

Blunted Prefrontal Cortical ¹⁸Fluorodeoxyglucose Positron Emission Tomography Response to Meta-Chlorophenylpiperazine in Impulsive Aggression

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Background: Impulsive aggression is a prevalent problem and yet little is known about its neurobiology. Pre-clinical and human studies suggest that the orbital frontal cortex and anterior cingulate cortex play an inhibitory role in the regulation of aggression.

Methods: Using positron emission tomography, regional metabolic activity in response to a serotonergic stimulus, meta-chlorophenylpiperazine (m-CPP), was examined in 13 subjects with impulsive aggression and 13 normal controls. The anterior cingulate and medial orbitofrontal regions were hypothesized to respond differentially to m-CPP in patients and controls. In the frontal cortex, regional metabolic glucose response to m-CPP was entered into a group (impulsive aggressive, control) × slice (dorsal, middle, orbital) × position (medial, lateral) × location (anterior, posterior) × hemisphere (right, left) mixed-factorial analysis of variance design. A separate group (impulsive aggressive, con-

trols) × anteroposterior location (Brodmann areas 25, 24, 31, 29) × hemisphere (right, left) analysis of variance was used to examine regional glucose metabolism in the cingulate gyrus.

Results: Unlike normal subjects, patients with impulsive aggression did not show activation specifically in the left anteromedial orbital cortex in response to m-CPP. The anterior cingulate, normally activated by m-CPP, was deactivated in patients; in contrast, the posterior cingulate gyrus was activated in patients and deactivated in controls.

Conclusions: The decreased activation of inhibitory regions in patients with impulsive aggression in response to a serotonergic stimulus may contribute to their difficulty in modulating aggressive impulses.

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ALTHOUGH VIOLENT crime has decreased in the past decade, violent incidents involving impulsive aggression rather than planned violence are increasing.¹ These include juvenile violence, domestic violence, and workplace acts of aggression.^{2,3} Violence and homicide are significantly associated with mental illness, especially antisocial and borderline personality disorder.⁴ Considering the serious consequences of impulsive-aggressive behavior, its neurobiology has received little scrutiny.

Evidence from metabolite and neuroendocrine studies has linked abnormalities in central serotonin activity to impulsive aggression.⁵⁻⁸ The association of lesions in the orbitofrontal cortex (OFC) and anterior cingulate gyrus (ACG) with disinhibited aggression suggests that faulty regulation of negative emotion, through

a reduced serotonin-mediated activation of the prefrontal cortex, may predispose an individual to impulsive aggression.⁹

BRAIN REGIONS AND AGGRESSION

Studies of brain lesions suggest regional control of aggression, with the ACG and OFC playing central roles.¹⁰⁻¹⁵ The critical influence of the OFC and the ACG in human aggression is exemplified by the case of Phineas Gage, who, after a penetrating brain injury, became hostile and verbally aggressive. Computerized reconstruction of Gage's skull demonstrated the location of his brain lesion in the anteromedial cortex, the OFC and the ACG, with more marked damage in the left hemisphere.¹⁶

Most lesions in the medial OFC also include damage to the ACG. In the human brain, the ACG has 2 main subdivi-

SUBJECTS AND METHODS

SUBJECTS

Thirteen patients with impulsive aggression (8 men, 5 women; mean [SD] age, 31.7 [8.5] years; range, 20-43 years; 9 right-handed, 3 left-handed, 1 mixed) who met *DSM-IV* criteria for 1 or more personality disorders were included. Patients with a history of schizophrenia, psychotic disorder, or bipolar type I affective disorder were excluded. Patients with current major depressive disorder were also excluded since this has been associated with impaired brain regional response to fenfluramine.³⁸ All patients had been medication-free for 6 weeks or more (9 of 13 had never taken medication). An age- and sex-matched group of 13 normal subjects was also studied (8 men, 5 women; mean [SD] age, 31.6 [8.1] years; range, 21-43 years; 11 right-handed, 1 left-handed, 1 mixed).

Subjects were screened for severe medical or neurological illness, head injury, history of alcohol/drug dependence, and substance abuse in the past 6 months. All subjects had negative urine toxicology screen results for drugs of abuse, and women had negative pregnancy tests on each positron emission tomography (PET) scan day. Participants provided written informed consent in accordance with the guidelines of our institutional review board. Patients were recruited for the study through advertisement in local newspapers (90%) and through referrals from outpatient psychiatric clinics at the Bronx Veterans Affairs Medical Center (Bronx, NY) and Mount Sinai School of Medicine (New York, NY) (10%). Of 85 subjects screened, 13 subjects were successfully recruited into the patient group. Patients were excluded, in order of frequency, because of current substance abuse, a chronic medical problem such as diabetes or heart disease, pregnancy, the presence of current major depression, and in one case, the presence of current psychotic symptoms. In addition, one subject declined participation because of fear of the radioactive isotope. In the control group, approximately 90 candidates responded to our advertisement. Many subjects were excluded because of the presence of an Axis I or Axis II diagnosis in themselves (detected at screening) or a first-degree relative.

Axis I and personality disorder diagnoses were made through interviews with a psychologist using the Structured Clinical Interview for *DSM-IV* Axis I disorders³⁹ and the Structured Interview for *DSM-IV* Personality Disorders (SIDP-IV),⁴⁰ respectively. Trait aggression was assessed using the Module for Intermittent Explosive Disorder-Revised (IED-R)⁴¹ and depression with the Hamilton Depression Rating Scale (HDRS).⁴² All subjects completed the Buss-Durkee Hostility Inventory (BDHI)⁴³; both total (BDHI_{total}) and composite Irritability-Assaultiveness subscale (BDHI_{IRR-ASS}) scores have been associated with biological markers of aggression⁷ (**Table 1**).

All patients met the following criteria: (1) significant physical and/or verbal aggression meeting criteria for IED-R ($\kappa=0.92$); (2) impulsivity as assessed by the SIDP-IV

“impulsiveness” criterion for borderline personality disorder ($\kappa=0.78$), including behavior such as reckless driving or impulsive sexual behavior; and/or (3) self-damaging acts (predominantly self-mutilatory cutting of the skin) as assessed by the SIDP-IV “self-damaging” borderline criterion (A5) (interrater reliability, $\kappa=0.90$). Controls met none of the 3 above-defined criteria and had no personal or first-degree family history of psychiatric illness.

Prolactin and cortisol levels, obtained from all subjects except for 2 controls (technical difficulties with the intravenous line precluded blood sampling), were measured as described previously, and the peak minus baseline was calculated (Δ prolactin, Δ cortisol).⁴⁴

PROCEDURE

On 2 separate occasions, each participant received m-CPP or placebo (counterbalanced to control for order effects). At 8 AM, after an overnight fast, 1 intravenous line was inserted into each forearm (1 used for blood sampling, the other for injection of m-CPP/placebo and ¹⁸fluorodeoxyglucose). An 0.08-mg/kg solution of m-CPP/placebo in an identical syringe of 20 mL of saline was given by slow push over 90 seconds. Immediately following, 5 mCi (185 MBq) of ¹⁸fluorodeoxyglucose was administered into the venous set rubber diaphragm behind the subject's back as a 4560-second slow push. The subject remained in a resting state in a sound-attenuated, dimly lit room for the 35-minute tracer-uptake period, after which the subject was escorted to an adjacent bathroom to void. The subject was then positioned in the PET scanner using a previously prepared thermosetting plastic mask. The imaging data-acquisition period lasted about 40 minutes. Scans were separated by at least 1 week to allow for drug elimination (3-4 days) and to coincide with a weekly scan schedule. All subjects and staff were blind to the dosing/placebo regimen. On each scan day, patients were evaluated with the HDRS.

IMAGING

Positron emission tomography scans were carried out as described elsewhere^{33,45} (General Electric Medical Systems scanner model 2048, General Electric, Milwaukee, Wis; [resolution 4.5 mm in plane, 5.0 mm axially]). Fifteen slices at 6.5-mm intervals were obtained in 2 sets to cover the entire brain. Slice counts of 1.53 million counts are typical. Scans were reconstructed with a blank and a transmission scan using the Hanning filter (width, 3.15 mm). The same individually molded thermoplastic face mask was used for each scan to keep the head stationary during image acquisition and to assist in PET/magnetic resonance imaging (MRI) image coregistration. Positron emission tomography images were obtained in nCi/pixel and standardized as relative metabolic rate (rGMR) by dividing each pixel by the mean value for the entire brain (defined by brain edge from coregistered MRI). While this limits interpretations of single-structure absolute activity, this method is widely used when evaluating hypotheses related to patterns of metabolic rate across brain areas and

sions: the dorsal cognitive division (including the dorsal part of Brodmann areas [BAs] BA24 and BA32) and the rostral-ventral affective division (including the rostral part of BA24, BA32, and BA25).^{17,18} The affective sub-

division receives wide input from regions, including the hippocampus, amygdala, medial OFC, and dorsal raphe, and projects to the basal ganglia, subthalamic nuclei, and lateral hippocampus.^{18,19} In an animal model,

was used in 4 earlier imaging studies of serotonin activation.^{33,34,37,38} Within 1 week of their PET scans, participants underwent MRI examination as described previously⁴⁶ (General Electric Signa 5X, acquisition parameters: repetition time, 24 milliseconds; echo time, 5 milliseconds; flip angle, 40°; slice thickness, 1.2 mm; matrix, 256 × 256; field of view, 23 cm). Magnetic resonance images were resectioned to standard Talairach-Tournoux⁴⁷ position. Positron emission tomography–MRI coregistration used the algorithm of Woods et al.⁴⁸ Brain edges were visually traced on all MRI axial slices. Intertracer reliability on 27 individuals is 0.99 for area.

On the basis of earlier studies,^{33,34,37} the cingulate, orbitofrontal, and medial frontal regions were hypothesized to respond differentially to serotonin agonists in patients and controls. These areas were located in advance of any analysis in the Talairach-Tournoux atlas and their coordinates recorded (**Table 2**). For the cingulate, we used x-coordinates 5 mm from midline; for BAs, we chose the position of numerals or halfway between duplicate numerals, 5 mm from the cortical edge. The square region of interest (ROI) (5 × 5 pixels) was applied centered on that coordinate and at the proportion as the brain-bounding box in the Talairach-Tournoux atlas. An adjustment was made so that ROIs were moved closer to the centroid of the slice if the box fell partly outside the coregistered brain outline, as could happen in brains that were especially narrow in the y direction for boxes placed at 45° and 135°.

This method, the reverse Talairach hypothesis–driven strategy, was used for 3 reasons: (1) to minimize type I statistical errors in evaluating large numbers of ROIs in both hemispheres through the use of multiway repeated-measures analysis of variance (ANOVA) and a single F ratio test indicating the hypothesized diagnostic group × condition × region interaction; (2) to minimize type II errors resulting from assessing small individual, potentially noisy ROIs and failing to observe orbitofrontal system–wide response by combining ROIs; and (3) to provide standard and known brain atlas locations for replication. We also controlled type I error by not discussing main effects or interactions that are not interpretable (eg, main effect of slice level across structures measured at multiple axial slice levels) or peripheral to our interest (main effect of hemisphere across the normal controls and patients). Our analysis is limited in power by the sample size (n = 13 in each of the 2 groups).

STATISTICAL DESIGN

A 2 × 3 × 2 × 2 × 2 mixed-factorial ANOVA design was applied to rGMR data obtained from frontal ROIs. Dependent variables were expressed as difference scores (m-CPP – placebo) for rGMR within each ROI. The first variable consisted of the 2 participant groups (impulsive-aggressive and controls), and the remaining variables were all repeated measures, consisting of 3 slice levels (dorsal, middle, and orbital; corresponding to Talairach-Tournoux levels: +12, +4, and –4, respectively), 2 medial/lateral positions (medial and lateral prefrontal cortex), 2 anteroposterior locations (anterior and posterior), and

2 hemispheres (right and left). At the dorsal slice level (+12 slice), the medial regions included BA10 (anterior region) and BA32 (posterior region), and the lateral regions included BA46 (anterior region) and BA45 (posterior region). At the middle and orbital slice levels, the ROIs were the same as at the dorsal level except that the lateral regions were BA10 (anterior region) and BA47 (posterior region).

A separate ANOVA was performed on 4 BAs within the cingulate gyrus. This 2 × 4 × 2 mixed-factorial design was employed to examine the drug-placebo rGMR difference values within the BAs for the 2 cohorts. The first variable consisted of the 2 groups, the second variable consisted of 4 BAs in the anteroposterior position (BA25, BA24, BA31, and BA29), and the third variable consisted of 2 hemispheres. Brodmann area 25 was located on the +4 slice level and the 3 remaining cingulate regions were located on the +12 slice level. All statistical analyses involving repeated measures with more than 2 levels used Greenhouse-Geisser ϵ corrections to adjust probabilities for repeated-measures F values. Uncorrected degrees of freedom are reported. To detect the source of significant interactions between group and hypothesized BA, we carried out an ANOVA on each BA separately. For interactions involving slice level, replicated ROIs adjacent in position or hemisphere were not followed up because they were not part of our hypothesis or were neuroanatomically not important. In addition, we report results of the Mauchly sphericity test, the Levine homogeneity of variance test, and the multivariate Rao R.

To explore relationships between the prefrontal cortex and cingulate gyrus rGMR and clinical measures of the degree of impulsivity, measured by BDHI_{total} and BDHI_{IRR-ASS} scores, Spearman correlations were computed only for regions entered into the ANOVAs above.

EXPLORATORY SIGNIFICANCE PROBABILITY MAPPING

To provide a survey of the entire brain slice, we carried out voxel-by-voxel *t* tests on the same brain slices assessed by the stereotaxic ROI method. The significance probability mapping technique is similar to other approaches but uses MRI-based region alignment.⁴⁹ Continuous edges were manually drawn around the brain. Nine midline points equally spaced in the z direction were identified. Slices were then adjusted by the number of rows and columns so that every slice contained an equal number of pixels, with every edge pixel aligned and midline pixels positioned in a vertical strip at the edge center. Positron emission tomography images for the placebo and drug scans were coregistered to the same MRI similarly standardized, and unpaired *t* tests were carried out for the drug minus placebo difference scores. To confirm our original report of blunted response to fenfluramine and to provide validation of the reverse-Talairach ROI approach, we present these images with 1-tailed probability maps. To examine other already published studies and provide exploratory results for future investigators, we present 2-tailed probability maps.

electrical stimulation of the ACG in the cat brain ACG resulted in an increased latency in attack behavior.²⁰

While the ACG is implicated in affective-cognitive activity,¹⁸ the posterior cingulate gyrus is implicated in

sensory processing and perhaps in processing fear-inducing stimuli.^{21–25} The posterior cingulate has reciprocal pathways to the hippocampus, ACG, parahippocampal gyrus, and temporal areas.^{26,27}

Table 1. Impulsive-Aggressive Patients With Personality Disorders*

Patient No./ Sex/Age, y	Handedness	HAMD	Suicidal	BDHI	IRR-ASS	Self-Injury	Axis I Disorders	Axis II Disorders
1/M/38	L	14	0	38	12	0	Bipolar II, HX ETOH, IED-R	PPD, SPD, ASPD, NPD
2/M/23	R	15	0	47	14	0	MDD (past), HX ETOH, IED-R	NPD, BPD
3/F/22	R	11	1	22	10	0	MDD (past), DYSTH, IED-R	AVPD, BPD
4/F/20	R	14	0	41	13	0	MDD (past), GAD, SOCPHOB, IED-R	OCPC, BPD
5/M/24	R	10	0	53	17	0	HX ETOH, SOCPHOB, GAD, IED-R	PPD, SPD, OCPD, ASPD
6/M/38	R	2	0	14	2	0	HX ETOH, IED-R	PPD, SPD, AVPD, BPD
7/F/36	M	1	0	40	13	0	BDD, IED-R	NPD, AVPD
8/M/29	R	11	0	31	10	0	MDD (past), HX ETOH, IED-R	AVPD, BPD, ASPD
9/M/43	L	14	0	51	17	0	MDD (past), SOCPHOB, IED-R	PPD, OCPD, NPD, BPD
10/F/26	R	15	0	46	14	1	MDD (past), DYSTH, IED-R	PPD, OCPD, AVPD, BPD
11/F/42	L	9	1	49	18	0	MDD (past), DYSTH, IED-R	PPD, NPD, BPD
12/M/43	R	14	1	46	18	0	MDD (past), HX POLYSUB, IED-R	NPD, PPD, ASPD

*HAMD, Hamilton Depression Rating Scale; BDHI, Buss-Durkee Hostility Inventory; IRR-ASS, Buss-Durkee Hostility Inventory Composite Subscale of Irritability and Assaultiveness; self-injury, self-mutilatory cutting; HX ETOH, history of alcohol abuse; IED-R, intermittent explosive disorder-revised; PPD, paranoid personality disorder; SPD, schizotypal personality disorder; ASPD, antisocial personality disorder; NPD, narcissistic personality disorder; MDD (past), history of major depressive disorder; BPD, borderline personality disorder; DYSTH, dysthymia; AVPD, avoidant personality disorder; GAD, generalized anxiety disorder; SOCPHOB, social phobia; OCPD, obsessive-compulsive personality disorder; BDD, body dysmorphic disorder; and POLYSUB, history of polysubstance abuse.

Table 2. Talairach Coordinates for Localization

Brodman Area (BA)	X	Y	Z
Talairach Coordinates for Cingulate Boxes (Right Hemisphere)			
Anterior BA25	8	32	4
Middle BA24	8	33	12
Middle BA31	8	-57	12
Posterior BA29	8	-65	12
Talairach Coordinates for Frontal Boxes (Right Hemisphere)			
BA10 medial anterior	5	60	12
BA32 medial posterior	5	45	12
BA46 lateral anterior	48	25	12
BA45 lateral posterior	45	40	12
BA10 medial anterior	5	60	4
BA32 medial posterior	5	45	4
BA46 lateral anterior	45	45	4
BA45 lateral posterior	48	30	4
BA11 medial anterior	5	60	-4
BA11 medial posterior	5	45	-4
BA11 lateral anterior	42	50	-4
BA47 lateral posterior	48	30	-4

POSITRON EMISSION TOMOGRAPHY STUDIES AND AGGRESSION

Positron emission tomography (PET) studies of relative glucose metabolic rate (rGMR) have related abnormalities in the ACG and prefrontal cortex to impulsive aggression.²⁸⁻³⁰ In an anger-induction model, normal men showed increased rGMR in the left OFC and right ACG,³¹ perhaps reflecting the normal activation of inhibitory regions in response to anger stimulation.

A variety of serotonergic agents can modulate rGMR in the prefrontal cortex and in the ACG. d-Fenfluramine has been found to increase rGMR in the left ACG and in the prefrontal cortex in normal subjects.³² In our previous study, normal subjects showed increased metabolism in the ACG and OFC following fenfluramine administration, while patients did not.³³ These findings were replicated in a study of borderline personality disorder.³⁴ Meta-chlorophenylpiperazine (m-CPP), a non-

specific 5-HT agonist,³⁵⁻³⁶ increased rGMR in the right OFC, middle frontal gyrus, posterior cingulate, and thalamus in normal subjects.³⁷

Our study assesses rGMR in a larger sample of patients with impulsive aggression and normal controls after administration of m-CPP. We hypothesized that (1) patients would show decreased rGMR in the OFC and ACG after m-CPP relative to controls; (2) the posterior cingulate would not show blunting in patients vs controls; (3) in patients, medial regions of the OFC would show a more blunted response to m-CPP than would lateral regions, suggesting that the ACG with the adjacent OFC, which normally modulates aggression through a serotonergic mechanism, is underactive in impulsive aggression.

RESULTS

NEUROENDOCRINE MEASURES

Analysis of mean responses to m-CPP showed no significant between-group differences for either Δ prolactin levels (controls: mean [SD], 20.22 [21.34] ng/mL; median, 18.1 ng/mL; patients: 23.55 [18.78] ng/mL; median, 16.3 ng/mL; $t_{22}=0.41$, $P=.69$; Mann-Whitney $U=63.5$, $P=.64$) or Δ cortisol levels (controls: 11.45 [7.60] μ g/dL; median, 12.5 μ g/dL; patients: 12.97 [6.08] μ g/dL; median, 13.3 μ g/dL; $t_{22}=-0.54$, $P=.59$; Mann-Whitney $U=58$, $P=.46$).

CLINICAL MEASURES

The mean (SD) HDRS score of patients on the day of m-CPP administration was 10.5 (4.8), a typical score for patients with personality disorders who experience some dysphoria even when not clinically depressed. As expected, BDHI scores showed significant between-group differences (BDHI_{total}, controls: mean [SD], 20.23 [7.84]; range, 6-32; median, 22.0; patients: 40.54 [11.74]; range, 14-49; median, 46.0; $t_{24}=5.18$, $P<.001$; Mann-Whitney

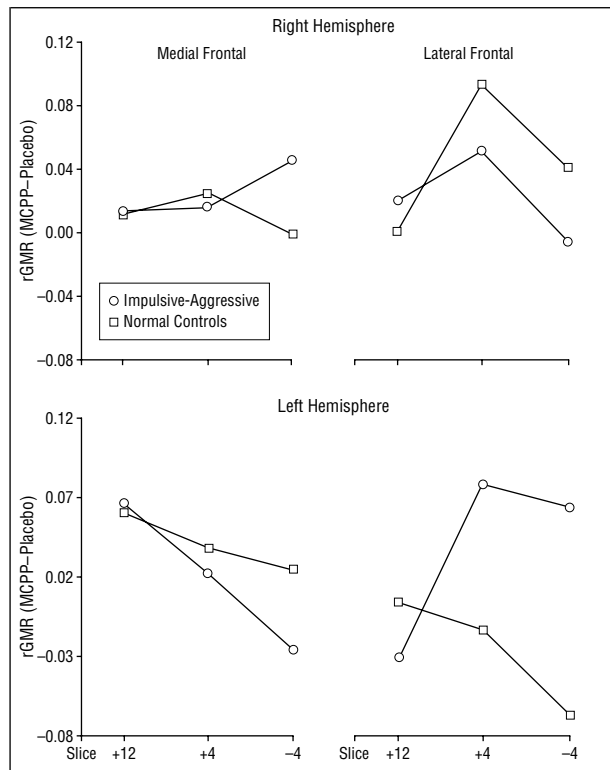


Figure 1. Frontal cortex regions. Mean relative glucose metabolic rate (rGMR) difference values (meta-chlorophenylpiperazine [m-CPP]- placebo) in prefrontal cortex regions of interest are shown for normal controls and patients with impulsive aggression (group \times slice \times medial/lateral \times hemisphere interaction; $F_{2,48}=5.20$, $P=.009$). At the most dorsal slice level (+12), the medial regions include BA10 and BA32 and the lateral regions include BA46 and BA45. For the middle (+4) and orbital (-4) slice levels, the medial regions include BA10 and BA32 and the lateral regions include BA10 and BA47.

$U=17.5$, $P<.001$; $BDHI_{RR-ASS}$, controls: mean, 5.93 [3.86]; range, 1-15; median, 6.0; patients: 13.54 [4.52]; range, 2-18; median, 14.0; $t_{24}=4.62$, $P<.001$; Mann-Whitney $U=17.5$, $P<.001$).

POSITRON EMISSION TOMOGRAPHY

Prefrontal Cortex

Effects of m-CPP. **Figure 1** shows mean rGMR difference scores (m-CPP - placebo) in frontal lobe ROIs for patients and controls. A 2 (group) \times 3 (slice) \times 2 (medial/lateral cortex) \times 2 (anterior, posterior location) \times 2 (hemisphere) ANOVA of rGMR difference scores revealed a significant group \times slice \times medial/lateral \times hemisphere interaction (univariate: $F_{2,48}=5.20$, $P=.009$; multivariate: Rao $R_{2,23}=4.54$, $P=.02$). In the right hemisphere, patients showed a blunted m-CPP response at the orbital slice level in the lateral but not medial frontal regions compared with controls. In the left hemisphere, this effect was reversed, with patients, unlike controls, showing a blunted response at the orbital slice level in medial but not lateral frontal regions. Although the interaction effect was statistically significant, simple-effects tests for each of the regions within the ANOVA failed to reach significance. The main effect of group ($F_{1,24}=0.04$, $P=.83$) and all other interpretable interaction effects with group

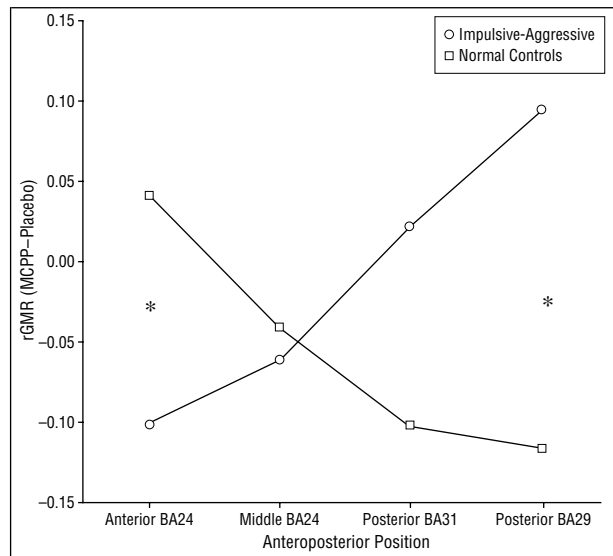


Figure 2. Cingulate gyrus regions (meta-chlorophenylpiperazine [m-CPP] effect). Mean relative glucose metabolic rate (rGMR) difference values (m-CPP - placebo) in the cingulate gyrus are shown for normal controls and patients with impulsive aggression (group \times anteroposterior cingulate region interaction; $F_{3,72}=7.12$, $P<.001$). Asterisks indicate significant group differences, $P<.05$.

(group \times medial/lateral; $F_{2,48}=0.08$, $P=.91$; group \times right/left; $F_{1,24}=0.40$, $P=.53$) failed to reach significance. Despite the fact that none of the post-hoc tests were significant, this interaction reflects a significant rGMR pattern that differs between the 2 groups.

Baseline. To determine whether the groups differed in baseline rGMR, we conducted a 2 (group) \times 3 (slice) \times 2 (medial/lateral cortex) \times 2 (anterior and posterior) \times 2 (hemisphere) ANOVA on the placebo scan data. There was neither a main effect of group nor an interaction effect, indicating that patients did not differ from controls in baseline rGMR in the frontal lobe ROIs examined.

Cingulate Gyrus

Effects of m-CPP. **Figure 2** shows mean rGMR difference scores (m-CPP - placebo) in the cingulate gyrus for patients and controls. A 2 (group) \times 4 (anteroposterior BA) \times 2 (hemisphere) ANOVA revealed a significant group \times anteroposterior region interaction (univariate $F_{3,72}=7.12$, $P<.001$; multivariate Rao $R_{3,22}=4.63$, $P=.01$), indicating that in the ACG (BA25), m-CPP response was blunted in patients compared with controls. The Levene test for homogeneity of variances (ANOVA on absolute within-cell deviation scores, degrees of freedom for all F values 1,24) shows none of the 8 variables to be significant (P range, .2-.97) (Rao $R_{3,22}=7.11$, $P=.002$ [Wilks Λ , 0.507]; Mauchly sphericity test Wilks $\Lambda=0.32$; $\chi^2_5=25.8$, $P<.001$).

When the order of drug and placebo administration was added as a fourth independent group dimension, neither the main effect of order ($F_{1,21}=0.73$, $P=.40$) nor the group \times order \times region interactions ($F_{3,63}=0.39$, $P=.76$) were statistically significant. In the posterior cingulate (BA31 and BA29), the effect was reversed, with patients showing a greater m-CPP response than controls (Figure

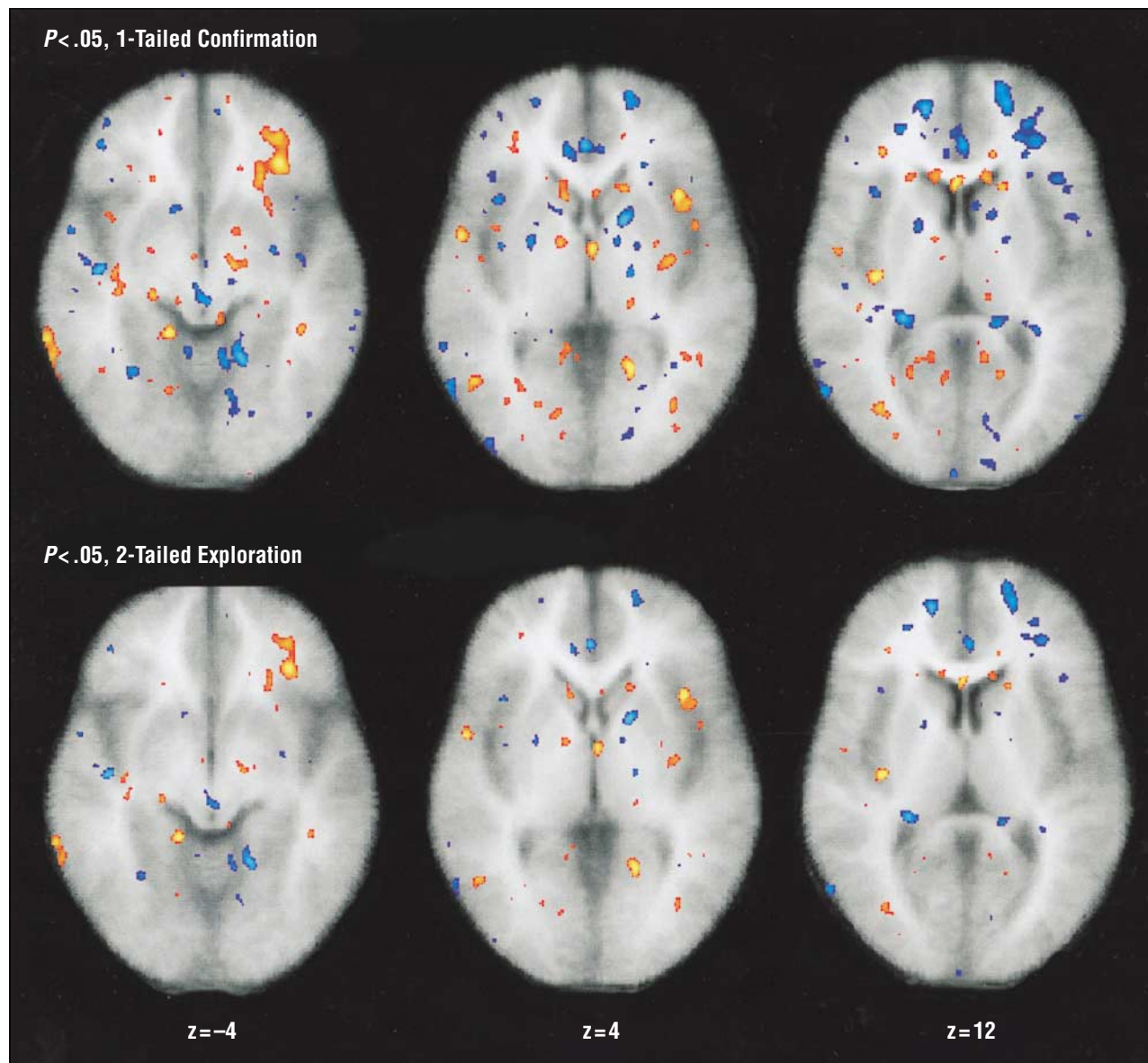


Figure 3. Statistical probability map. Relative metabolic rate differences (drug – placebo). Blue indicates that patient response to meta-chlorophenylpiperazine (m-CPP) was less than that of normal controls; red, patient response to m-CPP was greater than that of normal controls (1- and 2-tailed *t* tests, *P* < .05). Background is mean coregistered and shape-standardized magnetic resonance imaging.

2). An orthogonal set of individual planned comparisons confirmed that patients, compared with controls, showed a significantly weaker m-CPP response in the ACG (BA25) ($F_{1,24}=6.13$, $P=.02$) but a significantly greater m-CPP response in the posterior cingulate (BA29) ($F_{1,24}=7.92$, $P=.001$). There were no significant group effects for BA31 ($F_{1,24}=3.45$, $P=.08$) or for BA24 ($F_{1,24}=.13$, $P=.71$). Statistical probability mapping (**Figure 3**) of drug minus placebo scores confirm the blunted response in the ACG in patients (blue), especially slices $z=4$ and $z=-4$, and the greater response in the posterior cingulate (red, $z=12$).

Baseline. **Figure 4** shows mean rGMR in the cingulate gyrus on the placebo scan day. To determine whether patients and controls differed in baseline rGMR in the cingulate gyrus, we conducted a 2 (group) \times 4 (anteroposterior) \times 2 (hemisphere) ANOVA on the placebo scan data,

which revealed a significant group \times anteroposterior region interaction (univariate $F_{3,72}=5.63$, $P=.008$; multivariate Rao $R_{3,22}=7.12$, $P=.001$). Compared with controls, patients had lower rGMR in the posterior cingulate but not in the anterior (BA25) and middle cingulate (BA24) regions. Individual planned comparisons confirmed that patients had significantly lower rGMR than controls in BA31 and BA29 ($F_{1,24}=4.52$, $P=.04$ and $F_{1,24}=9.88$, $P=.004$, respectively). There were no group differences for BA25 ($F_{1,24}=3.10$, $P=.09$) and BA24 ($F_{1,24}=1.24$, $P=.27$).

rGMR AND CLINICAL RATINGS

Prefrontal Cortex

Baseline. In controls during the placebo condition, increased rGMR was associated with higher trait aggression

scores (BDHI_{total}) in the right BA46 at the dorsal ($r_s=0.61$, $P=.027$) and middle ($r_s=0.69$, $P=.009$) slice levels. In addition, higher-measure subscale BDHI_{IRR-ASS} scores were associated with increased rGMR in BA46 bilaterally in the middle slice level (right: $r_s=0.581$, $P=.04$; left: $r_s=0.61$, $P=.03$ in the right and left, respectively), and BA46 at the ventral slice level on the right ($r_s=0.64$, $P=.02$), as well as in BA10 bilaterally at the middle slice level (right: $r_s=0.49$, $P=.08$; left: $r_s=0.56$, $P=.05$). In patients, increased rGMR was associated with higher scores of aggression (BDHI_{total}) in the left BA46 at the middle- and ventral slice levels ($r_s=0.587$, $P=.03$; $r_s=0.59$, $P=.02$, respectively). Similarly, higher scores of aggression were associated with increased rGMR in the right BA10 at the ventral slice level ($r_s=0.639$, $P=.02$).

Effects of m-CPP. In controls, decreased m-CPP response in BA47 bilaterally was associated with higher BDHI_{total} score at the middle slice level ($r_s=-0.61$, $P=.02$; $r_s=-0.62$, $P=.02$). In addition, lower BDHI_{IRR-ASS} subscales were associated with increased rGMR in the left BA47 ($r_s=-0.55$, $P=.05$). An inverse correlation between rGMR and aggression scores was also observed in BA45 bilaterally ($r_s=-0.61$, $P=.03$; and $r_s=-0.66$, $P=.02$). In patients, a direct correlation was seen between m-CPP response in the right BA45 at the dorsal slice level (BDHI_{total}, $r_s=.56$, $P=.04$; BDHI_{IRR-ASS}, $r_s=0.58$, $P=.03$) and in the right BA10 at the middle slice level ($r_s=0.57$, $P=.04$).

Cingulate Gyrus

Baseline. In the baseline (placebo) condition, increased rGMR in right and left middle cingulate gyrus (BA24) in controls was associated with increased BDHI_{IRR-ASS} scores ($r_s=0.59$, $P=.03$ and $r_s=0.12$, $P=.69$, respectively). In contrast, increased rGMR in the left posterior cingulate (BA29) was associated with increased BDHI_{IRR-ASS} scores in patients ($r_s=0.52$, $P=.06$).

Effects of m-CPP. There were no significant Spearman correlations in either patients or controls between rGMR for BA25, BA24, BA31, and BA29 and measures of aggression.

COMMENT

Patients with impulsive aggression react aggressively in response to interpersonal emotional cues, such as conflict or perceived disrespect. We hypothesized that limbic structures (ie, the hippocampus and amygdala) may be activated by an interpersonal trigger. Then, through a mechanism facilitated by serotonin, inhibitory regions (ie, the ACG and OFC) are activated. In our current experiment, m-CPP provided a serotonergic activation that is expected to activate inhibitory areas in normal subjects.

Our data show that in response to a serotonergic stimulus, rGMR in the left medial posterior OFC is lower in patients with impulsive aggression compared with controls. Alternative regions connected to the medial OFC, including the lateral orbital cortex and areas of the fron-

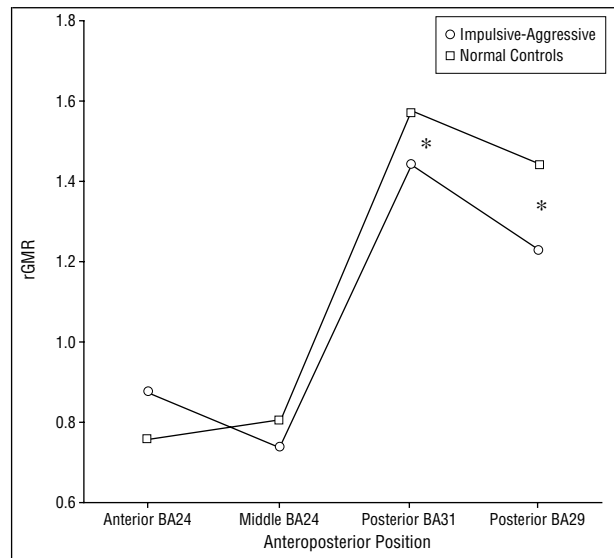


Figure 4. Cingulate gyrus regions baseline (placebo). Mean relative glucose metabolic rate (rGMR) in the cingulate gyrus on the placebo scan day in normal controls and in patients with impulsive aggression. Group \times anteroposterior cingulate region interaction; $F_{3,72}=5.63$, $P=.008$. Asterisks indicate significant group differences, $P<.05$.

tal cortex, are activated in patients. No group differences emerged in the baseline condition, suggesting that differences between patients and controls can only be observed under a serotonergic challenge. Although post hoc comparisons of the m-CPP response between groups in individual frontal ROIs were not significant, the model comparing drug activation between groups in medial vs lateral and orbital vs dorsal areas was significant. This supports our a priori hypothesis, that relative m-CPP rGMR in specific frontal areas (medial vs lateral; orbital vs dorsal) would be diminished in patients with impulsive aggression.

In the cingulate cortex, there were important differences in responses to m-CPP. The ACG (BA25) was activated in response to m-CPP in controls, whereas in patients, it was deactivated. In contrast, the posterior cingulate was deactivated in controls in response to m-CPP and was activated in patients (Figure 2). The overall model entered into the ANOVA and the post-hoc comparisons of responses to m-CPP in the ACG and posterior cingulate were significant. This suggests that in patients with impulsive aggression, activation of the posterior cingulate rather than the ACG is the gateway to the inhibitory medial OFC. Activation of the posterior cingulate is not accompanied by activation of the OFC and thus is less effective in modulating aggression in patients than in normal subjects.

LATERALITY

The diminished m-CPP response in the ACG and the adjacent medial OFC in patients was especially marked in the left hemisphere. Previous studies of emotional processing and frontal lobe laterality have suggested that the left hemisphere may be involved with “approach” and the right with “withdrawal.”⁵⁰ Left frontal regions have been described as the center for self-regulation and plan-

ning⁵¹ whereas right frontal regions may be involved with negative affects, such as fear and disgust.⁵⁰ Traumatic brain injury in the left dorsofrontal region gives rise to anger and hostility, whereas lesions of the right OFC result in anxiety and depression.¹⁴ Phineas Gage's lesion was predominantly left-sided.¹⁶ The reported predominance of the left hemisphere in the control of emotion was borne out in our study, which demonstrated a blunted metabolic response to m-CPP in the left medial OFC in patients relative to controls. The opposite effect was observed in the right OFC, where controls showed lower rGMR after m-CPP than did patients. Findings of significant aggression-related laterality have not been reported for the ACG and were not seen in our analysis.

MEASURES OF IMPULSIVE AGGRESSION AND rGMR

Clinical correlations between aggression and rGMR in the regions entered into the ANOVAs were performed, although the groups were not comparable because the scores of aggression fell into a much higher range in patients than in controls. Controls demonstrated a direct correlation between the degree of aggression and rGMR in BA46 bilaterally in the baseline condition. Patients showed a similar effect but it was limited to the left hemisphere. In response to m-CPP, however, controls with higher aggression scores exhibited increased m-CPP activation in BA47 and BA45. In contrast, patients with higher aggression scores showed lower m-CPP response in BA45 and no relationship in BA47. This gives further evidence that patients and controls may use frontal brain regions differently in regulating aggression.

In the cingulate region, there were no associations between m-CPP-stimulated rGMR and the degree of aggression in controls or patients. Thus, the m-CPP probe was sensitive enough to distinguish between groups that differ substantially in impulsive aggression (ie, patients vs controls) but not to pick up differences in the narrower range of aggressive behavior seen within groups.

The absence of patient-control differences in neuroendocrine responses to m-CPP may be the result of relatively small numbers of subjects in each cell, particularly when results are examined separately by sex. The use of a serotonin stimulus in conjunction with ¹⁸fluorodeoxyglucose-PET to examine specific activation of brain regions may be a more sensitive probe for serotonergic dysfunction in impulsive aggression than the challenge paradigm.

This study used a serotonergic probe to activate ACG and OFC. Future studies examining rGMR in response to aggression induction would provide even more powerful evidence of the relationship between the activation of specific brain regions and the control of aggression. Our study implicates the ACG and the medial posterior orbital cortex in the control of aggressive behavior, and suggests that serotonin may facilitate this control. m-CPP is known to act as a partial agonist at 5-HT_{2A} and 5-HT_{2C} receptors, but may also have a presynaptic site of action.³² As specific ligands become available, more specific pharmacologic targets underlying the serotonergically mediated activation of the OFC and the ACG observed with m-CPP can be identified.

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