more poorly on the task and exhibited decreased FA-related rostral ACC activation. Moreover, these results suggest that some feature of opiate addiction, apart from differences from controls in trait impulsiveness or personality, contributed to the disrupted FA-related ACC activation.

Was disrupted ACC activity in addicts related to performance on the task? For ROI no. 1, the Group × FA-related ACC activation ANCOVA model for discriminative sensitivity performance was significant [$F(4,20) = 3.03$, $p < .05$] along with a significant Group × FA-related ACC activation interaction [$F(1,20) = 4.02$, $p < .05$]. As shown in Figure 2C, increased FA-related ACC activation predicts increased discriminative sensitivity performance in MC participants, while no such improvement is noted in the opiate addicts. Within the model, after statistically accounting for the effects of log RT, FA-related ACC activation, and Group × FA-related ACC activation, Group no longer significantly predicted discriminative sensitivity [$F(1,20) = 3.31$, $p < .09$]; however, a trend-level relationship remained. In the ANCOVA model for response bias, only log RT significantly predicted log bias [$F(1, 20) = 4.7$, $p < .04$]. In ROI no. 2, the ANCOVA model did not significantly predict either discriminative sensitivity performance [$F(4,20) = 2.19$, $p < .1$] or response bias [$F(4,20) = 1.86$, $p < .16$]. Taken together, these analyses indicate that significant aspects of task performance (especially, sensitivity in discriminating targets from nontargets) can be modeled on the basis of individual differences in FA-related ACC activation at least for one region in Brodmann's area 32.

Discussion

Opiate addicts displayed poorer signal detection than control participants. Opiate addicts also displayed disruptions in rostral ACC activity associated with errors on the task. Moreover, ACC activity was related to both within-group and between-group differences in performance. Together, these data are consistent with the idea that measures of RR impulsivity in opiate addiction are associated with disruptions in ACC activity. A critical question, whether these measures of RR impulsivity are linked to more complex, clinically relevant manifestations of behavior such as likelihood of future relapse, remains to be resolved.

One can argue that both the attenuated FA-related ACC response and the subpar performance in the opiate dependent group are due not to the feature of opiate dependence, per se, but to other, possibly covarying characteristics such as other substance use, psychosis, withdrawal or methadone dosing, or poorer sensory processing or attention among the opiate addicts.

Although we selected participants with primary addictions to opiates, they were representative of the typical patient entering MMT (e.g., very high prevalence of co-occurring cocaine dependence [Grella et al 1997] and other substance use, especially tobacco [Berger and Schweigler 1972]). Cocaine users have recently been shown to exhibit performance and FA-related ACC response deficits (Kaufman et al 2003) very similar to those observed in this study. The subset analysis of opiate-addicted participants without cocaine dependence indicates that such deficits are not specific to either cocaine or opiate addiction. On the other hand, we cannot rule out the possible influence of other substances, particularly tobacco. In this sample, the comorbidity of opiate dependence and smoking exceeded

90%. We chose to exclude smokers from our control samples because we did not want to potentially contaminate our "nonaddicted" control groups with participants addicted to tobacco. Smokers score higher on impulsivity scales and more steeply discount delayed rewards than nonsmokers (Bickel et al 1999; Mitchell 1999), a pattern of results similar to that seen in opiate dependence (Kirby et al 1999; Madden et al 1997; Petry et al 1998). Future studies should investigate this potential confound.

Loss of rostral ACC activation with FA errors has also recently been reported in schizophrenia (Laurens et al 2003). As we had excluded psychosis in our addicted population, it seems unlikely that psychotic disorder is the basis for our findings. Tobacco use was unreported by Laurens et al (2003), so one cannot evaluate its potential contribution, though it is well known that the prevalence of smoking in schizophrenia approaches 90% (Lohr and Flynn 1992).

We also considered the possible influence of withdrawal state or methadone dosing. After one outlying participant was eliminated, the relationship between withdrawal scores and multivariate performance was not significant [Wilks' $F(3,8) = 1.30$, NS]. Neither methadone dose nor withdrawal scores produced any other significant relationship with individual performance measures or ACC activation with FA error. Hence, while it is possible that withdrawal status (especially, higher levels of withdrawal than represented in this sample) may affect certain aspects of performance, neither low-grade withdrawal nor short-term methadone dosing appears to strongly influence performance or FA-related ACC activation.

To minimize the possible contribution of gross sensory or attentional deficits, we carefully screened all participants for comorbid psychiatric/medical problems and for acute/chronic cognitive impairments (including intoxication). Overall, we had a fairly healthy group of opiate addicts. This may have contributed to the relatively selective, rather than generalized, pattern of cognitive deficits seen. In postsession debriefings, these addicted participants were quite aware of having made many FA errors; however, although we excluded gross deficits, we did not screen for more subtle deficits or attention-deficit/hyperactivity disorder (ADHD). It is well-known that individuals with ADHD perform poorly on Go/NoGo tasks (Trommer et al 1988). Prevalence estimates for undiagnosed ADHD in substance use disorder populations range from 20% to 35% (Levin et al 2003). Thus, it is quite possible that undiagnosed ADHD may contribute to these results. Future investigations of RR impulsivity in addiction should specifically screen for ADHD.

Inferences from this work are also constrained both by the limited frontal coverage obtained and by other characteristics we did not measure, such as psychopathy. Psychopathy has long been linked to similar RR impulsivity performance deficits (Newman 1987) and medial frontal hypofunction (Dikman and Allen 2000; Kiehl et al 2001), as well as to addiction (Cloninger et al 1988; Schubert et al 1988), allowing the potential for third variable mediation of the observed results; however, we also note that previous work suggests that the behavioral factor of psychopathy (e.g., the factor linked to Trait Impulsiveness) is most strongly linked to substance use disorder status (Hemphill et al 1994). In our sample, Trait Impulsiveness was not associated with performance or FA-related ACC response. Further investigations are clearly needed to clarify the relationship between RR impulsivity, Trait Impulsiveness, and psychopathy. It is important to emphasize that the ACC error response signal is only one component of probably several neural control systems (possibly involving brain regions not evaluated in this study) modulating RR aspects of task performance and behavior. Even with an attenuated ACC error response, opiate addicts perform the task competently, just not as competently as the controls who presumably advantageously utilize the ACC error response.

What might be the information processing function for ACC activation with FA errors? Because target probability varies, this Go/NoGo task puts a premium on the ability to integrate information over a series of trials to predict the likelihood that an upcoming stimulus is a target and to dynamically modify the likelihood estimate over the course of the task. Indeed, ACC activation with FA errors in this task bears a striking resemblance to the anticipatory skin response with suboptimal decisions noted by Bechara et al (1996) with their gambling task and to the medial frontal cortical activation with context-dependent "losses" recently reported by Gehring and Willoughby (2002). Opiate addicts lack this signal, presumably directly contributing to their poorer task performance. Interestingly, on a superficially similar gambling task, but one in which all contingencies are explicitly represented at each trial (e.g., no integration over trial history is required for optimal response), Rogers et al (1999) showed that opiate users performed indistinguishably from controls on measures of "quality of decision making" and "risk taking." If the ACC-related error response in our study reflects "somatic marking" (Damasio 1994), then it seems such marking is especially relevant to performance dependent on dynamic adjustment of likelihood estimates over a series of events.

In summary, several prior event-related fMRI studies identified this region of rostral ACC as selectively activated by failed response suppression (Braver et al 2001; Kiehl et al 2000; Menon et al 2001; Ullsperger and von Cramon 2001) in healthy, nonaddicted participants. This study extends these results by establishing a pathologic failure of this ACC error response in a clinical sample of opiate addicts and by establishing links between the function of this system and specific aspects of individual task performance. This ACC error response deficit may contribute to behavioral impulsivity, and further investigation is needed to determine whether it results from chronic substance use or contributes to the establishment or maintenance of addiction or both.

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