Ventral Striatal Activation During Reward Anticipation Correlates with Impulsivity in Alcoholics

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Background: Alcohol dependence is often associated with impulsivity, which may be correlated with dysfunction of the brain reward system. We explored whether functional brain activation during anticipation of incentive stimuli is associated with impulsiveness in detoxified alcoholics and healthy control subjects.

Methods: Nineteen detoxified male alcoholics and 19 age-matched healthy men participated in a functional magnetic resonance imaging (fMRI) study using a monetary incentive delay (MID) task, in which visual cues predicted that a rapid response to a subsequent target stimulus would either result in monetary gain, avoidance of monetary loss, or no consequence. Impulsivity was assessed with the Barratt Impulsiveness Scale-Version 10 (BIS-10).

Results: Detoxified alcoholics showed reduced activation of the ventral striatum during anticipation of monetary gain relative to healthy control subjects. Low activation of the ventral striatum and anterior cingulate during gain anticipation was correlated with high impulsivity only in alcoholics, not in control subjects.

Conclusions: This study suggests that reduced ventral striatal recruitment during anticipation of conventional rewards in alcoholics may be related to their increased impulsivity and indicate possibilities for enhanced treatment approaches in alcohol dependence.

Key Words: Alcoholism, dysfunction, fMRI, impulsivity, reward system, ventral striatum

Alcohol dependence is one of the most devastating disorders in men in industrialized nations and number one risk factor for more than 60 chronic diseases (1). Addictive behavior seems to be associated with dysfunctions of the dopaminergic mesolimbic reward system (2,3), which can elicit a conditioned attention allocation for alcohol-associated stimuli rendering them specifically salient. In functional magnetic resonance imaging (fMRI) studies with alcoholics, alcohol cues activated the ventral striatum (4–6), whereas in healthy volunteers, the same area responded toward conventional reward-indicating cues (7–10). Such an effect could describe a reorganization ("hijacking") of the priorities of reward circuitry, such that drug cues elicit more appetitive behavior than cues for conventional rewards (11–13). Furthermore, prefrontal control seems to be reduced in addiction (e.g., [14–17]).

It has been suggested that alcohol dependence and drug addiction are characterized by dysfunctional preference of immediate versus delayed reward, which manifests as impulsivity and may contribute to early disease onset and increased social problems (18–20). A series of studies suggested that alcoholics are more impulsive than control subjects (21–24) and that impulse control disorders (like pathological gambling and impulsive violent behavior) are more common among alcoholics than in healthy volunteers (23,25). In addition, the acute effect of alcohol itself also enhances impulsive behavior (26,27).

One factor contributing to impulsivity is a reduced ability to choose larger but delayed rewards compared with smaller but earlier rewards ("delay discounting" as an index of impulsive tendencies) (28–31). This dysfunctional delay gratification may be associated with neuronal dysfunction of reward anticipation and contribute to craving for immediate alcohol reward (12,21,32). In fact, neuronal correlates for immediate reward bias were observed in alcoholics (14).

Brain activation elicited by reward processing can be measured with a monetary incentive delay (MID) task and fMRI (10,33). In accordance with the hypothesis that reward anticipation is altered in impulsive individuals, impulsivity was negatively associated with functional activation of the ventral striatum during reward anticipation in patients with attention-deficit/hyperactivity disorder (ADHD) (34,35) but with increased activation proportional to the amount of anticipated reward as shown in healthy control subjects (29). Attention-deficit/hyperactivity disorder patients are a group of patients with heightened impulsivity similar to alcohol-dependent patients and there may be similar neurobiological mechanisms underlying these symptoms in both groups.

Several studies have confirmed the role of ventral and dorsal striatum and its ascending monoaminergic (i.e., dopaminergic) innervation from ventral tegmental area (VTA) in impulsive behavior. In a human study, van Gaalen *et al.* (36) demonstrated that tolerance to delay reinforcement was impaired after application of a dopamine receptor D1 antagonist, indicating a close link between dopaminergic neurotransmission and impulsivity. Cardinal *et al.* (37) and Cardinal and Howes (38) demonstrated that lesions of the nucleus accumbens provoked impulsive choice behavior in rodents, which preferred immediate small rewards to delayed larger ones. Increased delay discounting has been repeatedly observed in patients with alcoholism and drug abuse (39,40).

Cloninger *et al.* (41) developed a typology proposing that high impulsivity in alcoholics is associated with the personality

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traits of high novelty seeking and low harm avoidance and suggested a modulation of these traits by dopaminergic and serotonergic neurotransmission, respectively (19). Human and animal studies partially confirmed this hypothesis by suggesting that in alcohol dependence, serotonin dysfunction is associated with negative mood states, which may trigger impulsive behavior in individuals who feel anxious or threatened (20,42). Heinz *et al.* (20) showed that nonhuman primates who were isolated in their early childhood had a reduced serotonin turnover rate and were more anxious. After adolescence, these primates were especially aggressive and impulsive and displayed enhanced self-administered alcohol consumption. Based on rodent studies, King *et al.* (43) suggested that impulsivity is reduced when stimulation of serotonin 1A (5-HT1A) receptors increases brain activation in a corticostriatal circuitry including components of the ventral striatum.

To further explore the correlation between impulsivity and striatal activation elicited during the processing of gains and losses, especially during the anticipation period, we examined recently detoxified male alcoholics and healthy men with a monetary incentive delay (MID) task and fMRI and assessed impulsivity with the Barratt Impulsiveness Scale-Version 10 (BIS-10) (44), as well as negative mood states. To the best of our knowledge, our study is one of the first directly investigating reward anticipation and impulsivity in a homogeneous sample of alcohol-dependent patients, helping to better understand the neural substrates underlying this clinically important trait.

Based on the studies by Scheres *et al.* (34) and Ströhle *et al.* (35), we hypothesized that 1) the previously shown reduced ventral striatal activation for conventional rewards (12) would correlate inversely with impulsivity, and 2) that this correlation would be particularly strong in alcoholics compared with control subjects.

Methods and Materials

Subjects

Nineteen alcohol-dependent right-handed male patients and 19 age-matched healthy subjects were included in the study. Written informed consent was obtained from all participants. The study was approved by the Ethics Committee of the Charité Universitätsmedizin Berlin. All patients were diagnosed as alcohol-dependent according to ICD-10 and DSM-IV criteria and had no other neurological and psychiatric Axis I disorders and no past history of dependency or current abuse of other drugs than alcohol and nicotine as verified by random urine drug testing and Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) interview (47). The severity of alcoholism was assessed with the Alcohol Dependence Scale (48) and severity of alcohol craving was assessed with the Obsessive Compulsive Drinking Scale (OCDS) (49) (Table 1).

Healthy control subjects had no neurological and psychiatric Axis I or Axis II disorders (SCID-I and Structured Clinical Interview for DSM-IV Axis II Disorders [SCID-II] interviews) (47,50) and no history of psychiatric disorder in first-degree relatives. Before the fMRI experiment, patients had abstained from alcohol in an inpatient detoxification treatment program for at least 7 days (14 subjects < 14 days; 9 subjects < 10 days of sobriety) as verified by random administration of alcohol breath test. All patients were free of benzodiazepine or clomethiazole medication for at least 4 days and had no bodily withdrawal symptoms. Thirty-seven alcohol-dependent patients were screened: 19 were excluded due to comorbidities or magnetic resonance imaging (MRI) contraindications and 2 were excluded due to movement during scanning. Three patients with completed BIS-10 from a previous sample (12) were included.

Table 1. Clinical Data

	Alcoholics		Control Subjects	
	Mean	SD	Mean	SD
Age in Years	41.84	6.79	41.68	8.97
Obsessive Compulsive Drinking Scale (total score) [a]	22.09	5.43	2.36	2.92
HAMD[a]	3.92	3.00	1.09	1.45
STAI[a]	41.17	9.97	33.81	8.81
VAS Effort to Obtain Gain (1–10)	6.97	2.29	8.18	1.49
VAS Effort to Avoid Loss (1–10)	6.76	2.91	8.15	1.33
Mean Hit Rate in % Gain	67.84	11.97	65.98	12.38
Mean Hit Rate in % Neutral	49.71	20.47	45.47	13.26
Mean Hit Rate in % Loss	62.28	10.50	67.25	8.69
Total Gain in Euros per Run	17.75	5.69	18.82	6.82
Stanford Sleepiness Scale	2.43	1.02	2.29	.77
Edinburgh Handedness Inventory	85.12	25.98	96.08	12.54
Educational Years [a]	9.54	1.51	11.65	1.73
Socioeconomic Status (Hollingshead Index of Social Status) [a]	4.00	1.00	6.06	1.48
IQ Estimates (WST) [a]	93.09	8.00	108.12	7.91
Number of Cigarettes per Day [a]	25.21	9.09	9.68	8.65
Severity of Alcohol Dependence (ADS)	20.92	6.96	—	—
Duration of Alcohol Dependence (in years)	11.50	5.00	—	—
Alcohol Consumption During the Last Year in kg (Pure Alcohol)	102.13	79.26	4.06	4.27
Number of Professional Detoxifications	9.82	21.87	—	—
Length of Abstinence in Days	10.44	3.97		

ADS, Alcohol Dependence Scale; HAMD, Hamilton Depression Rating Scale; IQ, intelligence quotient; STAI, State Trait Anxiety Inventory; VAS, visual analog scale; WST, *Wortschatztest*.

[a]Student *t* test: $p < .05$.

Severity of anxiety was assessed with Spielberger's State Trait Anxiety Inventory (STAI) (46) and depression was assessed with the Hamilton Depression Rating Scale (45). All participants were right-handed as confirmed by the Edinburgh Handedness Inventory (51). Years of education, socioeconomic status measured with the Hollingshead Index of Social Status (52), and verbal IQ measured with a German vocabulary test (53) were collected. All patients and 13 of 19 control subjects were smokers. Subjects last smoked about 45 minutes before scanning to avoid withdrawal. Alertness during the task was assessed with the Stanford Sleepiness Scale (54) and self-reported effort for gain, loss, and neutral cues was assessed with visual analog scales (VAS) (55) (Table 1).

Assessment of Impulsiveness

Impulsivity was assessed with a German version of the Barratt Impulsiveness Scale-Version 10 (44), which contains 34 items overall subdivided into three different subscores of impulsivity: nonplanning, motor, and cognitive impulsiveness.

Monetary Incentive Delay Task

We used the monetary incentive delay task as described by Knutson *et al.* (10) to examine neural responses in volunteers during trials in which they anticipated potential monetary gain, loss, or no consequences. Participants' monetary gain depended on their performance in a simple reaction time (RT) task at the

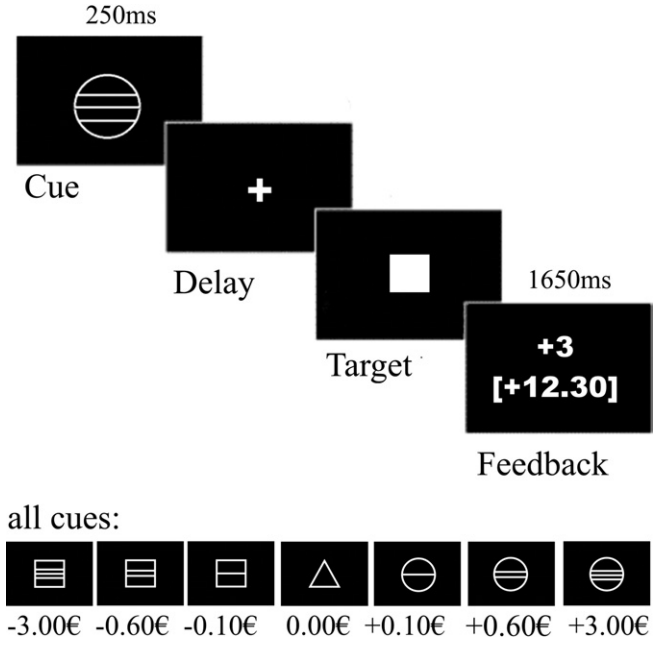

Figure 1. (Top) Task structure for a representative trial in the monetary incentive delay task. The procedure is described in the text. (Bottom) Cues used in the different trails, indicating whether different amounts of money (number of horizontal lines) could be won or lost or whether there would be no consequences depending on reaction time (circle, square, triangle).

end of each trial, which required pressing a button upon the brief presentation of a visual target (Figure 1, Supplement 1).

Money was shown in cash to the subjects before entering the scanner and they were informed that they would receive the money that they earned immediately after the scanning session. During structural scans, participants completed a short practice version of the task to minimize later learning effects and to ensure that participants had learned the association between cues and corresponding euro value (the latter was not displayed during the actual task).

In each trial, participants saw one of seven geometric figures (cue) for 250 msec, which indicated that they could either gain or avoid losing different amounts of money (€3.00, €.60, or €.10) if they pressed the response button during target presentation (white square presented for 200 msec up to maximum 1000 msec). Participants were instructed to respond as fast as possible during target presentation. The different cues are shown at the bottom of Figure 1. Between cues and target, a variable delay of 2250, 2500, or 2750 msec was inserted. After responding, a feedback was given for 1650 msec. Due to application of an adaptive algorithm for target duration, subjects succeeded on about 67% of the trials. Hits (= success) were defined as button presses within the time frame of the target presentation (maximum 1 sec), including wins as well as no-losses. Subjects performed two sessions consisting of 54 gain, 54 loss, and 36 neutral trials, which were presented in a random sequence. Each run lasted about 14 min with a mean trial duration of approximately 7.69 sec and a mean intertrial interval of 3.53 sec.

Functional Magnetic Resonance Imaging

Functional magnetic resonance imaging was performed on a 1.5 Tesla scanner (Magnetom VISION, Siemens, Erlangen, Germany) equipped with a standard circularly polarized (CP) head coil using gradient-echo echo-planar imaging (GE-EPI). For the acquisition of functional images, the following parameters were used: repetition time (TR) = 1870 msec, echo time (TE) = 40 msec, flip = 90°, matrix = 64 × 64, field of view (FOV) = 256, voxel size = 4 × 4 × 3.3 mm^3. Eighteen slices were collected approximately parallel to the bicommissural plane, covering the inferior part of the frontal lobe (superior border above the caudate nucleus), the whole temporal lobe, and large parts of the occipital region. Approximately 6 fMRI volumes were acquired per trial, resulting in 900 volumes total.

For anatomical reference, a three-dimensional (3-D) magnetization prepared rapid gradient echo (MPRAGE) was acquired (TR = 9.7 msec; TE = 4 msec; flip = 12°; matrix = 256 × 256; FOV = 256, voxel size = 1 × 1 × 1 mm^3). We minimized head movement using a vacuum pad.

fMRI Data Analysis

Functional magnetic resonance imaging data were analyzed using SPM5 (Wellcome Department of Neuroimaging, London, United Kingdom, http://www.fil.ion.ucl.ac.uk/spm).

After temporal (correction for slice acquisition delay) and spatial (movement correction, spatial normalization and smoothing with 8-mm full width at half maximum [FWHM]) preprocessing (for details, see Supplement 1), fMRI data were analyzed as an event-related design in the context of the general linear model (GLM) approach in a two-level procedure. On the first level in the single subjects SPM models, the seven different cue conditions (3× anticipation of gain, 3× anticipation of loss, and 1× anticipation of no outcome), the target, and five feedback conditions were modeled as events and convolved with the canonical hemodynamic response function (HRF) to account for the lag between event onset and expected increase of the blood oxygenation level-dependent (BOLD) signal. The five feedback conditions were successful reward feedback, failure to receive monetary reward, successful loss-avoidance, failure to avoid loss, and feedback of nonincentive trials. To account for variance caused by head movement, realignment parameters were also included as additional regressors in the model. For each subject, the linear contrast images for "gain cues > neutral cues" and "loss cues > neutral cues" were computed and taken to the second level. For the feedback phase, the contrasts "successful > nonsuccessful gain trials" and "successful > nonsuccessful loss-avoidance trials" were computed.

To detect group differences, a second level random effects analysis using a two-sample *t* test was conducted. Within-group activation was assessed with one-sample *t* tests.

The relationship between impulsivity and regional neural response during gain and loss anticipation (gain cues > neutral cues and loss cues > neutral cues) as well as during gain and loss feedback (successful > nonsuccessful gain trials and successful > nonsuccessful loss-avoidance trials) was assessed using the total BIS-10 score and the subscores (cognitive, motor, nonplanning) as covariates in multiple regression analyses using SPM5 for the whole sample. To further clarify the results, group-specific multiple regression analyses were conducted and restricted to voxels showing a significant main effect over all subjects. To reveal if correlations are specific for alcoholics compared with control subjects, additional SPM analyses tested group-by-covariate interactions in separate multiple regression analyses including the covariate (BIS-10 scale), the group-by-covariate interaction term (covariate × group), and smoking status.

Since smoking may modulate neural activity in dopaminergic brain regions (56–58), smoking status was used as a covariate in all SPM analyses (*t* tests and multiple regression analyses). To further ensure that findings were not confounded by smoking, number of cigarettes smoked per day was used as an alternative covariate instead of smoking status in additional analyses (Supplement 1).

Given our strong a priori hypotheses regarding the ventral striatum, we adjusted the results for false-positive findings applying a small volume correction (SVC) as implemented in SPM5 using binary masks from the publication-based probabilistic Montreal Neurological Institute (MNI) atlas (59) at a threshold of .75 probability (please refer to http://hendrix.imm.dtu.dk/services/jerne/ninf/voi/index-alphabetic.html, access date September 3, 2007) and a significance level of $p < .05$ familywise error (FWE)-corrected for the volume of interest (VOI) (left and right ventral striatum). All other results are reported at $p < .001$ uncorrected with a minimum cluster size of 10 voxels. Corresponding brain regions were identified with reference to the stereotaxic brain atlas provided by Talairach and Tournoux (60).

Behavioral Data Analysis

Behavioral data were analyzed with SPSS (SPSS Inc., Chicago, Illinois) using two-sample *t* tests for clinical data and repeated measures analysis of variance (ANOVA) for performance (i.e., hit rate and reaction time).

Results

Behavioral Data

Healthy subjects succeeded (i.e., responded during target presentation) on 65.98% (SEM = 2.84) of gain trials, on 67.25% (SEM = 1.99) of loss trials, and on 45.47% (SEM = 3.04) of neutral trials and earned €18.82 ± €6.82, on average. Alcohol-dependent patients succeeded on 67.84% (SEM = 2.41) of gain trials, on 62.28% (SEM = 2.75) of loss trials, and on 49.71% (SEM = 4.70) of neutral trials and earned €17.75 ± €5.69, on average. Total average earnings did not differ between the two groups ($t = .524$; $p = .603$). There was a significant main effect of cue ($F = 29.07$, $p < .001$), indicating more hit responses during gain ($t = 7.55$, $p < .001$) and loss ($t = 6.77$, $p < .001$) compared wit neutral trials (post hoc paired *t* tests) in both groups. There was neither a significant main effect of group ($F = .12$, $p = .91$) nor a significant group-by-cue interaction ($F = 2.85$; $p = .07$). Among the 144 trials, there were, on average, 7.84 misses (SD 13.81).

Mean reaction times revealed a significant main effect for cue ($F = 28.63$, $p < .001$), indicating faster responses during both gain and loss trials (RT gain > neutral: $t = 6.070$, $p < .001$ and RT loss > neutral: $t = 5.62$, $p < .001$) but no main effect for group ($F = .003$, $p = .960$) nor group-by-cue interaction ($F = .495$, $p = .558$) (Figure 2).

There were no significant differences between alcoholics and control subjects in mean self-reported alertness during the task assessed with the Stanford Sleepiness Scale (54) and no significant differences between groups in self-reported effort to achieve monetary gains or effort to prevent losses, as assessed with visual analog scales (all $t < 1.85$, all $p > .08$) (Table 1).

Impulsiveness, Mood States and Other Sample Related Variables

The total, cognitive, and motor scores of the BIS-10 were significantly higher in alcohol-dependent patients (79.46 ± 15.85) than in control subjects (69.13 ± 7.79; $t = -2.296$, $p = .030$). The cognitive and motor scores of the BIS-10 differed significantly between the two groups as well (cognitive: patients: 28.00 ± 5.40; control subjects: 23.81 ± 3.66; $t = -2.48$, $p = .020$; motor: patients: 24.69 ± 6.01; control subjects: 20.94 ± 2.29; $t = 2.31$, $p = .050$; nonplanning: patients: 26.77 ± 6.07; control subjects: 24.83 ± 4.37; $t = 1.24$, $p = .228$).

Alcoholics reported stronger alcohol craving than healthy control subjects (OCDS; $t = -11.66$, $p = .001$) and higher severity of depression (HAMD; $t = -2.92$, $p = .010$) and anxiety (STAI; $t = -2.07$, $p = .049$). In addition, we observed a significant negative correlation between impulsivity and depression ($r = -.662$, $p = .014$), but not anxiety, in alcoholics. Control subjects did not show any such significant correlations.

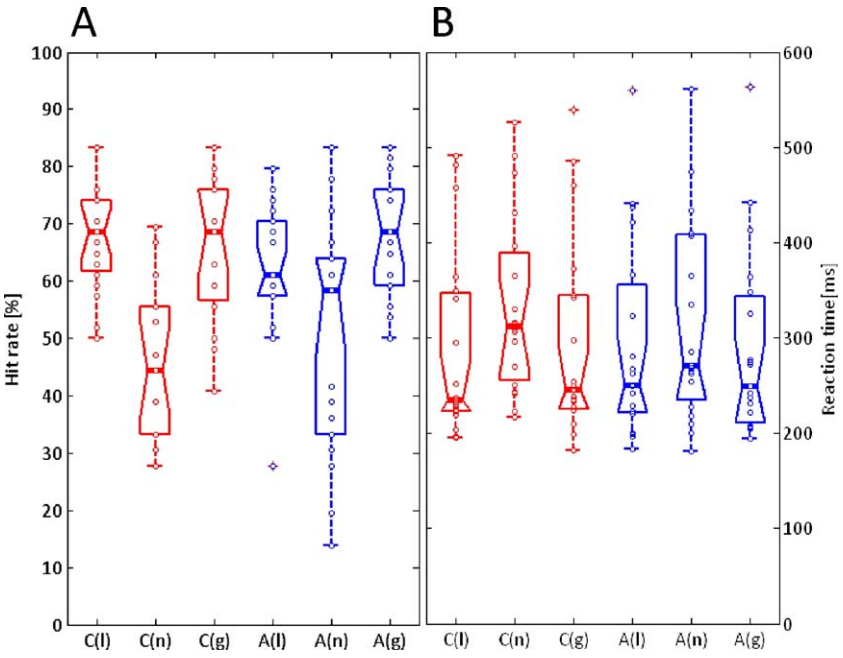

Figure 2. Hit rate **(A)** and reaction times **(B)** during MID task: Box plots show the distribution of subjects' mean effect sizes within hit rate and reaction time during MID task (left side: healthy control subjects; right side alcohol-dependent patients). The boxes have lines at the lower, median, and upper quartile values. Whiskers extend from each end of the box to the adjacent values within 1.5 times the interquartile range from the ends of the box. Notches display the variability of the median between samples. The width of a notch is computed so that box plots whose notches do not overlap have different medians at the 5% significance level. In addition, single subject data are displayed as dots. Healthy control subjects are displayed on left sides, patients on right sides; (l) indicates loss, (n) neutral, and (g) gain trails. g, gain; l, loss; MID, monetary incentive delay; n, neutral.

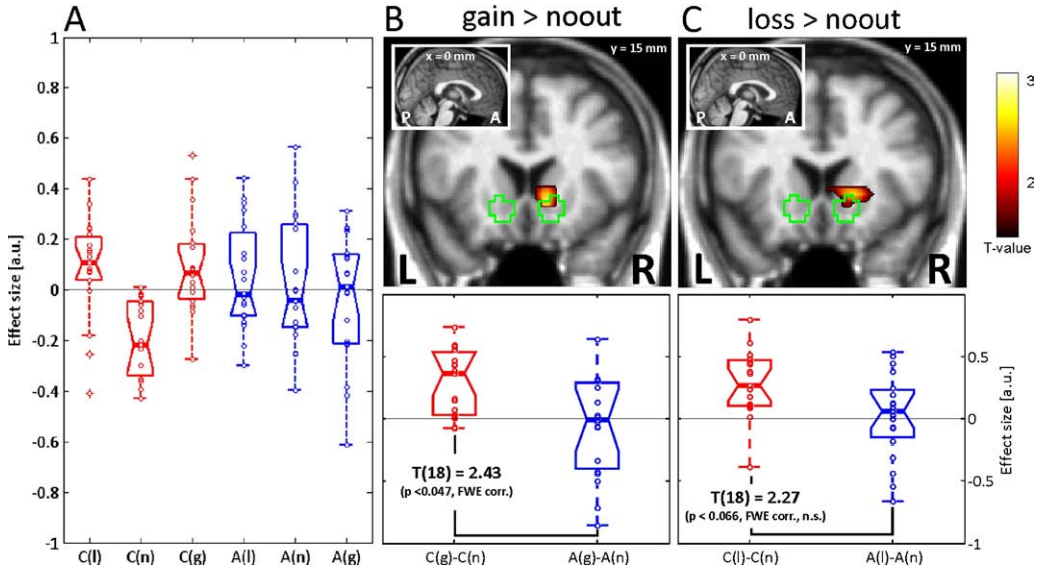

Figure 3. No increase in ventral striatal activation during gain anticipation in alcohol-dependent patients compared with healthy control subjects. **(A)** Box plots with parameter estimates for the BOLD response during anticipation of loss (l), neutral (n), and gain (g) in healthy control subjects (red) and alcohol-dependent patients (blue). **(B)** Top: Result of group comparison for the contrast "gain cues − neutral cues" with the outline of the ventral striatal VOI used for FWE corrections (drawn in green); displayed at MNI coordinate y = 15; right side = right hemisphere; plus sagittal view displayed at MNI coordinate x = 0. Bottom: Box plots of differences in parameter estimates for the BOLD response during anticipation of gain − neutral within the peak voxel of the VOI. **(C)** Top: Result of group comparison for the contrast "loss cues − neutral cues" with the outline of the ventral striatal VOI used for FWE corrections (drawn in green); displayed at MNI coordinate y = 15; right side = right hemisphere; plus sagittal view displayed at MNI coordinate x = 0. Bottom: Box plots of differences in parameter estimates for the BOLD response during anticipation of loss − neutral within the peak voxel of the VOI. A, anterior; a.u., arbitrary units; BOLD, blood oxygenation level-dependent; FWE, familywise error; L, left; MID, monetary incentive delay; MNI, Montreal Neurological Institute; P, posterior; R, right; VOI, volume of interest.

As expected, groups differed significantly in years of education ($t = 4.49$, $p = .002$) and socioeconomic status ($t = 4.54$, $p < .001$), as well as in IQ estimates ($t = 4.89$, $p < .001$). Alcoholics smoked significantly more cigarettes per day than healthy control subject ($t = -5.39$, $p < .001$) (Table 1).

Neural Activity During Anticipation of Potential Monetary Gain and Loss

During anticipation of monetary gain (contrast: gain > neutral cues), healthy control subjects showed a significant activation in the bilateral ventral striatum, right caudate tail extending into bilateral thalamus, and right insula. Alcoholics also displayed a significant activation of bilateral ventral striatum, as well as of right lateral globus pallidus, bilateral middle frontal gyrus (Brodmann area [BA] 10), right thalamus, and left superior temporal gyrus (BA 38) (Table 1 in Supplement 1).

Comparing alcoholics directly with healthy control subjects, a two-sample t test revealed significantly reduced activation in right ventral striatum (x = 12, y = 15, z = −6; $t = 2.43$, $p < .05$ FWE-corrected for ventral striatal VOI) during anticipation of gain versus neutral outcomes (Figure 3). Outside of the ventral striatum, alcoholics did not show any significantly different brain activation compared with healthy control subjects.

In healthy control subjects, anticipation of potential monetary loss (contrast: loss > neutral cues) was accompanied by significant activation of bilateral ventral striatum, left medial dorsal thalamus, bilateral putamen, bilateral parahippocampal gyrus (BA 28 and 34), right middle occipital gyrus (BA 19), right claustrum, left posterior cingulate (BA 30), right superior temporal gyrus (BA 22), and right cuneus (BA 18). Alcoholics also showed activations of bilateral ventral striatum, right middle frontal gyrus (BA 8), and right inferior frontal gyrus (BA 46) (Table 2 in Supplement 1).

Alcoholics displayed a trendwise reduction of activation compared with control subjects in right ventral striatum (x = 15, y = 12, z = −3; $t = 2.27$, $p = .07$ FWE-corrected for ventral striatal VOI). Again, outside of the ventral striatum, alcoholics did not show any significantly different brain activation compared with healthy control subjects (Figure 3).

Correlation Analyses Between Impulsivity and Anticipation

We correlated the differences in activation during 1) anticipation of monetary gain versus neutral outcomes and 2) anticipation of monetary loss versus neutral outcomes with the total score of the Barratt Impulsiveness Scale in all alcohol-dependent patients and healthy control subjects. During gain anticipation, there was a significant association between impulsiveness and brain activation in right ventral striatum (x = 15, y = 9, z = 3; $F = 23.35$, $p < .001$ uncorrected) and left anterior cingulate cortex (ACC) (x = 0, y = 33, z = −3; $F = 21.80$, $p < .001$ uncorrected). Post hoc group-specific SPM analyses revealed significant negative correlations in right ventral striatum (x = 12, y = 9, z = 3; $t = 3.83$, $p < .05$ FWE-corrected for main effect) and ACC (x = 0, y = 33, $z = -3$; $t = 3.53$, $p < .05$ FWE-corrected for main effect) (Figure 4). To test if the correlation finding was specific for alcoholics compared with control subjects, the interaction between BIS-10 total score and group was tested in SPM and revealed a group difference in ventral striatum (x = 9, y = 15, z = −6; $t = 2.36$, $p = .059$ FWE-corrected for ventral striatum VOI).

During anticipation of loss, there was a significant negative association between impulsivity and brain activation in left

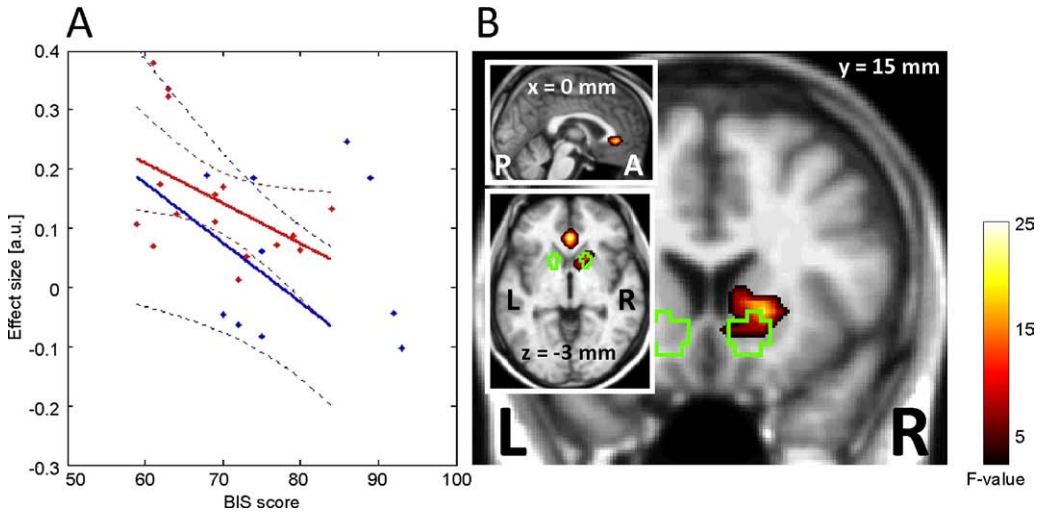

Figure 4. (A) Results of the group-specific post hoc regression analysis for control subjects (red) and patients (blue) including their 95% confidence intervals. **(B)** Results of the correlation analysis between Barratt Impulsiveness Scale and ventral striatal activation (contrast "gain cues − neutral cues") with outline of the ventral striatal VOI used for FWE corrections (drawn in green); displayed at MNI coordinate y = 15; right side = right hemisphere plus sagittal and coronal view of ACC, displayed at MNI coordinates x = 0 and z = 3. A, anterior; a.u., arbitrary units; ACC, anterior cingulate cortex; FWE, familywise error; MNI, Montreal Neurological Institute; P, posterior; R, right; VOI, volume of interest.

superior temporal gyrus (BA 41) (x = −45, y = −30, z = 18; $F = 20.27$, $p < .001$ uncorrected) and right lateral globus pallidus (x = 12, y = 3, z = 3; $F = 19.02$, $p < .001$ uncorrected) in all subjects. Post hoc group-specific SPM analyses revealed significant negative correlations in right lateral globus pallidus (x = 12, y = 0, z = 3; $t = 2.91$, $p < .05$ FWE-corrected for main effect). Interaction analyses revealed no significant group difference during loss anticipation.

To further specify our findings, the BIS-10 subscores were subjected to similar multiple regression analyses. The subscales revealed similar correlations with ventral striatum and ACC BOLD response during gain anticipation and a significant group-by-covariate interaction in the ventral striatum for cognitive and nonplanning subscales (Supplement 1).

The influence of possible confounds (motion, depression, anxiety, socioeconomic status, intelligence, years of education, and antisocial personality disorder) was controlled by additional analyses (Supplement 1).

Neural Activity During Feedback of Monetary Gain and Loss

Healthy control subjects revealed significantly stronger activations than alcohol-dependent patients during loss-avoidance feedback (contrast: successful vs. nonsuccessful loss-avoidance trials) in left ventral striatum, left precuneus (BA 31), right caudate tail, right claustrum, left middle temporal gyrus (BA 39), right superior temporal gyrus (BA 22 and 42), left middle frontal gyrus (BA 10), left insula, and left putamen, as well as right transverse temporal gyrus (BA 41) (for within-group activation see Table 3 in Supplement 1). There were no significant group differences or within-group activations during gain feedback.

There were no significant correlations between any impulsiveness scale and brain activation during feedback of gain or loss-avoidance either in control subjects or alcohol-dependent patients.

Discussion

The current findings suggest that reduced ventral striatal activation during reward expectation correlates with impulsivity in alcohol-dependent patients.

Alcoholics showed a significantly reduced activation of the ventral striatum during gain anticipation, as well as a trendwise decrease in ventral striatal activation during loss anticipation. These findings support the hypotheses that the ventral striatum is involved in processing of reward-related cues and that the reward system of alcoholics is less sensitive toward monetary incentives (12). These findings are consistent with the notion that the reward system in alcoholics is malfunctioning and may be biased toward processing of alcohol-associated stimuli (61). Grüsser *et al.* (62) showed that increased activation of the striatum during presentation of alcohol pictures was positively correlated with the prospective relapse risk, indicating that drugs of abuse hijack and reorganize the priorities of reward circuitry, so that they induce more appetitive behavior than cues for conventional rewards (11).

To investigate links between impulsiveness and brain activity, we correlated the activation during reward processing with the Barratt Impulsiveness Scale. Activation of the ventral striatum and anterior cingulate cortex during reward anticipation was inversely correlated with impulsivity only in alcoholics but not in control subjects. These findings are consistent with those of Scheres *et al.* (34) and Ströhle *et al.* (35), who also found a negative correlation between ventral striatal activation during reward anticipation and impulsiveness in ADHD subjects. Impulsive subjects may have difficulty maintaining reward expectation, even if they are responsive to reward outcomes, which might contribute to increased delay discounting (29). Moreover, reduced neuronal responsiveness to anticipated reward may provoke increased reward-seeking behavior as a means of compensation (63,64).

For anticipation of loss, group differences in ventral striatum were less marked and not associated with impulsivity. Both groups showed a negative correlation between heightened impulsivity and globus pallidum and superior temporal gyrus activation. The superior temporal gyrus is implicated in speech processing, as well as in complex cognitive tasks (like mental rotation tasks) (65). The globus pallidus, a region of ventral striatum connected with thalamus and prefrontal cortex, has been associated with behavioral control (66,67). The present

findings suggest that reduced activation in these regions during loss anticipation might also contribute to impulsivity. Loss anticipation may be associated with serotonergic functioning, whereas dopamine may be more prominent in gain anticipation (68). Direct association of brain activity with dysfunction of serotonin or dopamine neurotransmitters remain to be explored in future positron emission tomography (PET) studies (69,70). No associations were observed between feedback activation and impulsivity, which indicates a specific relationship of neural activation during anticipation and impulsiveness. In contrast, Bjork *et al.* (71) reported a positive association between impulsivity and reward feedback, indicating an increased sensitivity of impulsive subjects for reward delivery. During reward feedback, a similar increased response was found in ADHD patients (35). Differences during reward anticipation could be explained by sample characteristics (younger sample of patients with polyvalent substance abuse/dependence, e.g., cocaine and Axis I disorders), task design, and psychometric instruments (impulsivity facet of the Neuroticism Extraversion Openness-Five Factor Inventory [NEO-FFI], which is related to neuroticism).

The present findings also revealed a significant negative correlation between impulsivity and depression in alcoholics. This is in line with findings that harm avoidance predicts levels of depression (72), given that it has been suggested that harm avoidance is correlated with impulsivity (19,73). However, on the neural level, we did not observe a significant correlation between anxiety and depression and the activation in the ventral striatum, suggesting that alterations in the neuronal correlates of reward expectation in alcoholics may be more strongly related to impulsivity.

Our results confirm a series of findings demonstrating increased impulsivity in alcoholics compared with healthy control subjects (22,23,74). In rats, Belin *et al.* (75) observed that high impulsivity predicts the development of addiction-like behavior, including persistent or compulsive drug taking in the face of aversive outcomes. Beyond behaviors correlated with impulsivity, our study revealed direct neuronal correlates of impulsivity. Impulsive behavior is also influenced by social factors. For instance, primate studies revealed that social isolation in early childhood leads to reduced serotonin turnover, which increases anxious behavior, aggressive impulsive behavior, and enhanced alcohol consumption (20). In alcoholics, heightened impulsivity could therefore promote both the genesis and maintenance of alcohol dependence and may result from both genetic and social influences on monoaminergic neurotransmitter systems (76).

A potential limitation of our study might be the differences in education, socioeconomic status, and IQ. However, these differences did not interfere with task performance, as behavioral data clearly showed. Both groups also differed in the number of cigarettes smoked per day, which was controlled for in all analyses.

Overall, our findings suggest that reduced ventral striatal activation during reward anticipation and heightened impulsivity seem to be important features for alcohol dependence. Future studies will have to determine whether this dysfunction represents a preexisting condition or can be reversed over the course of treatment (either pharmacological or psychotherapeutic). The latter would emphasize the role of specific impulsivity-related psychotherapeutic interventions within the therapy of addiction, like attention focusing or stop techniques.

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