

# Correlation of Stable Elevations in Striatal $\mu$ -Opioid Receptor Availability in Detoxified Alcoholic Patients With Alcohol Craving

## A Positron Emission Tomography Study Using Carbon 11–Labeled Carfentanil

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**Background:** The pleasant effects of food and alcohol intake are partially mediated by  $\mu$ -opiate receptors in the ventral striatum, a central area of the brain reward system. Blockade of  $\mu$ -opiate receptors with naltrexone reduces the relapse risk among some but not all alcoholic individuals.

**Objective:** To test the hypothesis that alcohol craving is pronounced among alcoholic individuals with a high availability of  $\mu$ -opiate receptors in the brain reward system.

**Design:** Patients and comparison sample. The availability of central  $\mu$ -opiate receptors was measured in vivo with positron emission tomography (PET) and the radioligand carbon 11–labeled carfentanil in the ventral striatum and compared with the severity of alcohol craving as assessed by the Obsessive Compulsive Drinking Scale (OCDS).

**Setting:** Hospitalized care.

**Participants:** Volunteer sample of 25 male alcohol-dependent inpatients assessed after detoxification of whom

12 underwent PET again 5 weeks later. Control group of 10 healthy men.

**Main Outcome Measures:** After 1 to 3 weeks of abstinence, the availability of  $\mu$ -opiate receptors in the ventral striatum, including the nucleus accumbens, was significantly elevated in alcoholic patients compared with healthy controls and remained elevated when 12 alcoholic patients had these levels measured 5 weeks later ( $P < .05$  corrected for multiple testing). Higher availability of  $\mu$ -opiate receptors in this brain area correlated significantly with the intensity of alcohol craving as assessed by the OCDS.

**Conclusions:** Abstinent alcoholic patients displayed an increase in  $\mu$ -opiate receptors in the ventral striatum, including the nucleus accumbens, which correlated with the severity of alcohol craving. These findings point to a neuronal correlate of alcohol urges.

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**S**TIMULATION OF  $\mu$ -OPIATE RECEPTORS in the ventral striatum, including the nucleus accumbens, increases the hedonic effects of alcohol and food intake.<sup>1,2</sup> Alcohol-preferring rodents displayed low central endorphin concentrations and a high  $\mu$ -opiate receptor availability in the ventral and dorsal striatum and prefrontal cortex.<sup>3,4</sup> Using a superfusion system, de Waele et al<sup>5</sup> observed that ethanol caused a release of  $\beta$ -endorphins from the hypothalamus of ethanol-preferring AA (alco-alcohol) line of rats that was greater than the release in non-alcohol-preferring ANA (alco non-

alcohol) line of rats. Alcohol-induced endorphin release may interact with elevated  $\mu$ -opiate receptors in the ventral striatum, thus mediating the rewarding effects of alcohol consumption. Conversely, blockade of  $\mu$ -opiate receptors with naltrexone reduced the hedonic effects of alcohol intake and the relapse risk among alcoholic patients.<sup>6-10</sup>

In humans and nonhuman primates, the nucleus accumbens is a part of the ventral striatum, a central area of the brain reward system.<sup>11</sup> After detoxification, alcoholic patients may crave the rewarding effects of alcohol, and the severity of craving may depend on endorphin release and

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**Table 1. Clinical Data**

Variable	Alcoholic Patients (n = 25)	Age-Matched Healthy Control Subjects (n = 10)
Age, mean (SD), y	41.5 (6.9)	42.5 (12.7)
Lifetime alcohol consumption, mean (SD), kg*	774.4 (596.6)	55.4 (55.6)
Alcohol consumption in the past 3 months, mean (SD), kg*	17.3 (15.5)	0.3 (0.3)
Severity of Alcohol Dependence Questionnaire score, mean (SD)*	35.8 (10.9)	0.0
A118G $\mu$ -opiate receptor genotype	5/25	1/10
No. of smokers among study participants (excluding A118G)	15/20	1/9
Catecholamine- <i>O</i> -methyltransferase genotype, %		
Val/val	28	20
Val/met	44	50
Met/met	28	30
Beck Depression Inventory score, mean (SD)*	9.2 (8.7)	2.0 (2.5)
State-Trait Anxiety Inventory score, mean (SD)*	35.7 (10.5)	45.7 (5.0)
Obsessive Compulsive Drinking Scale score, mean (SD)*	14.1 (7.8)	1.7 (1.2)
Volume of erythrocytes, mean (SD), $\mu\text{m}^3$ *	97.4 (6.2)	92.5 (3.1)
Alanine aminotransferase, mean (SD), U/L	17.3 (12.7)	13.2 (3.6)
$\gamma$ -Glutamyltranspeptidase, mean (SD), U/L*	70.24 (61.3)	12.1 (3.2)

\*2-Sample *t* test, *P* < .05 (bilateral).

the availability of opiate receptors in the ventral striatum.<sup>3,6-8</sup> To test this hypothesis, we recruited abstinent male alcoholic patients and age-matched healthy men and measured  $V_3''$  in the ventral striatum, including the nucleus accumbens,<sup>12</sup> and in control areas (inferior prefrontal cortex, caudate, and putamen) with positron emission tomography (PET). Alcohol craving was assessed on the day of PET with the Obsessive-Compulsive Drinking Scale (OCDS).<sup>13</sup>

## METHODS

### PATIENTS AND CONTROL SUBJECTS

Twenty-five male alcohol-dependent patients and 10 healthy men were included in this study (**Table 1**). Patients had alcohol dependence according to the *International Classification of Diseases, 10th Revision* and *DSM-IV* criteria and had no other psychiatric Axis I disorder, no history of drug dependence, and no current drug abuse (random urine drug testing and Structured Clinical Interview for *DSM-IV* [SCID] interview<sup>14</sup>) except for nicotine abuse and caffeine consumption. The severity of alcoholism was assessed with the German version of the Severity of Alcohol Dependence Questionnaire,<sup>15</sup> and the amount of lifetime alcohol intake was measured with the Lifetime Drinking History.<sup>16</sup>

All patients had abstained from using alcohol in a supervised inpatient treatment program for 1 to 3 weeks (range, 6-22 days; random alcohol breath test and urine drug controls). In all participants, alcohol withdrawal was rather mild, subsided within the first 3 days, and was exclusively treated with benzodiazepine or clomethiazole; standard vitamin supplementation was given to all patients. At the time of the first PET, all participants had not been taking any psychotropic medication for at least 5 days. Patients were then treated in an outpatient program; 12 patients who had continued not to take any psychotropic medication underwent PET a second time 4 to 6 weeks later (37-51 days after detoxification).

Ten age-matched healthy men served as control subjects and had no psychiatric Axis I or II disorders (SCID I and II interview<sup>14,17</sup>). Random urine and blood tests were performed to exclude current alcohol or drug abuse, except for nicotine abuse

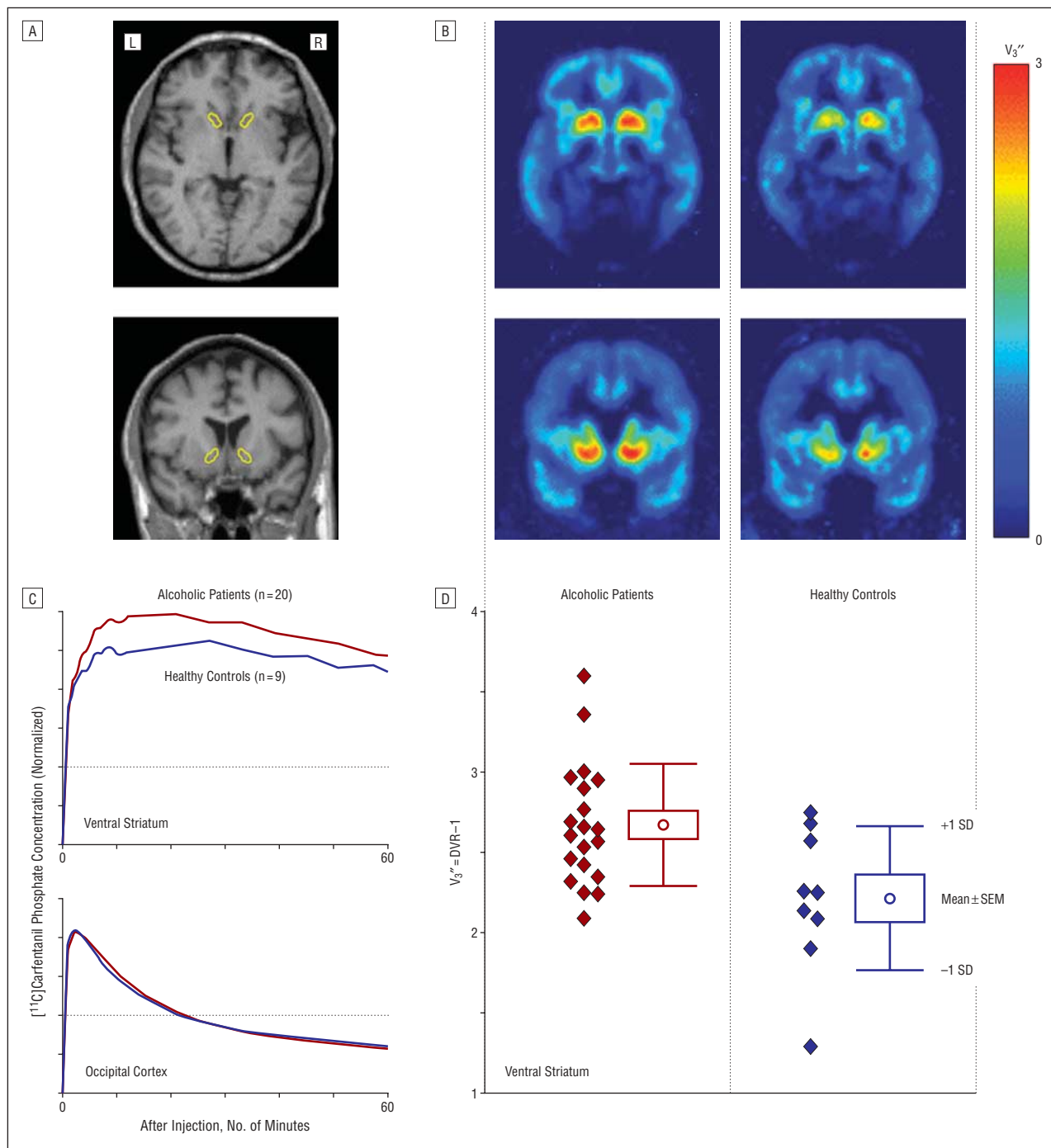
and caffeine consumption. Immediately before PET, alcohol craving was assessed with the OCDS, an internationally used score to assess obsessive alcohol craving and compulsive alcohol intake.<sup>13</sup> The study was approved by the Ethics Committee of the University of Heidelberg and was in accordance with the Helsinki Declaration. Informed written consent was obtained from all participants.

### PET METHODS

The availability of  $\mu$ -opiate receptors was assessed with PET and carbon 11 [<sup>11</sup>C]-labeled carfentanil, a radioligand that binds specifically and reversibly to  $\mu$ -opiate receptors.<sup>18</sup> After intravenous bolus injection of 10 to 22 mCi (400-800 MBq) of [<sup>11</sup>C]carfentanil (1.7-9.1  $\mu\text{g}$ ), the cerebral radioactivity distribution was measured with a PET scanner (GE Advance PET scanner; GE-Medical Systems, Milwaukee, Wis) with an axial field of view of 15 cm (2-dimension acquisition mode). For attenuation correction, a transmission scan with 500 000 kilo counts was used. Three external markers were attached to the skull to support realignment. We used filtered backprojection (128  $\times$  128 pixels = 30 cm) with a Hanning filter (cutoff, 4.6 mm) to reconstruct our images. Phantom studies indicated a final resolution of 4.6 to 6.4 mm.

### CALCULATION OF BINDING VALUES

Availability ( $V_3''$ ) of  $\mu$ -opiate receptors was assessed in regions of interest (ROIs) and in each voxel by the following formula:  $V_3'' = \text{DVR} - 1$ , with DVR being the distribution volume ratio between a target region and a reference region with negligible specific binding (occipital cortex).<sup>19</sup> According to the standard 2-tissue compartment model, this measure corresponds to  $f_2 \times \text{Bmax}/K_D$ , with  $f_2$  being the free fraction of tracer in the first tissue compartment; Bmax, the concentration of unoccupied ("available") binding sites ( $\mu$ -opiate receptors); and  $K_D$ , the equilibrium dissociation constant.<sup>20</sup> We calculated the DVR with a graphical analysis described by Logan,<sup>21</sup> which has recently been compared with full compartmental modeling of [<sup>11</sup>C]carfentanil, including arterial blood sampling in healthy participants.<sup>22</sup> For linear regression, a time interval of 18 to 60 minutes and the perpendicular error model<sup>23</sup> were chosen; the washout rate  $k_2'$  from the occipital cortex was set to 0.1  $\text{min}^{-1}$ .<sup>22</sup>



**Figure 1.** Brain imaging of central  $\mu$ -opiate receptor availability ( $V_3''$ ). Region of interest analysis: definition (A), interindividually averaged time-activity curves (C) and  $V_3''$  of all participants, obtained from Logan plot (D). B, Top left and right, Voxelwise averaged  $V_3''$  parametric images of detoxified alcoholic patients, abstinent for 1 to 3 weeks (top left) compared with healthy volunteers (top right). The highest  $V_3''$  in alcoholic patients and the largest difference between alcoholic patients and controls were found in the ventral striatum and the adjacent putamen. [ $^{11}\text{C}$ ]carfentanil indicates carbon 11-labeled carfentanil. In part D, the open circles represent the mean; the box surrounding the circles, standard error of the mean; and the bars, standard deviation.

We confirmed that [ $^{11}\text{C}$ ]carfentanil exhibited a similar kinetic behavior in our patient group by comparing the shape of time-activity curves (ROI technique) in the reference region of both groups (alcoholic patients and healthy controls): time-activity curves interindividually averaged for each group were visually identical (**Figure 1**). Furthermore, occipital [ $^{11}\text{C}$ ]carfentanil uptake expressed in percentage of injected dose (ID) per milliliter of tissue did not differ significantly between patients ( $10.4 \pm 2.3 \times 10^{-4}\%$  ID/mL) and healthy controls ( $9.6 \pm 1.6 \times 10^{-4}\%$  ID/mL). To exclude artifacts from data noise

and from a stochastic error in the reference tissue assumption, we compared the mean  $V_3''$  in each group with that obtained from the interindividually averaged curves.<sup>24</sup> All operations on time-activity curves were performed using Matlab statistical software (Mathworks Inc, Natick, Mass).

To test the a priori hypothesis of elevated  $\mu$ -opiate receptors in the ventral striatum of alcoholic patients (Figure 1), we predefined a 3-dimensional ROI in Montreal Neurological Institute (MNI) space according to Mawlawi et al.<sup>12</sup> Additional ROIs were defined for brain areas implicated in animal experi-

**Table 2.  $\mu$ -Opiate Receptor Availability in Alcoholic Patients and Healthy Volunteers**

Region of Interest	Size, mL	$\mu$ -Opiate Receptor Availability, Mean $\pm$ SD		
		Alcoholic Patients 1-3 wk After Detoxification	Alcoholic Patients 5-7 wk After Detoxification	Age-Matched Healthy Control Subjects
Prefrontal cortex	2 $\times$ 3.4	1.08 $\pm$ 0.14	1.11 $\pm$ 0.15	1.01 $\pm$ 0.27
Parietal cortex	2 $\times$ 4.4	0.53 $\pm$ 0.10	0.52 $\pm$ 0.09	0.51 $\pm$ 0.17
Caudate	2 $\times$ 0.40	2.04 $\pm$ 0.34	2.11 $\pm$ 0.32	1.75 $\pm$ 0.43
Putamen	2 $\times$ 0.67	1.83 $\pm$ 0.26	1.85 $\pm$ 0.28	1.58 $\pm$ 0.32
Ventral striatum	2 $\times$ 0.36	2.67 $\pm$ 0.38* (2.68 $\ddagger$ )	2.80 $\pm$ 0.43 $\ddagger$ (2.80 $\ddagger$ )	2.25 $\pm$ 0.43 (2.26 $\ddagger$ )

\*2-Sample *t* test vs controls:  $t=2.83$ ,  $P=.009$  (bilateral).

$\ddagger$ Mean group parameters assessed from interindividually averaged time-activity curves.

$\ddagger$ Exploratory analysis: 2-sample *t* test vs controls:  $t=3.00$ , descriptive  $P=.008$ .

ments (prefrontal cortex, putamen, caudate),<sup>3</sup> the parietal cortex (specific binding to  $\mu$ -opiate receptors, hypothetically not associated with alcoholism), and the occipital cortex (reference tissue for pharmacokinetic analysis).<sup>22</sup> The ROI analysis was also used to assess the stability of  $V_3''$  in those patients who underwent a second PET. The sizes of all ROIs are given in **Table 2**. These standard ROIs were applied to PET images, which were spatially normalized and realigned using the software package SPM99,<sup>25</sup> except that nonlinear transformations were disabled. For each participant, the ROI positions were adjusted manually (ROI shift by a maximum of 1 pixel in each dimension = 2 mm) to match the stereotactically normalized images of the perfusion phase (0-5 minutes after injection). Manual ROI adjustment and extraction of time-activity curves from the normalized PET data were performed with Matlab software developed locally. A validation against magnetic resonance imaging (MRI)-guided ROI positioning in 10 patients yielded a high intraclass correlation coefficient (mean of all 5 ROIs = 0.93; coregistered MRI: T1-weighted spoiled gradient acquisition in a steady state [GRASS] sequence; repetition time = 24 milliseconds, echo time = 5 milliseconds, 124 contiguous 1.5-mm-thick sagittal slices with a 240-mm field of view in a 256  $\times$  256 pixel matrix).

Realignment and stereotactic normalization of the PET data were performed with the software package SPM99.<sup>25</sup> The normalization matrix (affine transformation, 4  $\times$  5  $\times$  4 basis functions) was estimated by comparing early summation images 0 to 5 minutes p.i. with the standard SPM99 perfusion template.  $V_3''$  for each pixel was calculated using Matlab with the same software and same reference tissue curve as in the ROI analysis. All voxelwise analyses were performed with these absolute  $V_3''$  values; there were no additional normalizations (eg, SPM's whole brain normalization). Reported Talairach coordinates were calculated from SPM coordinates with a Java applet provided by the University of Münster, Münster, Germany ([www.neruo01.unimuenster.de/t2t/t2tconv/conv3d.html](http://www.neruo01.unimuenster.de/t2t/t2tconv/conv3d.html)).

### EXCLUSION OF CONFOUNDING GENETIC EFFECTS ON $V_3''$

Endogenous opioids may compete with carfentanil binding<sup>26,27</sup> at  $\mu$ -opiate receptors, and a rare single-nucleotide polymorphism at position 118 (A118G) was associated with a 3-fold increase in receptor affinity for  $\beta$ -endorphins.<sup>28</sup> One of the 10 control subjects and 5 of the 25 alcoholic patients carried this rare genotype. The number of alcoholic patients with the rare genotype seems too small for further analysis; however, they displayed numerically lower  $V_3''$  in the ventral striatum compared with the other alcoholic patients (2.25  $\pm$  0.12 vs 2.67  $\pm$  0.38,  $t=2.38$ ,  $P=.03$ ). To exclude a possible bias due to different geno-

type distribution in our patient and control groups, participants with the rare genotype variant were excluded from all group comparisons between patients and controls and from analysis of correlation with clinical parameters. The catecholamine *O*-methyltransferase genotype did not significantly interact with  $V_3''$ .<sup>29</sup>

### STATISTICAL ANALYSIS

In the confirmatory part of the analysis, we tested the hypothesis that detoxified alcoholic patients display altered  $V_3''$  in the ventral striatum, which correlates with alcohol craving. We used 2-tailed *t* tests and applied Bonferroni correction for assessment of 5 regions of interest (4 regions suggested by animal experiments,<sup>2,3</sup> ventral striatum, putamen, caudate, and prefrontal cortex, and 1 control area, parietal cortex).

To confirm striatal group differences with an operator-independent method, we calculated a voxelwise *t* test (variance voxel by voxel) on smoothed parametric images (12 mm) with SPM. To reduce random effects, white matter and gray matter with  $V_3''$  less than 1 were excluded (remaining volume of interest, 299 cm<sup>3</sup>), and the extent threshold was set to 5 voxels. We used SPM's "small volume correction" to correct for multiple testing with an anatomically defined a priori hypothesis. The striatal volume was specified by a voxel mask derived from automatically generated isocontours (average  $V_3''$  > 1.5, 12.1 cm<sup>3</sup>).

To assess correlations between striatal  $V_3''$  and clinical parameters without the need to correct for multiple testing, we derived the MNI coordinates of the largest difference in  $V_3''$  between alcoholic patients and controls (voxel of interest, see difference image shown in **Figure 2**) and confirmed that these coordinates were within SPM's cluster of significant group difference. Correlations between  $V_3''$  in this striatal voxel of interest and the severity of alcohol craving (OCDS) were assessed with simple regression. We also explored whether extrastriatal areas were correlated with OCDS scores with SPM's simple regression (voxel-level: threshold  $P=.001$ , cluster-level:  $P$  values corrected for entire volume).

In the exploratory part of the study, we assessed changes in  $V_3''$  in the subgroup of alcoholic patients who underwent PET twice, after 1 to 3 weeks of abstinence and 5 weeks later. With SPM (paired *t* test), we searched for changes over time in brain regions that may not have been covered by our ROI analysis. We also assessed effects of potentially confounding variables, such as smoking, age of onset, and family history of alcohol dependence, on  $V_3''$  in the ventral striatum. In this exploratory part of the study, all  $P$  values are given only for descriptive reasons.

## RESULTS

### GROUP DIFFERENCES IN $V_3''$

In the ROI analysis,  $V_3''$  in the ventral striatum, including the nucleus accumbens, was significantly increased in the 20 alcoholic patients after 1 to 3 weeks of abstinence compared with 9 healthy men ( $P=.044$  after Bonferroni correction [before Bonferroni correction,  $P=.009$ ], Table 2 and Figure 1). No significant differences between alcoholic patients and control subjects were observed in the other assessed regions (Table 2). Based on the observed group means and standard deviations, a sample-size analysis ( $\alpha=.05$ , power=90%) was calculated; 30 participants per group would be required to test for significant group differences in the putamen, and 173 participants would be required to test in the prefrontal cortex. Our data do not indicate relevant group differences in the parietal cortex (sample size analysis: >500 participants required per group).

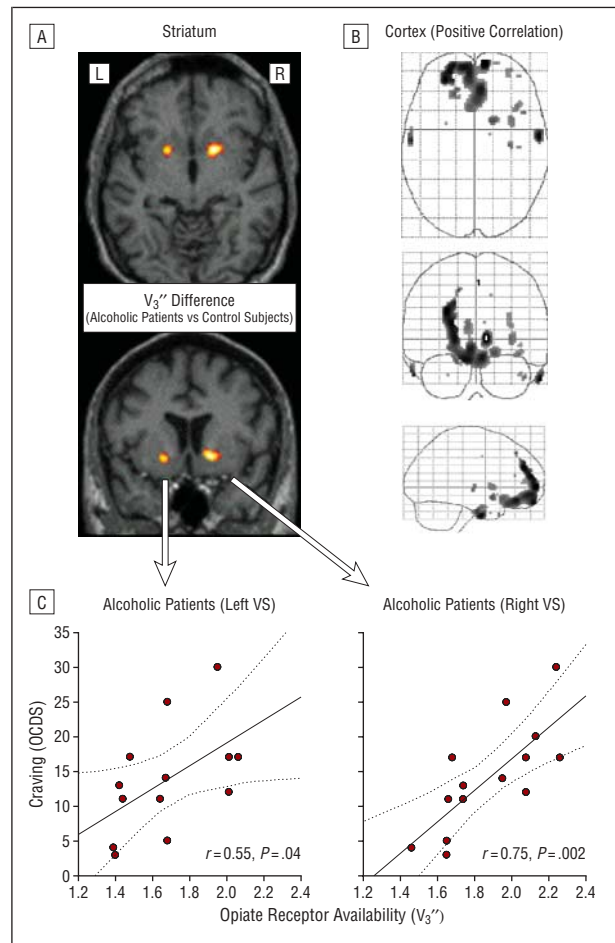
In the voxel-based analysis, the largest group difference in  $V_3''$  ( $\Delta V_3''$ ) was found in the bilateral ventral striatum and the adjacent putamen (right:  $\Delta V_3''=0.42$  at Talairach-Tournoux [17.8/9.2/-9.7]; left:  $\Delta V_3''=0.41$  at [-20.8/9.2/-9.7]). Analysis with SPM confirmed significant elevations in  $V_3''$  in the right and left ventral striatum of alcoholic patients (right:  $t=4.0$ , left:  $t=3.8$ ), surviving small volume correction with SPM99 (striatal volume, 12.1 cm<sup>3</sup>,  $P=.05$  corresponds to  $t=3.25$ ) with  $P=.01$  (right) and  $P=.03$  (left). No significant group differences in  $V_3''$  were detected outside the ventral striatum.

### CORRELATION BETWEEN $V_3''$ AND ALCOHOL CRAVING

Striatal  $V_3''$  in the voxel of interest showed a close positive correlation with alcohol craving measured with the OCDS (right:  $r=0.75$ ,  $P=.002$ ; left:  $r=0.55$ ,  $P=.04$ ). Cortical areas with significant positive correlation (maximum  $t=6.18$ , corrected  $P<.001$ ) were found in the frontal cortex (Brodmann area 10, Figure 2). On the other hand, in the ROI analysis, correlation between  $V_3''$  with OCDS scores was not significant (right:  $r=0.39$ ; left:  $r=0.21$ ; all  $P>.10$ ), in agreement with the observation that group differences were significant in only a part of the ventral striatum (Figure 2 and Figure 3).

### EXPLORATORY ANALYSIS OF THE STABILITY OF $V_3''$ AND POTENTIALLY CONFOUNDING VARIABLES

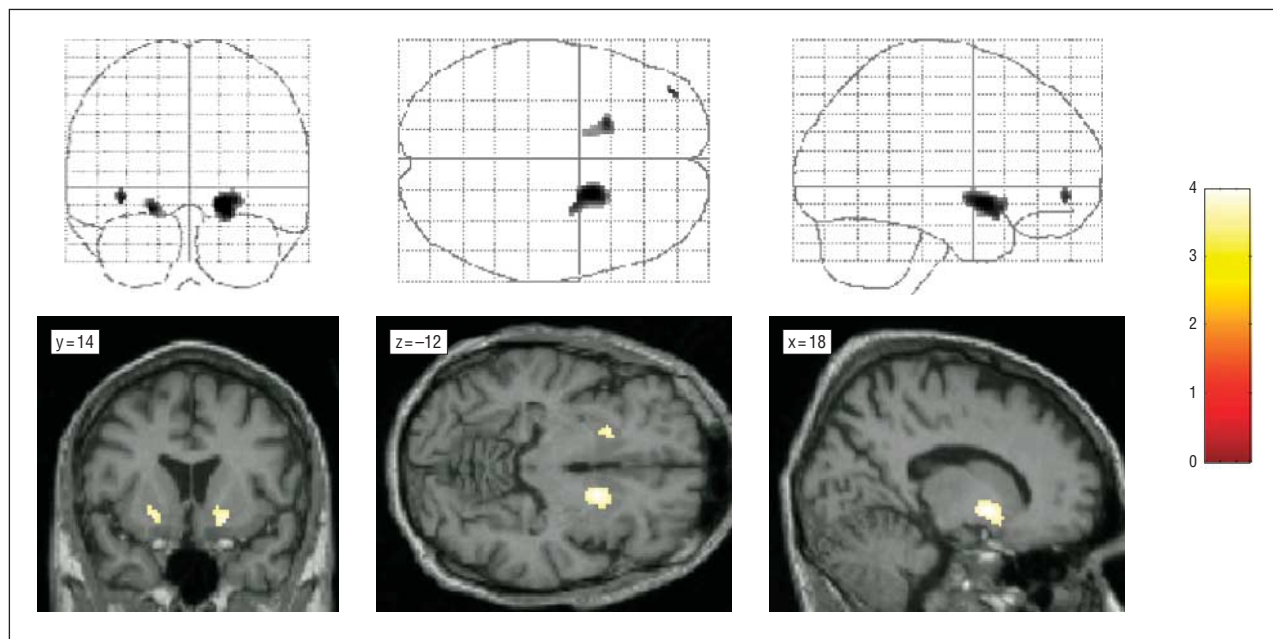
Twelve alcoholic patients underwent PET twice, first after 1 to 3 weeks of abstinence and again 5 weeks later. Between the first and the second PET scan,  $V_3''$  was remarkably stable in all patients and all investigated ROIs (ventral striatum: mean individual change, +1%; range, -13% to +12%; Table 2), despite the fact that relapses were detected in 3 patients and may have remained undetected in additional patients. In the SPM analysis (voxel-wise paired  $t$  test), we did not find significant changes in  $V_3''$  over time. The absolute changes in  $V_3''$  ( $\Delta V_3''$ ) be-



**Figure 2.** Correlation between  $\mu$ -opiate receptor availability ( $V_3''$ ) and alcohol craving. A, Absolute group difference in  $V_3''$  between alcoholic patients (bottom portion) and control subjects (top portion). The voxel with the largest group difference was selected to assess the correlation with severity of alcohol craving (Obsessive Compulsive Drinking Scale [OCDS] score) in alcoholic patients (C). B, SPM99 analysis of correlation between  $V_3''$  and OCDS (voxel-level threshold:  $P<.001$ ,  $t>3.93$ ). The large cluster in the left frontal cortex survived correction for the entire volume (corrected  $P<.001$ ). VS indicates ventral striatum.

tween the first and the second PET scans were small: maximum  $\Delta V_3''=+0.16$  (anterior cingulate).

To exclude age effects as possible confounders, we calculated a simple regression ( $V_3''$  over age) in each group (alcoholic patients and control subjects) and an analysis of covariance, with diagnosis being the only categorical factor: in all investigated ROIs, the slope of the regression line did not differ significantly from zero. Age effects estimated with analysis of covariance were negligible (age-associated loss of  $V_3''$  in the ventral striatum, -0.015 per decade). In the striatal ROI (average of left and right),  $V_3''$  did not differ significantly between alcoholic patients with a family history positive ( $n=10$ ,  $2.67\pm 0.46$ ) or negative ( $n=10$ ,  $2.66\pm 0.31$ ,  $t=0.06$ , descriptive  $P=.95$ ) for alcoholism, with early (type 2,  $n=7$ ,  $2.76\pm 0.39$ ) vs late (type 1,  $n=13$ ) age of onset of alcoholism ( $2.62\pm 0.38$ ,  $t=0.76$ , descriptive  $P=.46$ ), or who were nonsmoking ( $n=5$ ,  $2.57\pm 0.25$ ) or smoking ( $n=15$ ,  $2.70\pm 0.41$ ,  $t=0.67$ , descriptive  $P=.51$ ). All (alcoholic and nonalcoholic) smokers ( $n=16$ ,  $2.65\pm 0.45$ ) did not differ significantly from nonsmokers ( $n=13$ ,  $2.37\pm 0.41$ ,



**Figure 3.** Analysis of differences in central  $\mu$ -opiate receptor availability between abstinent alcoholic patients and healthy control subjects, using public domain software SPM99. The analysis revealed significant differences between alcoholic patients (after 1-3 weeks of abstinence) and healthy controls in  $\mu$ -opiate receptor availability in the bilateral ventral striatum and adjacent putamen ( $P < .05$  corrected for the striatal volume of interest). The small cluster in the frontal cortex did not survive correction for multiple testing.

$t = 1.72$ , descriptive  $P = .10$ ); the number of cigarettes smoked per day was only weakly correlated with the  $V_3$  in the ventral striatum ( $r = 0.21$ , descriptive  $P = .32$ ). Among the 20 alcoholic patients, the  $V_3$  in the ventral striatum was only weakly correlated with the number of cigarettes smoked ( $r = -0.13$ , descriptive  $P = .65$ ), age of onset ( $r = -0.34$ ,  $P = .19$ ), the severity of alcohol dependence (Severity of Alcohol Dependence Questionnaire score:  $r = 0.22$ , descriptive  $P = .40$ ), or the severity of liver dysfunction (eg,  $\gamma$ -glutamyltranspeptidase:  $r = 0.18$ , descriptive  $P = .51$ ).

A multiple regression analysis was used to assess the effects of diagnosis, family history, and average number of cigarettes per day on  $V_3$  in the ventral striatum of alcoholic patients and control subjects. The 3 factors explained 35% of the variance ( $F_{3,19} = 3.42$ ,  $P = .04$ ), with diagnosis of alcoholism emerging as the only significant factor ( $\beta = -.70$ , partial  $r = -0.56$ ,  $P < .009$ ; family history:  $\beta = .10$ , partial  $r = 0.12$ ,  $P = .60$ ; cigarettes smoked per day:  $\beta = -.23$ , partial  $r = -0.21$ ,  $P = .40$ ).

#### COMMENT

To our knowledge, this is the first study that demonstrates a significant elevation in  $\mu$ -opiate receptor availability in the ventral striatum in abstinent male alcoholic patients, which correlated with the severity of alcohol craving. The ventral striatum, including the nucleus accumbens, has been implicated in primary and secondary (cocaine and monetary) rewards<sup>30,31</sup> and may represent a central area of the brain reward system.<sup>32-34</sup> Animal experiments and human studies suggest that compensatory up-regulation of central  $\mu$ -opiate receptors predispose patients toward excessive alcohol intake.<sup>2,3</sup> Our data do not indicate whether the increase

in  $\mu$ -opiate receptor availability is a cause or consequence of excessive alcohol intake.<sup>2,3,35</sup> However, the elevated  $\mu$ -opiate receptor availability in alcoholic patients persisted during the first 6 weeks of abstinence and was not consistently changed by intermittent relapses. Zubieta et al<sup>36</sup> also report increases in  $\mu$ -opiate binding in cocaine-dependent volunteers shortly after discontinuation of use and their persistence after 1 month of abstinence, suggesting that these mechanisms may in fact transcend alcohol and may also be implicated in craving for other drugs of abuse.

Carfentanil is a  $\mu$ -opiate receptor agonist that can be displaced by endogenous endorphins from its binding site.<sup>26,27,29</sup> Elevated carfentanil binding to central  $\mu$ -opiate receptors may reflect an increase in the density of opiate receptors or reduced competition with endogenous opioids.<sup>3,26,27,29</sup> In the dopaminergic system,  $D_2$ -receptor agonists seem to be more vulnerable to displacement by endogenous neurotransmitters than antagonists.<sup>37</sup> It has not yet been tested whether this is also the case for binding of carfentanil, a  $\mu$ -opiate receptor agonist<sup>18</sup>; currently, there are no selective  $\mu$ -opiate receptor antagonists available for PET studies.

If elevated  $\mu$ -opiate receptor availability in the ventral striatum of abstinent alcoholic patients reflected a lower release of endorphins, then why should treatment with the antagonist naltrexone, which further reduces  $\mu$ -opioid signaling, help decrease alcohol consumption? Several studies<sup>3,4</sup> have indicated that endorphin levels rise during a drinking session. Blockade of  $\mu$ -opiate receptors may reduce the pleasure obtained from alcohol<sup>6</sup> so that drinking sessions are ended sooner. Alternatively, if the density or affinity of postsynaptic  $\mu$ -opiate receptors is up-regulated in the ventral striatum, as indicated in this study, naltrexone may normalize the con-

centration of available receptors. Once alcohol intake is stopped during detoxification, alcohol-dependent patients may crave the rewarding effects of alcohol.<sup>32-34</sup> In animal experiments, central  $\mu$ -opiate receptors mediated alcohol-seeking behavior, which was elicited by drug-related environmental stimuli.<sup>38</sup> In accordance with this observation, we found a significant correlation between a high  $\mu$ -opiate receptor availability in the ventral striatum and the intensity of alcohol craving measured by the OCDS.

In a voxel-by-voxel comparison using SPM99, we also observed significant correlations between high  $\mu$ -opiate receptors in the frontal cortex and OCDS scores. Frontostriatal neurocircuits have been implicated in the regulation of complex behavior.<sup>31,34</sup> High  $\mu$ -opiate receptors in these neurocircuits may interfere with executive behavior control and bias retrieval of the harmful consequences of drug intake.

Several limitations of the study should be addressed. First, brain atrophy<sup>39</sup> during early abstinence may induce partial volume effects that could result in *underestimation* of the "real"  $\mu$ -opiate receptor availability among alcoholic patients. This is not an issue for the ventral striatum where we observed an *increase* in  $\mu$ -opiate receptor availability. However, the absence of significant *cortical* group differences in our data does not rule out increased cortical  $\mu$ -opiate receptor availability in abstinent alcoholic patients. Second, although we did not observe a significant interaction between smoking status and  $\mu$ -opiate receptor availability, this study cannot exclude effects of nicotine or cotinine plasma levels or caffeine intake.<sup>40,41</sup>

In summary, our data extend the findings of earlier PET studies,<sup>30,31</sup> which showed the implication of the ventral striatum, including the nucleus accumbens, in cocaine and monetary rewards to alcoholism in humans. Compared with healthy controls, detoxified patients displayed increased  $\mu$ -opiate receptor availability in a neural network that has been associated with drive states and drug craving.<sup>2,3,30-34</sup> Blockade of central  $\mu$ -opiate receptors with naltrexone reduced the relapse risk of alcoholic patients in most but not all trials.<sup>6-10</sup> On the basis of our findings, we hypothesize that naltrexone is effective in the subgroup of patients with the highest  $\mu$ -opiate receptor availability in the ventral striatum. This hypothesis is currently being tested.

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