

Incentive-elicited striatal activation in adolescent children of alcoholics

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ABSTRACT

Aims Deficient recruitment of motivational circuitry by non-drug rewards has been postulated as a pre-morbid risk factor for substance dependence (SD). We tested whether parental alcoholism, which confers risk of SD, is correlated with altered recruitment of ventral striatum (VS) by non-drug rewards in adolescence. Design During functional magnetic resonance imaging, adolescent children of alcoholics (COA; age 12-16 years) with no psychiatric disorders (including substance abuse) and similarly aged children with no risk factors responded to targets to win or avoid losing \$0, \$0.20, \$1, \$5 or a variable amount (ranging from \$0.20 to \$5). Results In general, brain activation by either reward anticipation or outcome notification did not differ between COA and age/gender-matched controls. Cue-elicited reward anticipation activated portions of VS in both COA and controls. In nucleus accumbens (NAcc), signal change increased with anticipated reward magnitude (with intermediate recruitment by variable incentives) but not with loss magnitudes. Reward deliveries activated the NAcc and mesofrontal cortex in both COA and controls. Losses activated anterior insula bilaterally in both groups, with more extensive right anterior insula activation by losses in controls. NAcc signal change during anticipation of maximum rewards (relative to non-reward) correlated positively with both Brief Sensation-Seeking Scale scores and with self-reported excitement in response to maximum reward cues (relative to cues for non-reward). Conclusions Among adolescents with no psychiatric disorders, incentive-elicited VS activation may relate more to individual differences in sensation-seeking personality than to presence of parental alcoholism alone. Future research could focus on adolescents with behavior disorders or additional risk factors.

Keywords Adolescence, alcohol, at-risk children, impulsivity, incentives, nucleus accumbens, reward, sensation-seeking, striatum, ventral.

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INTRODUCTION

A critical research question is why some alcohol drinkers transition to alcohol dependence (AD) [1]. Both neurobiological [2,3] and psychosocial [4] factors confer risk for AD (reviewed in [5]). For example, children with negative affect symptomatology are more likely to drink during adolescence [6,7], and biological children of alcoholics are at increased risk for alcoholism (reviewed in [8]). Indeed, twin and adoptee studies implicate a latent heritable component underlying the comorbidity between depression, anxiety and AD [9]. Substance dependence (SD) risk may also be conferred by an inherited latent cognitive/behavioral factor [10] that jointly increases incidence of both SD and other externalizing disorders [11]. Marmorstein and colleagues [12] found

recently that parental dependence on *any* of several drugs confers increased risk to offspring both for disruptive behavior disorders as well as for life-time dependence on either the parent's drug of choice or on other drugs. Notably, in longitudinal study of boys, depression in early adolescence increased the odds ratio of alcohol use disorder in young adulthood only in depressed boys with conduct disorder symptomatology [13]. Finally, Kendler *et al.* [14] reported that AD was associated much more strongly with a latent genetic factor underlying both AD and conduct disorder and antisocial personality disorder than to the latent factor underlying shared risk for mood disorders.

Inasmuch as incentive motivation entails both cognitive and emotional components, might familial AD risk be reflected in idiosyncratic brain responses to cues to obtain

rewards or avoid negative outcomes? One motivation-related account of SD vulnerability is the reward deficiency syndrome (RDS) hypothesis [15], which posits that individuals prone to addiction have a neurotransmitter-related deficit in mesolimbic motivational circuitry, such that abused drugs are uniquely able to normalize dopamine levels in the ventral striatum (VS). According to the RDS theory, adolescents at risk of AD should show reduced VS recruitment by (non-drug) reward-predictive cues. Indeed, detoxified alcoholics showed subnormal VS recruitment by cues to respond for non-drug reward [16].

It is possible that some component of this decrement in adults with AD might have resulted from a premorbid difference, as opposed to the effects of chronic alcohol on brain structure and function. Using functional magnetic resonance imaging (MRI) with a monetary incentive delay (MID) task [17,18], we determined whether parental alcohol dependence alone is associated with blunted VS recruitment by incentive cues among psychiatrically healthy adolescents. According to the RDS hypothesis, in light of the heritability of AD, we hypothesized that a family history of alcoholism alone (in the absence of externalizing disorders) would be associated with blunted VS responsiveness to cues for non-drug rewards.

METHODS

Subjects

Informed consent and testing procedures were approved by the Institutional Review Board of the National Institute on Alcohol Abuse and Alcoholism (NIAAA). Adolescents participated along with a parent informant. Subjects were right-handed, with no significant medical illness as determined by physical examination, clinical chemistry profile and urine drug screen. Axis I disorders detected in either self-report or parent interviews using the structured Diagnostic Interview for Children and Adolescents (DICA) [19] for DSM-IV were exclusionary. During DICA interviews, none of the subjects reported having ever smoked cigarettes regularly.

Children of alcoholics (COA) (n=13; age 12–16, mean 13.9 ± 0.4 ; eight males) had at least one biological parent (father only n=6; mother only n=2; both parents n=5) who met life-time DSM-IV criteria for AD according to the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) [20]. Probable fetal alcohol exposure revealed in drinking history interviews with parent informants was exclusionary. No COA exhibited craniofacial or behavioral evidence of fetal alcohol spectrum disorders. Seven COA were recruited through a parent undergoing treatment for AD at the National Institutes of Health. The remaining COA were community-recruited.

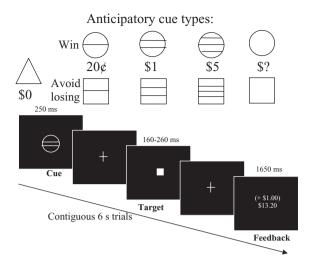


Figure I Monetary incentive delay (MID) task. The task was comprised of trials 6 seconds in duration which were presented contiguously in two 9.5-minute runs. In each trial, the subject saw one of nine anticipatory cues indicating the opportunity to either win money (circle series), avoid losing money (square series) or win/lose no money (triangle) by pressing a button while the following white square target was presented on the screen. The subject then saw feedback of whether he or she had hit the target

Neither additional parental psychiatric diagnoses nor custody status [whether the COA currently lived with the AD parent(s)] were assessed. Adolescent controls (n=13; age 12-16, mean 13.8 ± 0.4 ; eight males) were community-recruited, where no biological parent reported having a life-time diagnosis of SD on the SSAGA.

Each adolescent subject and his/her parent informant also completed the self- and parent-completed versions of the Child Behavior Checklist [21], respectively. We analyzed the higher of the parent- versus self-reported scores. Finally, adolescents completed the Brief Sensation-Seeking Scale (BSSS) [22], an adolescent variant of the Zuckerman Sensation-Seeking Scale-V [23] (sample item: 'I would love to have new and exciting experiences, even if they are illegal') to relate motivational brain activation to sensation-seeking personality.

MID task

Stimuli were presented on a screen at the foot of the scanner bed by a projection monitor, and viewed using a head coil mirror. Subjects viewed contiguous, pseudorandomly presented 6-second trials comprised of: cue presentation, anticipatory delay, target presentation and success-dependent feedback (Fig. 1). Subjects were instructed to respond on a button box while each trial's target was displayed. Subjects could win money or avoid losing money for pressing during target presentation.

First, one of nine cue shapes (which defined the trial type) was presented for 250 mseconds. Four reward cues

(circles) signaled that if the subject responded during the subsequent target presentation, he or she would win money. Amounts included 20¢ (18 trials), \$1 (18 trials), \$5 (18 trials) or a covert amount ranging from 20¢ to \$5 (six trials each with 20ϕ , \$1 or \$5 reward). Similarly, four loss-avoidance cues (squares) signaled the possibility of losing either 20¢, \$1, \$5 (18 trials each) or a covert amount from 20ϕ to \$5 (six trials each with 20ϕ , \$1 or \$5 loss) if the subject failed to respond to the subsequent target while it was presented. Cues signaling nonincentive outcomes (36 trials: triangles) were also presented and subjects were instructed to respond to subsequent targets, but that trial outcomes would not alter their winnings. Each cue was replaced by a crosshair for a variable interval (anticipation period, 2000– 2500 mseconds). Then, a white target square was presented for a variable length of time 180-280 mseconds). The trial then concluded with feedback (1650 mseconds) following the disappearance of the target, which notified participants of whether they had won or lost money during that trial and also displayed their cumulative earnings.

Prior to scanning, subjects were shown an envelope containing the cash they could win, and were read an instruction script which defined the consequences signaled by the trial-onset cues. Then, during a 5-minute practice session, reaction times to targets were measured covertly, and a distribution of target presentation durations was selected such that each participant would succeed on ~66% of trials during the scan. Once in the scanner, each participant engaged in two runs of the MID task, followed by a structural scan (described below) for anatomical co-localization. Following the scan, subjects performed computerized ratings (four-point scales) of how 'excited', 'happy', 'fearful' and 'unhappy' they felt when they saw each of the task cues. Subjects were then paid their task earnings. Subjects also received \$100 compensation for lost time during the psychiatric and medical screening visit and MRI visit.

FMRI acquisition

Imaging was performed using a 3 T General Electric MRI scanner (General Electric, Milwaukee, WI, USA) and a quadrature head coil. Functional scans were acquired using a T2*-sensitive echoplanar sequence with a repetition time (TR) = 2000 mseconds, echo time (TE) = 40 mseconds, flip = 90°. We collected 24 2.0-mm-thick contiguous axial slices encompassing the base of the orbitofrontal cortex to the apex of the corpus callosum. In-plane resolution was 3.75 ± 3.75 mm. Structural scans were acquired using a T1-weighted sequence (TR, 100 msec; TE, 7 mseconds; flip, 90°), which facilitated co-registration of functional data. Each subject's head

was restrained with a Vacu-Fix System deflatable cushion (S&S X-Ray Products, Inc., Houston, TX, USA).

fMRI analysis

Pre-processing

Blood oxygen-level dependent (BOLD) signals were analyzed using Analysis of Functional Neural Images (AFNI) software [24] as follows: (i) volumes were concatenated across task sessions; (ii) voxel time-series were interpolated to correct for non-simultaneous slice acquisition and (iii) volumes were corrected for head motion. Motioncorrection output indicated that no participant's head moved more than 1.5 mm in any dimension between volumes or more than 3 mm overall in any dimension over the whole task. Data were smoothed spatially with a 4 mm FWHM isotropic smoothing kernel, then smoothed temporally with a despiking algorithm to attenuate deviations in signal greater than 2.5 standard deviations from the mean followed by bandpass filtering, which smoothed cyclical fluctuations in signals that were not temporally indicative of a hemodynamic response (either greater than 0.011/second or less than 0.15/second).

Individual subject statistical maps

Each subject's time-series data were analyzed with a simultaneous multiple regression which incorporated event-related regressors of interest. These were modeled with canonical gammavariate hemodynamic response functions (HRF) time-locked to the presentation of the anticipatory cue and to the notification of outcomes (hits and misses modeled separately). Additional regressors controlled for residual head motion after volume correction and baseline and linear trends. Activations were then detected by area-under-curve linear contrasts (LC) between: (i) anticipation of responding for all monetary gains (20¢, \$1, \$5 or covert) versus non-incentive (\$0), (ii) anticipation of responding to avoid all monetary losses (20¢, \$1, \$5 or covert) versus non-incentive (\$0), (iii) gain versus non-gain outcomes in gain trials and (iv) loss versus non-loss outcomes in loss trials.

Groupwise statistical maps

Individual subject maps of LC t-statistics were transformed into Z scores and warped to common Talairach space and combined into a group map using a meta-analytical formula [average $Z \times$ square root (n)] [17,18]. Activations are reported where voxels singly activated to a statistical significance threshold of P < 0.001 comprised a contiguous cluster of sufficient volume to obtain a familywise corrected type I error rate ≤ 0.05 using Monte Carlo simulation.

Volume-of-interest (VOI) analysis

Recruitment of the nucleus accumbens (NAcc) by cues to respond for reward has been demonstrated extensively with this paradigm [17.18.25.26]. To characterize NAcc signal change elicited by reward and loss anticipation, we measured BOLD signal change in the NAcc in VOI analyses. For each subject, a mask for each of the left and right NAcc was custom-drawn in Talairach-space to encompass gray matter at the ventromesial junction between the caudate and putamen (Fig. 5, center). In the coronal plane, the inferior and mesial boundaries of the mask were circumscribed by the substriatal aspect of the external capsule and the lateral ventricles. In the absence of discernable dorsolateral boundaries of the NAcc [27], the superior and lateral mask boundaries were set arbitrarily at Talairach z = 0 and $v = \pm 12$, respectively. The mask extended 6-12 mm anterior to the anterior commissure. Signal data were extracted from the mask as follows: (i) signal at each voxel was converted to a percentage signal change from the mean for that voxel across the entire time-series; (ii) signal was averaged by trial type and translated spatially into Talairach space; and (iii) signal change was averaged across voxels encompassed by the mask at each time-point then re-calculated as the difference from (mask-averaged) signal recorded at trial onset.

For each of the reward and loss-avoidance trial types, incentive-related signal change was calculated as net peak signal increase relative to the peak increase measured in the non-incentive trials. Extracted trial-averaged data were analyzed in mixed-model analyses of variance (ANOVA) across the left and right NAcc masks, with net signal change as the independent variable. Incentive magnitude (20ϕ , \$1 or \$5 or covert), side (left, right) and incentive valence (reward, loss-avoidance) were within-subject factors, and group (COA, control) the between-subject factor.

Behavior analysis

We performed mixed-model analyses of variance of each of affective ratings, hit rates and reaction times (RT) in each of reward and loss-avoidance trial series, with incentive magnitude (five levels: 0, 20ϕ , 1 and 1 and 1 and 1 and 1 as the within-subject factor and group (two levels: COA and control) as the between-subject factor.

RESULTS

Ouestionnaire measures and task behavior

All subjects scored in the normal range of the CBCL, with nearly identical distributions of internalizing (mean raw score 5.8) or externalizing (mean raw score 6.9) subscale scores between the groups. Controls and COA also scored

similarly on the BSSS [mean 22.7 \pm 5.7 and 22.1 \pm 4.3, respectively; not significant (NS)]. Subjects showed faster RT to maximum reward (209 \pm 23 mseconds) and maximum loss-avoidance (212 ± 26 mseconds) targets compared to their RT to non-incentive control targets (mean 234 ± 23 mseconds), resulting in a main effect of incentive magnitude on RT across both reward $(F_{(4.96)} = 7.219, P < 0.0001)$ and loss-avoidance $(F_{(4.96)} = 4.070, P < 0.01)$ trial types. There were no main or interactive effects of COA group on reaction time or omission errors (failures to respond to targets altogether) in either reward or loss trials. Target hit rates did not differ between COA (64.3%) and controls (65.1%) in reward trials, but there was a trend for COA to hit slightly fewer loss-avoiding targets (60.5%) than did controls (68.4%); main effect of group $F_{(1,24)} = 4.154$, P = 0.053). Accordingly, COA had lower mean task earnings (\$44.5) than controls (\$58.50), but this difference was not significant (P > 0.20).

Due to technical error, three post-scan affect question-naires were not recorded. There were significant main effects of incentive magnitude on each of the four affective ratings, where participants reported greater happiness $(F_{(3,63)}=14.880,\ P<0.0001)$ and excitement $(F_{(3,63)}=22.863,\ P<0.0001)$ as potential reward amounts increased and also reported greater unhappiness $(F_{(3,60)}=11.927,\ P<0.0001)$ and fearfulness $(F_{(3,57)}=20.219,\ P<0.0001)$ as potential loss amounts increased. There was a significant group × incentive interaction effect on unhappiness ratings $(F_{(3,60)}=4.495,\ P<0.01)$, where COA reported lower levels of unhappiness (mean 1.6) when seeing the cue signaling potential for a \$5 loss compared to controls (mean 3.1) (simple effect t-test P<0.01).

Statistical maps

Reward versus non-reward anticipation

Anticipation of responding for reward (all magnitudes collapsed) versus anticipation of responding for non-reward activated the left NAcc in controls and right NAcc in COA (Table 1; Fig. 2).

Loss versus non-loss anticipation

Anticipation of responding to avoid loss (all magnitudes collapsed) versus anticipation of responding for non-loss did not activate any brain regions in either controls or in COA.

Gain versus non-gain outcomes

Individually calibrated task difficulty resulted, on average, in approximately 47 reward notifications

Table 1 Activations by cues signaling potential rewards versus cues signaling no incentive.*

	Talairach Co	ordinates†	t-value	Uncorrected P						
Controls										
Left nucleus accumbens	-10	8	-5	4.585	< 0.00001					
COA										
Right caudate head	7	9	4	3.917	< 0.0001					
Right nucleus accumbens	7	11	-3	3.490	< 0.001					
Mesial thalamus	1	-8	8	3.612	< 0.001					
Right midbrain	4	-20	-8	3.595	< 0.001					

^{*}Anticipation of cues for active-avoidance of losses versus cues for non-incentive did not activate any brain regions in either group. †Voxel coordinates listed in all tables were the peak of a contiguous cluster sufficient to obtain a familywise corrected type I error rate of P < 0.05 using Monte Carlo simulation. COA: children of alcoholics.

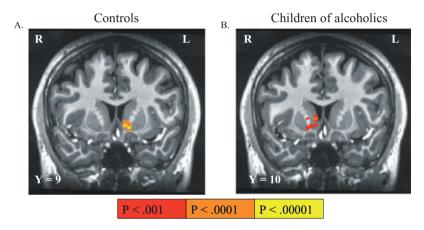


Figure 2 Activation by anticipation of responding for rewards. In this and subsequent figures: (i) all images are right–left reversed per radiological convention, (ii) the underlay is a TI-weighted structural (co-registration) image from a representative control subject, (iii) the Talairach coordinate of the image plane is indicated at lower left and (iv) activations (warm colors) of voxel clusters survive familywise error rate correction to P < 0.05). Anticipation of responding for rewards contrasted with anticipation of non-reward activated the ventral striatum in both controls (A) and children of alcoholics (COA) (B). Anticipation of responding to avoid losses, however, did not activate any brain regions in either COA or controls

contrasted with approximately 25 notifications of failures to win reward in each subject. In both controls and in COA, this contrast activated the anterior mesofrontal cortex, the posterior cingulate cortex, mesial occipital cortex and the VS bilaterally, with activated voxels extending from the NAcc posteroventrally into superior amygdala (Table 2; Fig. 3).

Loss versus loss-avoidance outcomes

Individually calibrated task difficulty resulted, on average, in approximately 26 loss notifications contrasted with approximately 46 successful loss avoidances in each subject. This contrast activated bilateral anterior insula and deactivated portions of putamen and inferior frontal cortex in both controls and in COA (Table 3; Fig. 4), with greater extent of right insula activation in controls.

Voxelwise t-tests of group differences in linear contrast activations

We performed post hoc voxelwise t-tests of the group difference in LC beta weights, with familywise error rate correction on each 'difference' map to adjusted P < 0.05. These tests indicated no significant group difference in VS activation by reward versus non-reward anticipation on either side, and no significant group difference in either mesial frontal, posterior cingulate or mesial occipital cortices by reward versus non-reward notification. However, COA showed a decrement in activation by loss (versus non-loss) notification in right anterior insula (illustrated at right of Fig. 4).

Signal change in nucleus accumbens VOI

There were significant main effects of side (left > right; $F_{(1.24)} = 5.021$, P < 0.05), incentive valence

Table 2 Activations by reward (versus non-reward) notifications.

	Talairach	t-value Uncorrected P							
Controls									
Left ventral putamen	-17	9	-7	6.284	< 0.000001				
Right nucleus accumbens	10	9	-5	6.266	< 0.000001				
Left amygdala	-18	-9	-13	5.743	< 0.000001				
Right amygdala	18	-9	-14	4.909	< 0.00001				
Left dorsal thalamus	-9	-11	15	6.152	< 0.000001				
Mesial orbitofrontal cortex	2	45	-6	4.913	< 0.000001				
Right inferior frontal gyrus	42	29	11	5.498	< 0.000001				
Left inferior frontal gyrus	-41	25	10	5.582	< 0.000001				
Right inferior occipital gyrus	48	-61	-2	5.368	< 0.000001				
Left inferior occipital gyrus	-42	-58	-5	5.500	< 0.000001				
Mesial posterior cingulate gyrus	0	-38	24	6.430	< 0.000001				
Right posterior cingulate gyrus	6	-56	17	5.398	< 0.000001				
Left posterior cingulate gyrus	-8	-58	14	5.626	< 0.000001				
COA									
Left nucleus accumbens	-8	9	-6	5.474	< 0.000001				
Right Nucleus accumbens	10	9	-7	6.952	< 0.000001				
Left amygdala	-16	-9	-11	7.260	< 0.000001				
Right amygdala	16	-7	-11	6.680	< 0.000001				
Dorsomesial thalamus	-1	-12	9	5.717	< 0.000001				
Mesial orbitofrontal cortex	2	46	-8	6.291	< 0.000001				
Right inferior frontal cortex	38	49	-1	5.037	< 0.000001				
Left inferior frontal cortex	-44	39	-1	4.144	< 0.0001				
Right inferior occipital cortex	49	-60	-9	6.122	< 0.000001				
Left inferior occipital cortex	-41	-60	-6	6.286	< 0.000001				
Mesial posterior cingulate gyrus	2	-53	10	7.324	< 0.000001				
Right posterior cingulate gyrus	9	-68	9	5.866	< 0.000001				
Left posterior cingulate gyrus	-15	-65	9	5.977	< 0.000001				

COA: children of alcoholics.

(reward > loss-avoidance; $F_{(1,24)} = 15.986$, P < 0.001) and incentive magnitude (high > low; $F_{(1,24)} = 15.986$, P < 0.001) on peak BOLD signal increase (relative to nonincentive trials) in the NAcc. This is illustrated in Fig. 5. There were no significant main (P > 0.6) or interaction effects (all P > 0.2) of subject group (COA versus control) on incentive-elicited signal change [removal from analysis of COA with an AD mother (only) did not change these results appreciably]. Finally, there was a trend for a valence by magnitude interaction effect ($F_{(3,72)} = 2.141$, P = 0.10) on NAcc signal change. Post hoc analyses indicated that this trend resulted from a significant main effect of incentive magnitude in reward trials ($F_{(3,72)} = 6.813$, P < 0.001), which was not evident in loss-avoidance trials (P > 0.5). There were also trends for greater left- > rightsided activation by reward $(F_{(1,24)} = 4.017, P = 0.056)$ and loss-avoidance ($F_{(1,24)} = 3.988$, P = 0.057) anticipation considered singly.

Psychometric correlates of NAcc activation

Because signal change in the NAcc was greatest during high-reward (\$5) trials, we calculated a unitary

measure of incentive-elicited NAcc activation as the difference in peak signal change elicited by anticipation of \$5 reward minus peak signal change elicited by anticipation of responding for non-reward. Net rewardrelated excitement was calculated as the difference between self-reported excitement when seeing the cue for the \$5 reward minus self-reported excitement when seeing the cue for non-reward. Activation in both left and right NAcc correlated with net excitement in Spearman's rank-order bivariate correlation (left: r = 0.560, P < 0.01; right: r = 0.469, P < 0.05). In multiple regression, partial correlations between net excitement and net signal change were greater after controlling for each subject's difference in RT between the \$5 reward and non-incentive trials (as a second independent variable) (left: beta = 0.621, P < 0.01; right: beta = 0.535, P < 0.05). In addition, BSSS scores correlated with net signal change in the left (but not right) NAcc, both in bivariate correlation (Spearman's r = 0.420, P < 0.05) and after controlling for each subject's trial-type difference in RT (beta = 0.432, P < 0.05). These partial correlations are depicted as leverage plots in Fig. 6. The net difference in RT between the two

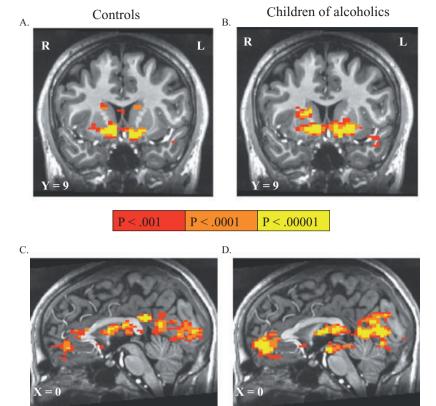


Figure 3 Activation by notification of rewards. Notification of rewards (contrasted with notification of failure to win reward) activated the VS in both controls (A) and in children of alcoholics (COA) (B). Reward notification also activated mesial frontal and occipital cortices in both controls (C) and COA (D)

Table 3 Activations and deactivations by loss (versus loss avoidance) notifications.*

	Talairach	t-value Uncorrected P			
Controls					
Left caudate	-9	4	9	4.102	< 0.0001
Right caudate (head)	11	9	5	3.898	< 0.0001
Left anterior insula	-37	11	-3	5.215	< 0.000001
Right anterior insula	33	11	-1	5.524	< 0.000001
Right dorsal posterior thalamus	7	-27	1	6.279	< 0.000001
Midbrain	0	-19	-7	5.128	< 0.000001
Right anterior cingulate gyrus	6	36	5	5.271	< 0.00001
Right posterior cingulate gyrus	17	-64	15	4.255	< 0.0001
Left inferior frontal cortex	-38	48	-6	-5.401	< 0.000001
Right inferior frontal cortex	30	55	-5	-4.599	< 0.00001
Left posterior putamen	-27	-7	5	-5.390	< 0.000001
Right posterior putamen	26	-8	6	-4.100	< 0.0001
COA					
Left caudate	-9	7	9	5.716	< 0.000001
Right caudate	10	5	11	4.639	< 0.00001
Left anterior insula	-29	18	-7	5.300	< 0.000001
Right anterior insula	37	15	-5	4.306	< 0.0001
Midbrain	-2	-27	1	3.705	< 0.0001
Right anterior cingulate gyrus	7	41	9	4.749	< 0.00001
Mesial inferior frontal cortex	6	47	-13	-3.886	< 0.0001
Left posterior putamen	-28	-4	-3	-7.637	< 0.000001
Right posterior putamen	26	-8	7	-8.109	< 0.000001

^{*}Deactivations are denoted in italics. COA: children of alcoholics.

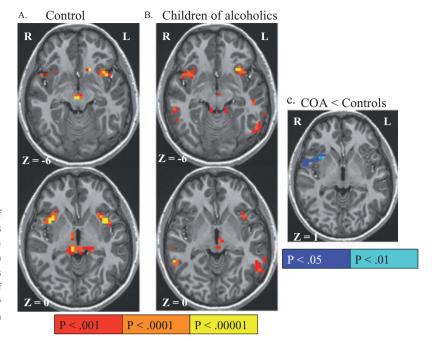


Figure 4 Activation by notification of losses. Notification of all losses (versus notification of successful loss avoidance) activated bilateral anterior insula in both controls (A) and children of alcoholics (COA) (B). A direct voxelwise *t*-test of this activation revealed significantly reduced activation by this contrast in COA in right anterior insula (C)

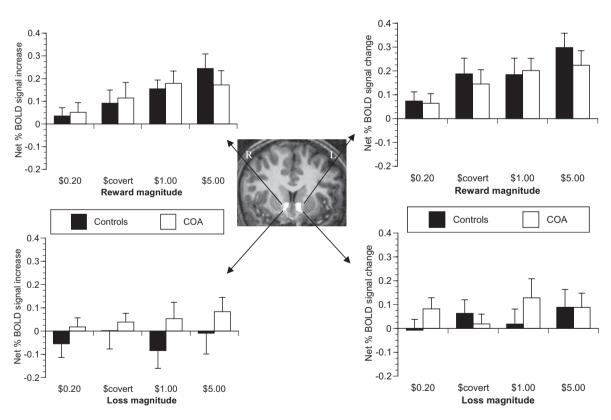


Figure 5 Peak cue-elicited signal change in volumes of interest. Trial-type-averaged time series data were extracted from a mask custom-drawn for each subject in the nucleus accumbens (NAcc; center). Peak anticipatory signal increase from trial-onset occurred 6 seconds post-cue. NAcc recruitment increased with incentive magnitude in reward trials, but not in loss-avoidance trials, with overall greater NAcc recruitment by reward cues compared to loss-avoidance cues. There were no main or interactive effects of children of alcoholics status on NAcc signal change

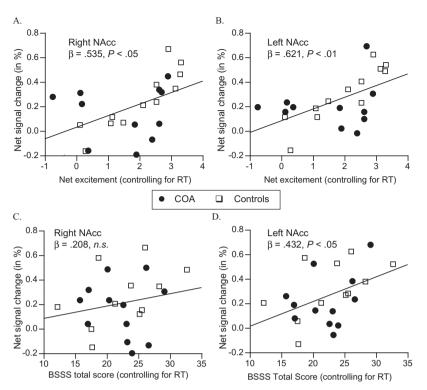


Figure 6 Relationship between nucleus accumbens (NAcc) signal change and psychometric measures. In both right (A) and left (B) NAcc, individual differences in net reward-related signal change correlated with subjects' self-report ratings of net 'excitement' at seeing the cue for maximum reward. This was evident both in bivariate correlation, and after controlling for the subject's reaction time difference between the maximum and zero incentive targets. Reward-related signal change correlated with Brief Sensation-Seeking Scale scores in left (D) but not right (C) NAcc. Solid circles denote children of alcoholics. Open squares denote controls

trial types did not itself correlate partially with net signal change.

DISCUSSION

Incentive-elicited striatal and mesofrontal activation by the MID task was substantially similar between adolescent COA with minimal mood and behavior symptomatology and controls with no family history of AD. Both groups showed VS activation during reward anticipation. An apparent groupwise activation laterality difference resulted from thresholding, where both group maps revealed subthreshold activation (P < 0.01) in the opposite side of the NAcc, together with no side × group interaction effect (P > 0.5) on activation in the VOI analysis. Both groups also showed similar recruitment of mesofrontal cortex and VS by notifications of reward. Finally, both groups showed bilateral anterior insula activation in response to notification of losses, consistent with insula recruitment by aversive stimulus delivery in other reports [28].

Bilateral NAcc signal change was greater for reward anticipation compared to loss-avoidance anticipation, such that signal change increased in proportion to magnitude in reward trials only. Other fMRI paradigms have also revealed a bias of the NAcc toward recruitment by anticipation [29] or delivery of [30] positively valenced incentives (over negatively valenced incentives). Across all subjects, the VOI analysis indicated stronger incentive-anticipation activation in the left compared to the right

NAcc. This may reflect the mobilization of an operant response by the contralateral (right) hand. Notably, NAcc activation by reward-predictive cues in a variant of this paradigm was absent in trials where no operant response for the reward was required [31].

We predicted that the COA would show blunted VS recruitment by reward anticipation relative to controls in accord with the RDS hypothesis and the VS recruitment deficit in AD patients [16]. Instead, we found no consistent pattern of altered reward-anticipation processing in these COA. We propose several possible explanations for the absence of a group difference. First, it may be the RDS applies only to deficient mesolimbic recruitment by non-drug primary rewards, and not to abstract rewards such as money. Secondly, it may be that the deficit in VS recruitment by cues for non-drug reward reported previously [16] resulted primarily from chronic alcohol withdrawal-induced impairment of incentive neurocircuitry [32]. For example, rats in withdrawal from chronic ethanol exposure required more current to elicit intra-cranial self-stimulation [33]. Thirdly, it is also possible that the sample size lacked statistical power to detect groupwise differences. However, both developmental [17] and disorder-dependent [26] differences in NAcc recruitment during the MID task have been detected with smaller sample sizes. A post hoc power analysis of the group difference in net NAcc recruitment by maximum reward indicated a requirement of more than 80 subjects to be significant, implying a very small effect.

We posit instead that these COA were only at mildly elevated risk for SD. First, dysphoric mood [6,7] and externalizing symptomatology [34] in childhood each directly portend increased risk of adolescent substance use or abuse. We excluded any COA with either a behavioral or mood disorder (about 50% of applicants), perhaps selecting for a pool of COA who were resilient and developing normally. Recently, Heitzig et al. [35] reported significantly blunted NAcc recruitment but increased mesofrontal cortex recruitment by positively valenced words in adolescent COA with histories of problem drinking compared to controls and non-drinking COA. Secondly, we did not select for children of actively drinking alcoholic parents. Most COA had at least one parent in recovery, whose alcoholism may not have been as severe as in non-treatment-seeking alcoholics. Ozkaragoz et al. [36] reported worse executive cognitive functioning in young adolescent sons of active alcoholic fathers compared to sons of recovering alcoholics. Thirdly, we did not select for presence of comorbid psychopathology in the alcoholic parent(s) of these COA. Studies of individual differences among COA have demonstrated that children of parents with comorbid AD and either antisocial personality disorder or affective disorder are at particular risk [37]. Finally, we did not select for COA with multiple first- or second-degree relatives with AD. Barnow et al. [38] reported a positive relationship between CBCL scores and family density of AD. In sum, simply having a single alcoholic biological parent alone may provide only a relatively weak phenotype as an individual difference in fMRI study, compared to the potential for altered limbic recruitment by incentives in adolescents with multiple risk factors.

In contrast with the lack of effects of parental alcoholism, reward-anticipation activation in left NAcc correlated with sensation-seeking personality, which is considered by some theorists to be one dimension of impulsivity (e.g. [39] reviewed in [40]). Some investigators have framed normative [41] and clinically significant [42,43] adolescent impulsivity, as well as SD [44] as the outcome of a dysregulated opponent process wherein circuitry governing approach to positively valenced incentives is insufficiently opposed by frontocortically mediated behavior control. Extending incentive processing research to children and adolescents with externalizing disorders is therefore of interest, because processing differences could explain in part the findings from twin [10,11,45,46] and longitudinal [47] studies that attribute addiction vulnerability to a heritable generalized behavior control deficit [48]. Specifically, the opponent-process hypothesis would predict that adolescents vulnerable to addiction would be characterized by hypersensitivity of the mesolimbic 'reward' circuit [41] to learned [49] cues to respond for reward [50].

In conclusion, a mixed population of adolescent COA with minimal mood or behavior symptoms did not demonstrate deviant recruitment of mesolimbic circuitry by reward cues or deliveries. This study extends previous findings [17,41,51] that recruitment of the VS by reward-predictive cues occurs by adolescence. In addition, these data suggest that among adolescents with no clinical syndromes, individual differences in recruitment of incentive neurocircuitry by laboratory incentives may relate to valuation of risky or novel situations. COA with minimal mood and behavior problems may represent a resilient subgroup by virtue of normative incentive processing. Future studies of adolescents who have either: (1) significant mood and behavior symptoms, (2) multiple relatives with AD or (3) AD parents with comorbid psychiatric disorder might reveal abnormalities in recruitment of incentive neurocircuitry. Future longitudinal research could also assess whether deviant mesolimbic incentive processing in adolescence relates to subsequent

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