ORIGINAL ARTICLE

Positron Emission Tomography of Regional Brain Metabolic Responses to a Serotonergic Challenge and Lethality of Suicide Attempts in Major Depression

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Background: Lower serotonergic activity correlates with high-lethality suicide attempts in major depression. Postmortem studies of serotonin receptors in suicides localize changes to the ventral prefrontal cortex (PFC). We studied serotonergic response in ventral PFC in depressed patients surviving a high-lethality suicide attempt.

Methods: Depressed patients with a history of a high-lethality suicide attempt (n=16) were compared with those with low-lethality attempts (n=9) for level of depression, suicidal intent and ideation, impulsivity, aggression, and neuropsychological test performance. Subjects were scanned while medication free after a single-blind placebo and after fenfluramine hydrochloride administration on a second day. Brain responses were measured by positron emission tomography imaging of fludeoxyglucose F 18 and serial prolactin levels. Scans were compared by means of statistical parametric mapping. Correlations of changes in relative regional cerebral uptake (rCMRglu) with clinical and neuropsychological measures were assessed.

Results: Depressed high-lethality suicide attempters had lower rCMRglu in ventral, medial, and lateral PFC compared with low-lethality attempters. This difference was more pronounced after fenfluramine administration. Lower ventromedial PFC activity was associated with lower lifetime impulsivity, higher suicidal intent (planning), and higher-lethality suicide attempts. Higher verbal fluency was positively correlated with rCMRglu in the same regions.

Conclusions: Prefrontal localized hypofunction and impaired serotonergic responsivity are proportional to the lethality of the suicide attempt and may mediate the effects of suicide intent and impulsivity on lethality. Positron emission tomographic neuroreceptor studies are needed to determine whether postmortem serotonin receptor findings are also present in vivo and contribute to the abnormal rCMRglu responses.

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SUICIDE ATTEMPTERS have decreased serotonergic function compared with psychiatric control subjects as measured by prolactin response to fenfluramine hydrochloride[1,2] and lower cerebrospinal fluid levels of 5-hydroxyindoleacetic acid.[3,4] Higher-lethality suicide attempts in depressed subjects are associated with even lower cerebrospinal fluid 5-hydroxyindoleacetic acid levels[5] and a more blunted prolactin response to fenfluramine.[1] Postmortem serotonin receptor binding mapping studies indicate that cortical serotonergic abnormalities associated with suicide are localized to the ventral prefrontal cortex (PFC).[6] Neuroendocrine challenges and cerebrospinal fluid measures do not provide information about the anatomic location of abnormality. We did not find any studies of glucose metabolism in response to fenfluramine and suicidal behavior with the use of positron emission tomography (PET). However, changes in glucose metabolism in the PFC have been reported in impulsive murderers compared with nonimpulsive murderers,[7] impulsive aggressive subjects compared with normal controls,[8] and subjects with borderline personality disorder compared with healthy volunteers. Typically in these studies either there is a large proportion of suicide attempters[9] or the attempter status of the subjects is not described.[7,8] Therefore, we studied regional brain serotonergic function in depressed patients with a history of a high-lethality suicide attempt compared with that of depressed patients with a history of low-lethality suicide attempt by PET of relative regional cerebral uptake of fludeoxyglucose F 18 (^{18}F) (rCMRglu) in response to serotonin elevation after a fenfluramine challenge relative to a placebo challenge.

METHODS

SUBJECTS

Twenty-five patients with a major depressive episode diagnosed on the basis of the Structured Clinical Interview for *DSM-III-R*,

Patient Version,[10] and with a score of 16 or greater on the 17-item Hamilton Depression Rating Scale[11] were entered into the study after giving written informed consent as approved by the institutional review board. All patients had a lifetime history of at least 1 suicide attempt. Patients were classified according to the score on the Beck Medical Lethality Scale[12] accorded to the degree of medical damage caused by their most lethal attempt. The scale scores medical damage from 0 (no injury) to 8 (fatal), with anchor points dependent on the method of attempt. Low-lethality attempters scored 3 or less. High-lethality attempters scored 4 or more, that is, requiring hospitalization for medical treatment of the sequelae of the attempt. The mean interval between the most recent suicide attempt and the time of study was more than 4 years (mean±SD, 61.4±90.5 months) to avoid medical effects of the attempt on study results. Patients were also administered the Beck Scale for Suicidal Ideation,[13] Suicide Intent Scale[12] measuring intent at the time of the most lethal attempt, Beck Depression Inventory,[14] Barratt Impulsivity Scale,[15] and Brown-Goodwin Aggression Scale.[16] Twenty-two of the 25 subjects received a battery of neuropsychological tests as part of their participation in related protocols. Scores were obtained in 7 composite domains of functioning, including general intellectual function, motor function, attention, verbal memory, visual memory, language fluency, and executive function. Our group has previously shown that high-lethality attempters performed worse than low-lethality attempters in executive function, and worse than nonpatients in general intellectual function, attention, and memory; thus, we examined the relationship of these tests to rCMRglu in the fenfluramine condition[17] in this sample.

Patients were medication free for a minimum of 14 days (6 weeks in the case of fluoxetine hydrochloride and 1 month in the case of oral antipsychotics) before PET studies. Six patients were drug naive. Patients were allowed up to 3 mg daily of lorazepam during the washout phase, but not in the 3 days before scanning. Patients were free of medical illnesses on the basis of history and results of physical examination and laboratory tests, including liver function tests, hematologic profile, thyroid function tests, urinalysis, and toxicology. Pregnant women were excluded. Premenopausal female subjects were studied within 5 days after onset of menses.

FENFLURAMINE CHALLENGE

Subjects had PET studies on 2 consecutive days after fasting from midnight and throughout the challenge test. They received placebo on the first day and fenfluramine on the second day in a single-blind design. On each study day, an intravenous catheter was inserted at approximately 8 AM and a solution of 5% dextrose and 0.45% saline was infused. Prolactin levels were drawn 15 minutes and immediately before fenfluramine or placebo administration to ascertain baseline levels. An oral dose of approximately 0.8 mg/kg of fenfluramine hydrochloride (or identical pills containing placebo) was administered at 9 AM. Prolactin, fenfluramine, and norfenfluramine levels were drawn hourly for 5 hours after medication administration. Subjects remained awake during the procedure. Prolactin levels were ascertained by immunoradiometric assay.[18,19] The lower level of sensitivity of the method is 0.3 ng/mL, with an interassay coefficient of variation of 4%. Prolactin response to fenfluramine at each time point was calculated as the difference between the prolactin level on the fenfluramine day and the prolactin level at the corresponding time point on the placebo day. These values were compared in low- and high-lethality attempters. Fenfluramine and norfenfluramine levels were measured by a gas-liquid chromatography method.[20,21]

PET STUDIES

Because fenfluramine effects peak about 3 hours after administration, and in an attempt to capture the maximal response to fenfluramine, a bolus injection of approximately 5 mCi ^{18}F was administered 3 hours after the administration of placebo or fenfluramine. Subjects gazed at a uniform visual stimulus (crosshairs) in a dimmed room during the first 15 minutes of the ^{18}F distribution phase. Subjects were then transferred to the scanner, where they lay supine. A custom-made thermoplastic mask was used to minimize head movement. The head was positioned so that the lowest scanning plane was parallel to the canthomeatal line and approximately 1.0 cm above it, and then the infrared lights' positions on the mask were marked. For the second study, the head was positioned as closely as possible to the position in the first study by using the original mask. A scanner (ECAT EXACT 47; Siemens Energy & Automation, Inc, Knoxville, Tenn; in-plane spatial resolution, 5.8 mm; axial resolution, 4.3 mm full-width half-maximum at center) was used to acquire a 60-minute emission scan in 2-dimensional mode in a series of twelve 5-minute frames. The attenuation correction was measured by a 15-minute ^{68}Ge/^{68}Ga (germanium 68–gadolinium 68) transmission scan. Images were reconstructed with a Shepp radial filter, with a cutoff frequency of 35 cycles per projection rays (S) and a ramp axial filter, with a cutoff frequency of 0.5 S.

IMAGE ANALYSIS

Regions of significant differences in rCMRglu between high- and low-lethality subjects on placebo day and fenfluramine day were evaluated by means of Statistical Parametric Mapping (SPM), Version 96.[22] Automated image coregistration[23] was used to align the 12 frames within each study.[24] The resulting summarized image was transformed into standard stereotaxic atlas space.[25] Each image was smoothed by applying an isotropic gaussian kernel to increase the signal-noise ratio. Analysis of covariance was applied within each condition, controlling for global CMRglu. For each group (high- and low-lethality suicide attempters), the adjusted mean rCMRglu and variance were computed at each pixel for both placebo day and fenfluramine day. These were used to compute *t* tests of the differences of the means between groups for each study day at each pixel, and converted to *z* scores for graphical display as parametric maps. In addition, the threshold of each image was modified so that only the clusters with the 3 highest global maxima were displayed in the SPM output. All values were corrected for multiple comparisons by SPM on the basis of "the theory of continuous random fields, assuming the statistic image to be a good lattice representation of an underlying continuous stationary random field. Results for the Euler characteristic lead to corrected p-values for each voxel hypothesis."[22]

Within the area of statistically significant difference on the fenfluramine day, the height threshold was raised until each of the regional maxima in that region became a separate cluster representing more discrete regions of interest (ROIs). With the *z* score threshold set at 3.29 ($P<.001$), 2 regions were identified and used as ROIs for quantitative statistics. One ROI was in the anterior cingulate and the medial frontal gyri (ROI 1) and the second was in the anterior cingulate and right superior frontal gyri (ROI 2). Proportionately normalized counts (total gray matter counts) were determined for both ROIs, and the relationship between these was explored with correlational analyses.

Pearson correlations were calculated to assess relationship between the proportionately normalized rCMRglu value for each ROI and clinical variables including age, lifetime maximum lethality of suicide attempts, scores on the Suicide Intent Scale, Beck Scale for Suicidal Ideation, Beck Depression Inventory, Barratt Impulsivity Scale, Brown-Goodwin Aggression Scale, and Hamil-

Table 1. Clinical and Demographic Characteristics of Low-Lethality and High-Lethality Depressed Suicide Attempters*

Variable	Low Lethality	High Lethality	*df*	*t* Test	*P* Value
Sex, No. (%) M	4/9 (44)	6/16 (38)	1,23	. . .	.16
Age, y	30.4 ± 8.7*	42.9 ± 10.4	23	–3.04	.006
Age at first depressive episode, y	16.7 ± 5.3	25.6 ± 14.4	20.8†	–2.24	.04
No. of depressive episodes	4.1 ± 2.5	5.7 ± 6.1	23	–0.74	.47
Age at first suicide attempt, y	22.3 ± 8.4	32.4 ± 14.1	21.1†	–2.20	.04
No. of suicide attempts	2.3 ± 2.7	2.6 ± 1.3	23	–0.29	.78
Suicidal ideation score at admission	17.6 ± 3.5	14.8 ± 12.4	16.59†	0.78	.45
Suicide intent scale score at time of most lethal attempt	14.1 ± 3.9	18.9 ± 4.8	21	–2.42	.03
Hamilton Depression Rating Scale (17-item) score	21.0 ± 3.0	22.3 ± 5.3	23	–0.68	.50
Beck Depression Inventory score	30.6 ± 6.9	31.0 ± 11.8	22	–0.10	.92
Barratt Impulsivity Scale score	66.7 ± 13.0	44.6 ± 12.5	19	3.76	.001
Brown-Goodwin Aggression Scale score	16.1 ± 3.9	18.7 ± 5.0	21	–1.28	.21

*Data are mean ± SD unless otherwise indicated.
†Levene's test for equality of variances was significant. Thus, equal variances were not assumed.

ton Depression Rating Scale. Because the neuropsychological variables were not normally distributed, Spearman correlation coefficients were calculated for age-adjusted, aggregate index scores for language fluency (combined letter and category fluency scores) and mean rCMRglu in each ROI.

Linear regressions were constructed to examine the effect of age on statistically significant correlations between clinical variables and metabolism in the 2 ROIs. Pearson correlations were also used to examine the relationship between clinical variables that were significantly associated with rCMRglu in each ROI and the lifetime maximum lethality of suicide attempt.

Differences between high- and low-lethality attempters in prolactin response to fenfluramine and placebo at each hour were examined by means of a general linear model for repeated measures that factored in sex. Drug levels were calculated as the sum of fenfluramine and norfenfluramine blood levels at each hour and compared in the 2 groups with a general linear model for repeated measures.

RESULTS

CLINICAL CHARACTERISTICS OF HIGH- AND LOW-LETHALITY ATTEMPTERS

Table 1 describes clinical and demographic characteristics of the sample. High-lethality attempters were older at the time of study, had less lifetime impulsivity, and had greater suicide intent at the time of their most lethal attempt. High-lethality attempters were older at the time of their first attempt but did not differ in total number of suicide attempts from low-lethality attempters. High-lethality attempters were also older at the onset of their first episode of major depression but had the same number of depressive episodes as low-lethality attempters. At the time of study, the 2 groups had comparable severity of depression. Mean lifetime aggression scores were 16% higher in the high-lethality attempters, but the difference was not statistically significant.

RELATIVE REGIONAL CEREBRAL DEOXYGLUCOSE UPTAKE RATES IN HIGH- AND LOW-LETHALITY ATTEMPTERS

Figure 1 illustrates the results of voxel-based analyses of rCMRglu (analysis of covariance controlling for global glucose metabolic rates) in high-lethality depressed suicide attempters compared with low-lethality depressed suicide attempters. On the placebo day (Figure 1A), there was a single major area of lower rCMRglu ($P=.005$) bilaterally in the superior frontal (Brodmann areas [BAs] 8, 9, and part of 6), anterior cingulate (BAs 24 and 32), and inferior frontal (BA 44) gyri of high-lethality attempters compared with low-lethality attempters. On fenfluramine administration (Figure 1B), this difference became more pronounced as the size of the region of relatively lower rCMRglu in the high-lethality attempters became more extensive but also more circumscribed, encompassing the anterior cingulate (BAs 24 and 32) and superior frontal (BAs 6, 8, and 9) gyri. Cluster size increased 32% from 5230 to 6879 voxels. Most of the increase involved the anterior cingulate; the medial PFC and lateral PFC component disappeared on the left and diminished on the right. On day 1 (Figure 1C), there was an area of higher rCMRglu ($P=.007$) involving cerebellum in high-lethality attempters compared with low-lethality attempters. On the fenfluramine day, there were no regions with significantly higher rCMRglu in high-lethality attempters compared with low-lethality attempters (Figure 1D).

Raising the height threshold to $u=3.291$ ($P<.001$) for the fenfluramine day study generated 2 smaller ROIs from the area where rCMRglu was significantly increased in high-lethality attempters. We provide stereotactic coordinates of the maximum-intensity pixels in each ROI (**Figure 2**). The first ROI (ROI 1) was located bilaterally in the anterior cingulate and medial frontal gyrus (BAs 32 and 8). The second ROI (ROI 2) was located in the right midcingulate and superior frontal gyri (BAs 24 and 6).

The rCMRglu in ROI 1 decreased 7.0% and 7.3% from the placebo day after fenfluramine administration in low-lethality attempters and high-lethality attempters, respectively. The rCMRglu in ROI 2 decreased 7.4% and 7.8% from the placebo day after fenfluramine administration in low-lethality attempters and high-lethality attempters, respectively (**Figure 3**). The 2 ROIs were significantly correlated with each other on both placebo and fenfluramine days (respectively, $r_{25}=0.64$, $P<.001$, and $r_{25}=0.60$, $P<.001$).

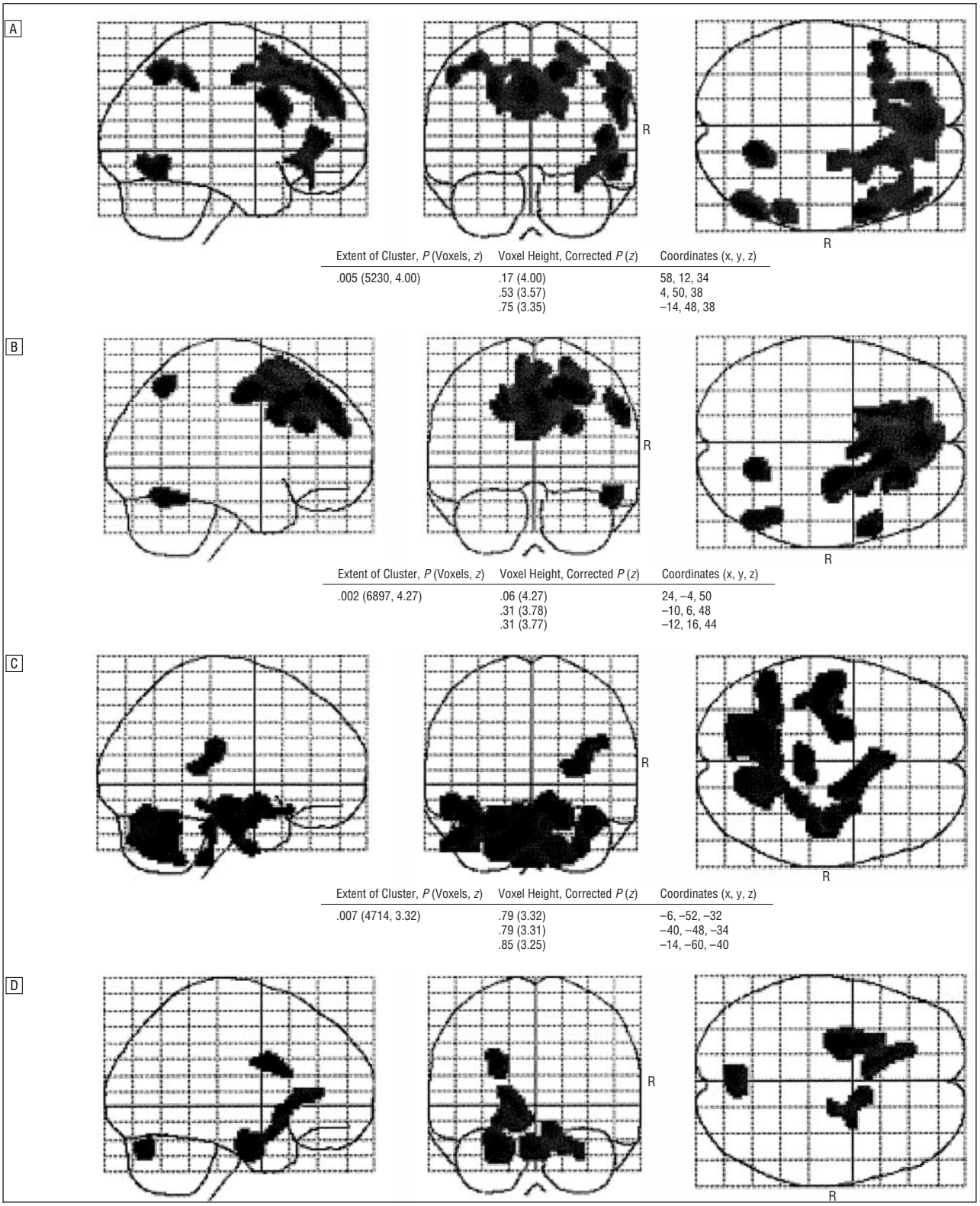
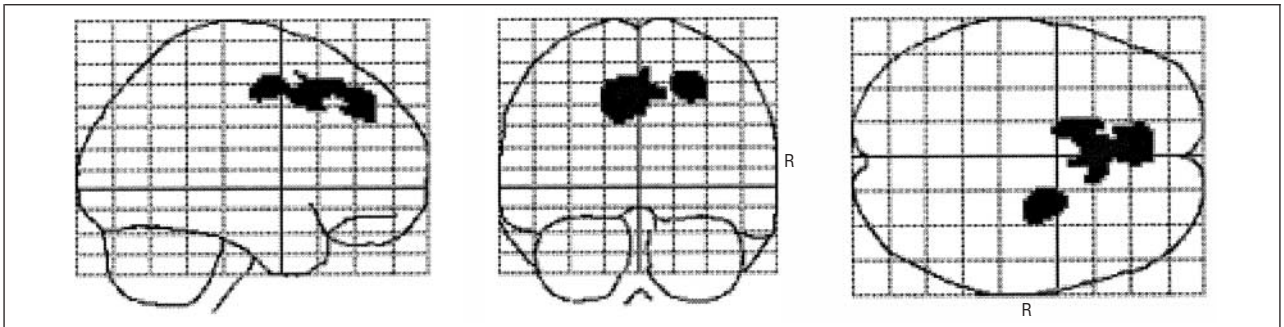


Figure 1. A, Areas of lower relative regional cerebral metabolism rate for glucose in high-lethality compared with low-lethality attempters on the placebo day. Shown at bottom are corrected *P* values for extent of cluster and voxel height and respective (x, y, z) coordinates in significantly different clusters (5 other clusters, not significantly different). B, Areas of lower relative regional cerebral metabolism rate for glucose in high-lethality compared with low-lethality attempters on the fenfluramine hydrochloride day. Shown at bottom are corrected *P* values for extent of cluster and voxel height and respective (x, y, z) coordinates in significantly different clusters (3 other clusters, not significantly different). C, Areas of higher relative regional cerebral metabolism rate for glucose in high-lethality compared with low-lethality attempters on the placebo day. Shown at bottom are corrected *P* values for extent of cluster and voxel height and respective (x, y, z) coordinates in significantly different clusters (a region in the midbrain, which may correspond to the raphe nuclei, and 4 other clusters were not significantly different). D, Areas of higher relative regional cerebral metabolism rate for glucose in high-lethality compared with low-lethality attempters on the fenfluramine day. A region in the midbrain, which may correspond to the raphe nuclei, and 3 other clusters did not reach statistical significance for either extent of cluster or voxel height.



Extent of Cluster, *P* (Voxels, *z*)	Voxel Height, Corrected *P* (*z*)	Coordinates (x, y, z)
ROI 1: .02 (637, 3.78)	.31 (3.78)	–10, 2, 48
	.31 (3.77)	–12, 12, 44
	.36 (3.71)	–8, 38, 38
ROI 2: .07 (222, 4.27)	.06 (4.27)	24, –8, 50

Figure 2. Regions of interest (ROIs) generated in high- compared with low-lethality depressed suicide attempters by increasing the height threshold (*z*) to shrink the regions of significant difference shown in Figure 1D. Shown at bottom are the corrected *P* values for extent of the cluster and voxel height and respective (x, y, z) coordinates.

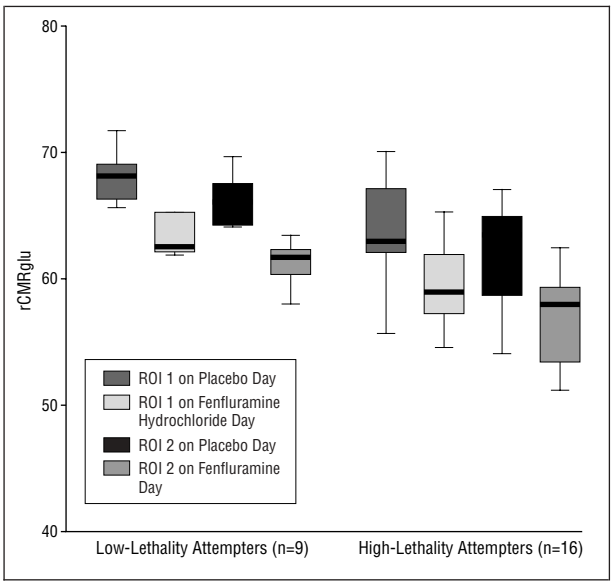


Figure 3. Box plots for relative regional cerebral metabolism rate for glucose (rCMRglu) in medial frontal and superior frontal gyri (region of interest [ROI] 1) and in right medial frontal and right superior frontal gyri (ROI 2) in low- and high-lethality suicide attempters. Dark horizontal line indicates median; box, 75% confidence intervals; and limit lines, range excluding outliers.

RELATIONSHIP OF PET IMAGING MEASURES TO CLINICAL FEATURES

Pearson correlations between clinical measures and rCMRglu in the 2 ROIs are reported for the fenfluramine day, since the correlation between lethality and rCMRglu was stronger and was statistically significant on the fenfluramine day ($r=-0.37$, $P<.07$, and $r=-0.60$, $P<.004$, respectively). The rCMRglu in ROI 1 (bilateral anterior cingulate and medial frontal gyrus) was negatively correlated with age, lifetime maximum lethality of suicide attempt, and suicide intent for the most lethal suicide attempt. The rCMRglu in ROI 1 was also positively correlated with impulsivity, but not with depressive symptoms (measured by the Hamilton Depression Rating Scale or Beck Depression Inventory), suicidal ideation, or lifetime aggression scores (**Table 2**). Maximum lethality scores and age were negatively correlated with mean rCMRglu in ROI 2 (right midcingulate and superior frontal gyri). Impulsivity and mean rCMRglu in ROI 2 correlated positively. Mean rCMRglu in ROI 2 was not correlated with depressive symptoms as measured by the Hamilton Depression Rating Scale or Beck Depression Inventory, suicidal ideation, suicidal intent, or aggression. Thus, ROIs 1 and 2 had the same pattern of clinical correlates except for suicide intent score, which correlated only with ROI 1.

In this sample, suicide intent and impulsivity correlated with suicide attempt lethality (**Table 3**) but not with each other ($r_{19}=-0.26$, $P=.29$). Age correlated positively with lethality, that is, older people carried out more lethal suicide attempts (Table 3). Age also correlated inversely with impulsivity ($r_{21}=-0.45$, $P=.04$) but not with intent ($r_{23}=-0.03$, $P=.91$). When both age and impulsivity were included in the model, age was still a predictor of lethality, but it was weaker (impulsivity: standardized B=–0.63, $t=-4.32$, $P<.001$; age: standardized B=0.32, $t=2.21$, $P=.04$). Thus, impulsivity may mediate the effect of age on the lethality of suicidal acts.

Lethality correlated negatively with both ROIs (Table 3). However, only ROI 1, but not ROI 2, correlated with suicide intent (Table 2). Entering age into the model did not alter these relationships (intent: standardized B=–0.53, $t=-3.13$, $P=.005$ with age added to the model for ROI 1; and intent: standardized B=–0.25, $t=-1.43$, $P=.17$ with age added to the model for ROI 2). Thus, the relationship between activity in the ROIs and suicide intent was independent of age.

Higher rCMRglu in both regions correlated with impulsivity (Table 2) and inversely with lethality (Table 3). Including age in the models preserved the significant association between impulsivity and ROI 2 (model: $P=.005$; standardized B for impulsivity=0.43, $t=2.16$, $P=.05$), but not ROI 1 (model $P=.08$; standardized B for impulsivity=0.36, $t=1.57$, $P=.14$). Thus, age mediates the relationship between impulsivity and PFC activity in ROI 1. There was a slight reduction in the correlation between

Table 2. Correlation of Relative Regional Cerebral Glucose Metabolism Rate After Fenfluramine Administration* in Medial Frontal and Superior Frontal Gyri (ROI 1) and Right Medial Frontal and Right Superior Frontal Gyri (ROI 2) and Clinical Variables

Clinical Variable (No. of Cases)	Pearson *r* for ROI 1	*P* Value	Pearson *r* for ROI 2	*P* Value
Age (25)	−0.41	.04	−0.56	.004
Maximum lethality on Beck Lethality Scale (25)	−0.46	.02	−0.68	.000
Suicidal Ideation Scale (21)	−0.10	.67	0.02	.92
Suicide Intent Scale at time of most lethal attempt (23)	−0.52	.01	−0.23	.27
Barratt Impulsivity Scale (21)	0.45	.04	0.58	.005
Brown-Goodwin Aggression Scale (23)	0.18	.43	−0.07	.74
Hamilton Depression Rating Scale (17 items) (25)	−0.16	.44	−0.20	.34
Beck Depression Inventory (24)	−0.13	.54	−0.18	.39

Abbreviation: ROI, region of interest.
*Fenfluramine was administered as fenfluramine hydrochloride.

rCMRglu in ROI 2 and impulsivity. When age and impulsivity were included in a model to predict lethality, the overall significance of the model was not affected, but it reduced the correlation of brain activity with impulsivity and lethality (model $P<.001$; standardized B for impulsivity = −0.63, $t=-4.32$, $P<.001$).

Metabolism in ROI 2 was negatively correlated with executive performance ($\rho=-0.45$, $P=.04$). It was also negatively correlated with performance on the attention and memory dimension ($\rho=-0.61$, $P=.002$). The lower the metabolism in this region on the fenfluramine day, the greater the cognitive deficits. However, lower metabolism in ROI 2 did not correlate with typical depression-related impairments of cognitive function. Metabolism in ROI 2 correlated positively with language fluency ($\rho=0.44$, $P=.04$).

The mean (SD) time elapsed between the suicide attempt and date of study was 70.8 (132.7) months for low-lethality suicide attempters and 57 (66) months for high-lethality suicide attempters ($t_{8.77}=-0.29$, $P=.78$). Elapsed time did not correlate with activity in the 2 ROIs on either study day (ROI 1 on placebo day: $r_{24}=0.32$, $P=.15$; ROI 2 on placebo day: $r_{24}=0.17$, $P=.43$; ROI 1 on fenfluramine day: $r_{24}=0.16$, $P=.46$; ROI 2 on fenfluramine day: $r_{24}=0.07$, $P=.76$). The length of the drug-free period also did not correlate with rCMRglu in either ROI during the placebo or fenfluramine condition.

PROLACTIN RESPONSE TO FENFLURAMINE IN HIGH- AND LOW-LETHALITY ATTEMPTERS

Both groups had a significant prolactin response to fenfluramine compared with placebo (for high lethality, $t_{15}=4.64$, $P<.001$; and for low lethality, $t_7=3.72$, $P=.007$). A general linear model with sex as a covariate showed that high-lethality attempters had significantly lower prolactin response to fenfluramine compared with low-lethality attempters (**Table 4**). However, maximal prolactin levels after fenfluramine administration did not correlate with rCMRglu in either region of interest (Pearson $r_{25}=-0.06$, $P=.78$ for ROI 1; and $r_{25}=-0.29$, $P=.15$ for ROI 2). There were no differences in fenfluramine plus norfenfluramine drug levels in hours 2 through 5 between the 2 groups (**Table 5**).

Table 3. Correlation of Clinical Variables and Lifetime Maximum Lethality of Suicide Attempt

Clinical Variable (No. of Cases)	Pearson *r*	*P* Value
Age (25)	0.53	.007
Suicidal Ideation Scale (21)	−0.14	.55
Suicide Intent Scale at most lethal suicide attempt (23)	0.43	.04
Barratt Impulsivity Scale (21)	−0.78	.000
Brown-Goodwin Aggression Scale (23)	0.17	.43
Hamilton Depression Rating Scale (17 items) (25)	0.13	.55
Beck Depression Inventory (24)	0.08	.70

COMMENT

Depressed high-lethality suicide attempters had relative hypofunction in PFC compared with depressed low-lethality attempters. That difference became more extensive after fenfluramine administration. Although decreases in rCMRglu after fenfluramine were of the same magnitude in both high- and low-lethality attempters (about 7%), the size of the region of group difference increased by 32% in the fenfluramine condition compared with placebo. The 2 ROIs were significantly correlated with each other on both placebo and fenfluramine days ($r_{25}=0.64$, $P=.001$ and $r_{25}=0.60$, $P=.001$, respectively), suggesting common regulatory influences and functions. However, since $r^2=0.41$, there may be independent regulation and mediation of different functions.

RELATIONSHIP OF SUICIDE ATTEMPT LETHALITY TO CLINICAL AND DEMOGRAPHIC VARIABLES

High-lethality attempters were older, were less impulsive, and had higher suicidal intent. Although they had a later onset of depressive episodes, they were not more depressed, either subjectively or objectively, and did not have a history of more episodes of depression. They also were not more aggressive. Although the distinction between suicide attempters and nonattempters may be the latter's greater subjective depression, suicidal ideation, and lifetime aggression,[26] the difference between high- and low-lethality attempters appears restricted to suicidal intent, age, and impulsivity. Furthermore, that high-

Table 4. Difference (Fenfluramine-Placebo Day) in Prolactin Levels in Depressed High-Lethality Attempters Compared With Depressed Low-Lethality Attempters*

Time to Drug or Placebo Administration	Prolactin, Mean ± SD, µg/L		*df*	F	*P* Value
	Low Lethality	High Lethality			
–15 min	0.2 ± 1.9	1.1 ± 2.0	1,21	0.95	.34
0	–0.1 ± 1.4	1.4 ± 1.9	1,21	3.79	.07
1 h	0.5 ± 1.3	–0.3 ± 2.2	1,21	0.61	.44
2 h	7.5 ± 9.5	2.2 ± 3.6	1,21	3.72	.07
3 h	13.5 ± 10.2	3.9 ± 4.9	1,19	8.95	.007
4 h	13.7 ± 9.8	8.6 ± 11.4	1,19	1.02	.33
5 h	10.3 ± 7.6	6.4 ± 5.1	1,21	1.90	.18

SI conversion factor: To convert prolactin levels to picomoles per liter, multiply by 43.478.
*General linear model with sex as a covariate showed that high-lethality attempters had significantly lower response to fenfluramine hydrochloride ($F_{1,1,17}$ = 12.23, P = .003). Sex was also significant ($F_{1,1,17}$ = 9.8, P = .006).

Table 5. Peak Fenfluramine Plus Norfenfluramine Levels in Depressed High-Lethality Attempters Compared With Depressed Low-Lethality Attempters*

Time to Drug or Placebo Administration, h	Fenfluramine Hydrochloride + Norfenfluramine, Mean ± SD, ng/mL		*df*	F	*P* Value
	Low Lethality	High Lethality			
1	18.4 ± 14.6	8.4 ± 9.4	1,19	3.64	.07
2	57.8 ± 37.4	49.9 ± 31.3	1,22	0.29	.59
3	63.9 ± 17.6	58.7 ± 21.2	1,20	0.34	.57
4	69.1 ± 20.0	58.5 ± 22.6	1,20	1.14	.30
5	69.4 ± 16.5	62.3 ± 23.8	1,22	0.56	.46

*General linear model showed no difference between high- and low-lethality attempters ($F_{1,16}$ = 2.15, P = .16).

lethality attempters had later onset of depression and of suicidal behavior but not a different number of episodes or attempts suggests that patients who are older at the time of first depressive episode and first suicide attempt may have different biological and clinical characteristics (such as less impulsivity and more intent) and, consequently, higher risk for lethal suicidal behavior than those with earlier onset.

In this study, suicide intent and impulsivity correlated independently with suicide attempt lethality. Our group[5] and others[27] have reported that low-lethality attempters are more impulsive than high-lethality attempters. In addition, impulsivity declines with age and more thoroughly planned suicidal acts occur with increasing age.[28] We confirm previous reports that suicide intent has a positive correlation with lethality of suicide attempts,[29] including our finding that suicide intent distinguishes low- and high-lethality attempters.[30] Thus, clinical differences between high- and low-lethality attempters in this sample are consistent with the literature and suggest that the age effect on lethality of attempts is mediated via impulsivity.

RELATIONSHIP OF PET IMAGING MEASURES TO CLINICAL FEATURES

Higher rCMRglu in both ROIs was associated with lower lethality. Suicidal intent and impulsivity had different relationships to the ROIs. Higher activity in both regions was associated with greater impulsivity and lower age. Age and impulsivity were negatively correlated. It is possible that age influences suicide lethality via an age-related decrease in PFC activity that reduces impulsivity. In contrast, suicide intent correlated inversely only with ROI 1, but not ROI 2 or age. The effect of suicidal intent on lethality may be mediated by a more restricted area of the PFC and appears to be independent of age and impulsivity (**Figure 4**).

Increased glucose metabolism in PFC is associated with more impulsivity. Raine et al[7] compared impulsive murderers with nonimpulsive murderers and reported that impulsive murderers had lower metabolism in PFC than nonimpulsive murderers. However, psychiatric diagnosis, medication status, and measures of impulsivity and aggression were not reported, and these may be confounding variables. Siever et al[8] compared 6 impulsive aggressive patients with 5 healthy volunteers with a method similar to ours and found that impulsive aggressive subjects had less metabolic activation after fenfluramine administration than healthy volunteers did. Impulsive aggression is associated with reduced serotonergic functioning, but most studies did not assess aggression and impulsivity separately.[16,31-33] These 2 traits often coexist in subjects and are frequently comorbid with disorders with reduced serotonergic function, such as alcoholism and suicidality. Suicide attempt status in the subjects in the studies by Raine et al[7] and Siever et al[8] were not reported. Soloff et al[9] studied 5 subjects with borderline personality disorder and found them to have lower prefrontal activation after fenfluramine adminis-

tration than healthy volunteers. Four of the 5 subjects were suicide attempters, and whether the differences between the subjects and normal controls are due to borderline personality disorder, suicidal behavior, or impulsivity cannot be determined. We did not conduct a comparison with healthy volunteers. However, we found that the more impulsive depressed patients, those with low-lethality attempts, had higher rCMRglu in PFC, and the region of difference became more extensive after fenfluramine administration compared with the less impulsive high-lethality attempters. Our subjects were free of current alcohol abuse or dependence and did not differ significantly in terms of lifetime aggression.

The negative correlation between lethality and mean rCMRglu in PFC after fenfluramine challenge is consistent with our hypothesis that PFC function has a role in suicidal behavior.[34] Postmortem studies have shown that alterations in serotonin transporter binding and serotonin 1A binding in suicide victims compared with psychiatric controls are localized to BAs 11, 12, 45, and 46 for serotonin transporter and more ventrolateral PFC areas for serotonin 1A, respectively, in the ventral PFC.[6,35] Lesion studies have linked the ventral and medial PFC to behavioral inhibition,[36] which may be partly mediated by serotonin input into these brain regions. Our in vivo PET study found abnormalities in PFC (BAs 6, 8, 9, 24, and 32) that are close but not identical to the regions with reported postmortem receptor changes. This may be due to the use of different indexes of brain function. Fludeoxyglucose uptake is mainly determined by the energy requirements of the glutamate-glutamine pathway cycling through pyramidal neurons and astrocytes in the cortex.[37] Serotonin inhibits pyramidal cell activity indirectly via γ-aminobutyric acid–ergic neurons and also has direct input onto pyramidal cells.[38] Another reason for a different location of the in vivo vs postmortem findings may be the limited accuracy of neuroanatomic localization with the use of SPM. In vivo studies measuring specific serotonin receptor binding in PFC are needed to determine whether the serotonergic hypofunction we have described in high-lethality attempters is associated with the same receptor changes as those found in suicide victims.

VERBAL FLUENCY AND SEROTONERGIC FUNCTIONING

We have reported that depressed subjects with high-lethality suicide attempts have impairments in verbal fluency that are more pronounced than in those with low-lethality attempts or those with depression but no suicidal behavior.[17] Our current findings suggest that language fluency, an executive function, may be related to metabolism in the PFC (ROI 2). Smith et al[39] used water O 15 PET to study 8 recovered depressed men after tryptophan depletion. The patients performed a paced verbal fluency task during PET studies. Increasing depression scores after tryptophan depletion were correlated with decreased neural activity in frontal cortical areas (ventral anterior cingulate and orbitofrontal cortex). In addition, increasing depression was negatively correlated with cognitive task-related activation in the anterior cingulate cortex. Thus, reduction of central serotonergic functioning by tryptophan depletion may decrease frontal activation and be related to poorer verbal fluency. This is consistent with our finding that higher rCMRglu is associated with better performance on verbal fluency tasks after fenfluramine administration. We did not find a relationship between rCMRglu and severity of depression. However, as in the study by Smith et al,[39] the lower the rCMRglu, the poorer the fluency. It is possible that impaired verbal fluency reflects executive function deficits that may inhibit the suicide attempter's ability to devise solutions to a crisis situation rather than act on suicidal ideation. Whether impairment of verbal fluency has a direct relationship to suicidal behavior that is mediated by rCMRglu in response to fenfluramine in the PFC or a similarly mediated inverse correlation with impulsive behavior requires more study.

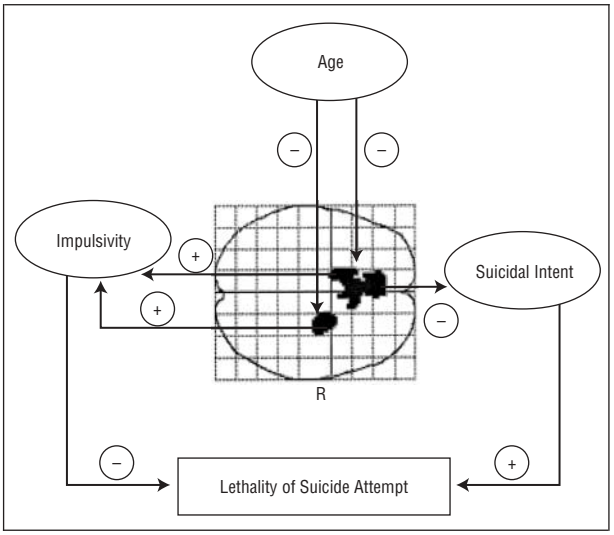


Figure 4. Hypothesized relationship between clinical and biological variables: effects on suicide attempt lethality. Plus sign indicates positive correlation; minus sign, negative correlation.

FENFLURAMINE CHALLENGE AND LETHALITY OF SUICIDE ATTEMPT

Both lower cerebrospinal fluid 5-hydroxyindoleacetic acid and a more blunted prolactin response to fenfluramine are present in high-lethality compared with low-lethality suicide attempters with major depression.[1,5] The results of the present study confirm our finding of a blunted prolactin response to fenfluramine in a new group of patients and extends the results by finding that a PFC abnormality is associated with more lethal suicidal acts but not correlated with prolactin response to fenfluramine. This separate, though related, line of evidence suggests that serotonergic function differs in high- and low-lethality suicide attempters.

LIMITATIONS OF THE STUDY

The clinical variables demonstrate relationships supported by studies involving larger samples, which suggests that the findings may be generalizable to other hospital populations. However, the sample size is small. Because activity in the ROIs is inversely proportional to

the degree of medical damage sustained from the most lethal suicide attempt, we cannot rule out direct brain injury as an explanation for our finding. The interval of more than 4 years between suicide attempt and study and the lack of correlation between rCMRglu in either of the ROIs suggest that the finding is not a consequence of injury.

CONCLUSIONS

Depressed high-lethality suicide attempters had lower rCMRglu in anterior cingulate and superior frontal gyri compared with depressed low-lethality attempters. Lethality of the most serious lifetime suicide attempt was negatively related to rCMRglu in the anterior cingulate, right superior frontal, and right medial frontal gyri after fenfluramine administration. This suggests that there is PFC hypofunction in high-lethality depressed suicide attempters. In vivo studies measuring specific serotonin receptor binding in frontal cortex are needed to determine whether the serotonergic hypofunction we have described in high-lethality attempters is associated with the same receptor changes found in suicide victims.

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