Affective Circuitry and Risk for Alcoholism in Late Adolescence: Differences in Frontostriatal Responses Between Vulnerable and Resilient Children of Alcoholic Parents

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Background: Children of alcoholics (COAs) are at elevated risk for alcohol use disorders (AUD), yet not all COAs will develop AUD. The 2 primary aims of this study were to identify neural activation mechanisms that may mark protection or vulnerability to AUD in COAs and to map the same activation patterns in relation to risk behavior (externalizing or internalizing behavior).

Methods: Twenty-two adolescent COAs were recruited from an ongoing community longitudinal study of alcoholic and matched control families. They were categorized as either vulnerable ($n = 11$) or resilient ($n = 11$) based on the level of problem drinking over the course of adolescence. Six other adolescents with no parental history of alcoholism, and no evidence of their own problem drinking were recruited from the same study and labeled as low-risk controls. Valenced words were presented to the participants in a passive viewing task during functional magnetic resonance imaging. Activation to negative versus neutral words and positive versus neutral words were compared between groups. Behavior problems were assessed with the *Youth Self-Report* (YSR).

Results: The resilient COA group had more activation of the orbital frontal gyrus (OFG), bilaterally, and left insula/putamen than the control and vulnerable groups, in response to emotional stimuli. In contrast, the vulnerable group had more activation of the dorsomedial prefrontal cortex and less activation of the ventral striatum and extended amygdala, bilaterally, to emotional stimuli than the control and resilient groups. The vulnerable group had more externalizing behaviors which correlated with increased dorsomedial prefrontal activation and decreased ventral striatal and extended amygdala activation.

Conclusions: These results are consistent with dissociable patterns of neural activation underlying risk and resiliency in COAs. We propose that the pattern observed in the resilient COAs represents an active emotional monitoring function, which may be a protective factor in this group. On the other hand, the vulnerable group displayed a pattern consistent with active suppression of affective responses, perhaps resulting in the inability to engage adaptively with emotional stimuli.

Key Words: Vulnerability, Resiliency, Ventral Striatum, Prefrontal Cortex, Orbitofrontal Cortex.

O NE OF THE most compelling, still unresolved issues in alcoholism risk research today is that of individual differences: What causes some individuals to become alcoholic and not others? Individual differences in vulnerability involve interactions among genetic, neurobiological, and environmental factors over a significant portion of the life course (National Institute on Alcohol Abuse and Alcoholism, 2000; Zucker, 2006). It is well known that parental alcoholism raises risk for offspring alcoholism (Caspi et al., 1996; National Institute on Alcohol Abuse and Alcoholism, 2000; Russell, 1990) and that genetic influences account for 40 to 60% of the variance in alcoholism risk (e.g., Heath, 1995; Heath et al., 1997; Kendler et al., 1994). However, the remaining variance is not entirely accounted for by shared family environment (Jacob et al., 2001).

Some of this genetic risk is likely mediated through intermediate behavioral traits, such as behavioral undercontrol/externalization and emotional dysregulation/internalization (Caspi et al., 1996; Chassin and Ritter, 2001; Cloninger et al., 1988; Zucker, 1994; Zucker et al., 1995). Externalizing behavior problems are elevated in children of

alcoholic parents (COAs) (Slutske et al., 2002; Wong et al., 1999) and predict later problem alcohol involvement (Sher, 1993; Zucker, 2006). Among adolescents, measures of behavioral undercontrol have been correlated with early age of first use (McGue et al., 2001), greater use (Clark et al., 1999; Mason and Windle, 2002; White et al., 2001; Wills et al., 1996), accelerated alcohol involvement (Clark et al., 2005) and alcohol dependence (Rohde et al., 1996). COAs are also at increased risk for internalizing symptoms (e.g., negative emotion, behavioral inhibition) (Chassin et al., 1993) and measures of negative affectivity have been correlated with adolescent alcohol use (Colder and Chassin, 1993; White et al., 2001) and dependence (Rohde et al., 1996).

With regard to the neural level of analysis of these vulnerabilities, poor regulation of behavior and propensity to negative affect appear to involve closely related yet partially distinct neural circuitry. Numerous neuroimaging studies have shown that ventral anterior cingulate, prefrontal and insular cortices, amygdala and ventral striatum are involved in affective experience and regulation (see review in Phan et al., 2002). Control circuitry—that is, circuitry involved in regulating or suppressing reflexive behavior or cued information—includes portions of the prefrontal and posterior parietal cortices, basal ganglia and thalamus (Aron and Poldrack, 2005; Aron et al., 2003a,b; Casey et al., 1997, 2002). The model guiding our work supposes that subcortical aspects of these circuits (e.g., amygdala, ventral striatum) are related to emotional response (i.e., bottom up responding to stimulus), whereas prefrontal aspects of these circuits are involved in the dynamic regulation of affective responses and motivated behavior (e.g., Hariri et al., 2000, 2002; Nigg and Casey, 2005).

The above circuitry is also closely related to the circuitry involved in reward responsivity, salience attribution, and motivated behavior (Hyman and Malenka, 2001; Koob, 2003; Nestler, 1999). This circuitry, also thought to be relevant to addiction propensity, includes the ventral striatum, amygdala, areas of the prefrontal cortex, and the insular cortex (e.g., Kalivas and Stewart, 1991; Koob, 1999; Naqvi et al., 2007; Volkow et al., 2004). Variation in functioning of these related circuits may contribute to vulnerability or resilience in youth at risk.

Although structural (De Bellis et al., 2000; Medina et al., 2007; Nagel et al., 2005) and functional (Brown and Tapert, 2004; Tapert et al., 2001) differences in this circuitry have been found in adolescents with alcohol use disorders (AUDs) compared with controls, some of these alterations are likely to be caused by, rather than contributing to, alcoholism. On the other hand, some differences between alcohol abusers and control samples may precede alcoholism onset and thus constitute markers of precursive risk. After all, behavioral and affective markers early in life can predict later alcoholism (Caspi et al., 1996; Mayzer et al., 2001). Thus, it is reasonable to hypothesize that prealcoholic differences in the functioning of relevant neural systems will be related to risk for alcoholism.

To date, only a few imaging studies have attempted to address this question. Findings suggest that risk for alcoholism may be associated with smaller amygdala volume (Hill et al., 2001) and decreased amygdala activation to fearful faces (Glahn et al., 2007). However, those studies were conducted in young adults (average ages >20 years) who were not problem drinkers. Yet alcoholics often start problem drinking before that age (Grant and Dawson, 1997), so the individuals in these studies may have been selected for their resiliency rather than their vulnerability. That is, although they were selected based on family history to represent a vulnerable population, the fact that they are in their early 20s and not displaying alcohol problems may be indicative of some protective factor at work. In a functional magnetic resonance imaging (fMRI) study involving 12 to 14-year-old COAs, decreased activation in the left middle frontal gyrus was observed during response inhibition when compared with non-COAs (Schweinsburg et al., 2004). Interpretation of these findings as representing a neural marker of vulnerability remains tentative, however, until follow-up assessments regarding progression to AUD later in life become available.

Here, we attempt to address these limitations with a preliminary study of neural correlates of vulnerability and resiliency in adolescents selected from an on-going longitudinal study of families with parental alcoholism, along with a contrast sample of nonalcoholic families (Zucker et al., 2000). Two questions guided the present study. The first was whether differences in brain response to emotional stimuli could be identified between adolescent COAs who are showing signs of risky alcohol use (who we term "vulnerable") and COAs who are not displaying risky alcohol use (who we term "resilient"). Both groups begin with possible constitutional risk. However, the former group is at high risk for progression into AUD whereas the latter either did not inherit a risky phenotype from their alcoholic parent, or else carried protective factors. We were interested in neural signatures of such factors. A control group of adolescents with no alcoholic parent (and no risky alcohol use) was used to investigate the differences between these 2 possibilities. Differences in brain activation were first identified between the 2 COA groups (with and without risky alcohol use). Next, activation in these regions was compared with that of the non-COA control group. If the activation in the non-risky COAs differed from controls, but activation in the risky COAs did not, a resiliency mechanism would be supported. If the activation in the risky COA group differed from controls as well as the nonrisky COAs, the presence of vulnerability elements in the neural regions involved would be supported.

Functional imaging was conducted during the passive viewing of positive, negative, and neutral words. Valenced words have been shown to activate the inferior frontal, middle frontal and orbitofrontal cortices, cingulate gyrus, ventral striatum, amygdala, and hippocampus (Epstein et al., 2006;

Kensinger and Schacter, 2006; Kuchinke et al., 2005; Maddock et al., 2003). Differences were expected in the brain regions involved in emotion and motivation—particularly the amygdala, ventral striatum and regions of the prefrontal cortex—between COAs with high and low risky alcohol involvement. We considered that vulnerability might take the form either of underactivation of affective responding (as in an antisocial-psychopathic route, Blair et al., 2006), or a convergence of over-activation of affect and under-activation of top down cortical regions, as in a dysregulated pathway.

The second aim was to determine whether externalizing and internalizing behavioral traits (1) differed between the COAs with high versus low risky alcohol involvement and (2) if so, were related to brain activation. Given the close association of externalizing behaviors and AUD, we expected higher externalizing behavior in the COAs with high risky alcohol involvement, consistent with vulnerability to an AUD outcome. We further expected externalizing scores to be related to similar functional brain differences as vulnerability to AUD.

METHODS AND MATERIALS

Participants

Participants were 28 right-handed adolescents (15 males, 13 females), aged 16 to 20 years (mean 17.8 ± 1.3). These adolescents were recruited from families in an ongoing, prospective community study of families with high levels of parental alcoholism, along with a contrast sample of nonalcoholic families drawn from the same neighborhoods (Zucker et al., 2000). Longitudinal Study families in which the target child displayed evidence of fetal alcohol effects were excluded. Exclusionary criteria for the adolescent subjects in the present study were any neurological, acute, uncorrected or chronic medical illness; any current or recent (within 6 months) treatment with centrally active medications, including sedative hypnotics; and a history of psychosis or schizophrenia in first-degree relatives. In addition, the presence of an Axis I psychiatric or developmental disorder was exclusionary except in the case of conduct disorders, attention deficit disorder, or SUD. These latter Axis I disorders were allowed as their exclusion would preferentially eliminate participants at highest risk for SUD. Two sources were used to determine diagnosis. First, as part of the on-going longitudinal study, each participant was assessed with the Diagnostic Interview Schedule-Child (Costello et al., 1984) every 3 years starting at ages 9 to 11 years. Second, during the screening process as part of recruitment for the present study, each participant was asked whether they had been diagnosed with any psychiatric illness.

All participants gave written informed consent after explanation of the experimental protocol, as approved by the University of Michigan Institutional Review Board. Subjects under the age of 18 years signed their assent to participate in the study and at least 1 parent gave written informed consent.

Of the 28 participants, 22 were COA, that is, they were from families in which at least the father had a lifetime diagnosis of AUD, based on DSM IV criteria; mother diagnosis was free to vary. COAs were further categorized as either vulnerable ($n = 11$) or resilient ($n = 11$) based on a composite problem drinking index described below. The remaining 6 participants were low-risk controls with no parental history of AUD in either parent, and no evidence of their own problem drinking. The characteristics of each group are summarized in Table 1. There were no differences in the age of males and females overall or within each group ($p > .05$).

Measures

AUD Risk. The AUD vulnerability/resilience status was determined by combining 3 variables in a composite score: (1) whether there was early-onset drinking, defined as having more than a sip of alcohol by age 14 (yes = 1; no = 0); (2) whether ever drunk by the time of the most recent assessment, which occurred when participants were between 15 and 17 years of age (yes = 1; no = 0); and (3) number of different self-reported drinking problems (out of a possible 27; measure described below) between 11 and 17 years of age (based on a median split: 0 to 5.6 problems = 0, greater than 5.6 problems = 1). Using this method, each subject received a score ranging from 0 (no early onset, never drunk, and 5.6 or fewer drinking-problems between ages 11 to 17 years) to 3 (early onset, have been drunk, and greater than 5.6 drinking problems between ages 11 to 17 years). Those who scored 2 or 3 were considered vulnerable; while those who scored 0 or 1 were considered resilient (that is, they carried putative COA risk but did not express it). A third group, termed low risk, involved youth who were not COA and did not display problem drinking behavior (also see Nigg et al., 2007 and Zucker et al., 2003).

Number of drinking-related problems was assessed using the self-report Drinking and Drug History Form for Children, a children's version of the Drinking and Drug History Form for Adults (Zucker and Fitzgerald, 1994; Zucker et al., 1990). Onset of use items were elaborated from the adult form to be relevant for children and youth; otherwise, the measure covers the same substantive content–quantity, frequency, and variability of alcohol consumption; frequency of other drug use; and questions regarding consequences and problems related to alcohol use as perceived or experienced by children (a separate section inquires about drug problems but is not utilized here). The measure was administered yearly between the ages of 11 and 17, so responses were relatively contemporaneous to the drinking experience. For the present study, the number of different drinking-related problems out of a possible 27 (e.g., got into trouble with police because of drinking, driven a car after having a good bit to drink) ever reported by the subject between the ages of 11 and 17 years was the score.

Externalizing Behavior Problems. Behavior problems were assessed with the *Youth Self-Report* (YSR). The YSR, developed by Achenbach (1991), was completed by each participant when they were between 15 and 17 years old. It provides an assessment of the respondent's social and emotional functioning. The instrument has been normed on a nationally representative community sample of adolescents and yields standardized scores on 8 narrow band subscales (withdrawn, somatic complaints, anxious/depressed, social problems, thought problems, attention problems, delinquent behavior, aggressive behavior), 2 broad band subscales (externalizing and internalizing behavior) and a total behavior problems score (Table 1).

fMRI Task. Words with positive, negative, or neutral valence were viewed in a blocked design. Subjects were instructed to silently read each word and press a switch if they understood the word. Words were selected from the Affective Norms for English Words (ANEW) list, which provides a set of normative emotional ratings for a large number of words in the English language (Bradley and Lang, 1999). The words in the ANEW list were rated on the dimensions of valence and arousal on a scale of 1 (negative valence; low arousal) to 9 (positive valence; high arousal). For the present study, we chose negative words with an average valence rating of less than 3, neutral words with valence ratings between 4.5 and 5.5 and positive words with a valence rating greater than 7. Arousal ratings were greater than 5 for positive and negative words and greater than 2 for neutral words. The average arousal ratings for the final lists of positive and negative words did not differ from one another (6.1 ± 0.6

Table 1. Subject Characteristics for Control, Resilient, and Vulnerable Groups

	Control	Resilient	Vulnerable	Resilient versus vulnerable		
	(n = 6)	(n = 11)	(n = 11)	χ^2 or t	p	df
Males	50.0%	45.5%	63.6%	0.7	0.39	1
Age (years)	17.2 (1.6)	18.4 (1.0)	17.5 (1.3)	1.8	0.08	20
Wechsler Intelligence Scale IQ	117 (10)[a]	105 (10)	108 (12)	0.3	0.81	20
Problem alcohol use criteria						
First drink by age 14	18.2%[b]	36.4%	90.9%	7.1	0.008	1
Ever drunk	0[a,b]	63.6%	100%	4.9	0.03	1
Alcohol problems	0.3 (0.6)[a,b]	2.7 (2.3)	8 (3.0)	4.7	<.0001	20
Conduct disorder dx	0	9.1%	27.3%	1.2	0.27	1
Attention deficit disorder dx	0	0	9.1%	1.0	0.31	1
Substance use disorder dx[c]	0	0	27.3%	3.5	0.06	1
Any dx[d]	0[b]	9.1%	36.4%	2.3	0.13	1
Marijuana use (ever)	9.1%[b]	54.5%	81.8%	1.9	0.17	1
Youth report form[e]						
Withdrawn	2.2 (2.6)	2.0 (1.3)	3.3 (2.8)	1.4	0.18	20
Somatic complaints	2.0 (2.9)	1.5 (1.2)	2.3 (2.1)	1.1	0.28	20
Anxious/depressed	4.2 (5.0)	2.5 (2.3)	5.1 (6.6)	1.3	0.22	20
Social problems	1.2 (1.6)	1.2 (1.3)	1.7 (1.8)	0.8	0.43	20
Thought problems	0.7 (1.0)	1.2 (1.7)	2.0 (3.0)	0.8	0.43	20
Attention problems	2.7 (2.4)	3.3 (2.2)	5.5 (3.8)	1.6	0.12	20
Delinquent behavior	2.0 (1.7)[b]	3.7 (2.5)	6.1 (4.6)	1.5	0.15	20
Aggressive behavior	5.2 (4.5)	6.4 (2.5)	11.5 (7.7)	2.1	0.04	20
Total internalizing	8.0 (10.0)	5.6 (2.8)	10.1 (9.8)	1.5	0.16	20
Total externalizing	7.2 (5.6)[b]	10.1 (4.7)	17.6 (11.4)	2.0	0.05	20
Parent Dx (DSM IV Lifetime)						
Father alcohol abuse	excl.	27.3%	0	3.5	0.06	1
Father alcohol dependence	excl.	72.7%	100%			
Mother alcohol abuse	excl.	9.1%	9.1%	0	na	1
Mother alcohol dependence	excl.	18.2%	36.4%	1.0	0.33	1

Dx, diagnosis; excl., exclusionary criteria for control group. Standard deviations are given in parentheses.
[a]Control group differs from resilient group at p < 0.05.
[b]Control group differs from vulnerable group at p < .05.
[c]One subject had alcohol abuse, marijuana abuse and other drug abuse, 1 subject had marijuana abuse and other drug abuse, 1 subject had alcohol abuse and marijuana abuse.
[d]This includes conduct disorder, attention deficit disorder and/or substance use disorder.
[e]Raw scores.

and 6.3 ± 0.8, respectively) although both had greater arousal ratings than the neutral words (3.9 ± 0.4; $p < .0001$).

There were 3 runs, each including 6 blocks—2 blocks of each condition (positive, negative, neutral)—counterbalanced using the Latin Squares design, for a total of 6 block per condition across the entire experiment. Each block had 6 trials (single word presentations) lasting 4 seconds—3 seconds of stimulus-on and 1 second of stimulus-off (during which a fixation mark appeared in the middle of the screen), for a total of 36 words per condition. After each block, participants rested for 18 seconds during which time the screen remained blank. During the rest, participants were instructed to relax and continue watching the screen. The entire protocol in the scanner lasted 12 minutes and 36 seconds. The main contrasts of interest were negative minus neutral blocks and positive minus neutral blocks.

Following scanning, participants completed a questionnaire in which 54 words were listed. For each word, they rated: (1) whether they remembered seeing the word in scanner, (2) the valance of the word, and (3) the arousal of the word. Two-thirds of the words on the list were selected from those viewed in the scanner; one-third was distractors. These were equally divided between positive, negative, and neutral. The instructions given for valence and arousal ratings were identical to those used for ANEW list development (Bradley and Lang, 1999).

MRI Data Acquisition. Whole-brain blood oxygen level dependent (BOLD) fMRI data were acquired on a 3.0 Tesla GE Signa system (Milwaukee, WI) using a standard radio frequency (RF) coil. Functional imaging was performed using a T2*-weighted pulse

sequence with parameters: single-shot combined spiral in/out acquisition (Glover and Law, 2001), gradient echo, repetition time (TR) = 2000 milliseconds, echo time (TE) = 30 milliseconds, flip angle (FA) = 90°, field-of-view (FOV) = 20 cm, 64 × 64 matrix, slice thickness = 3 mm. The entire volume of 30 axial slices was acquired once every 2 seconds and the duration of the scan matched to the duration of the task. The imaging protocol parameters (thin slices, spiral in/out) were selected to minimized signal loss due to magnetic susceptibility effects. In particular, the "spiral in" k-space trajectory eliminates most signal loss due to in-plane dephasing by insuring signals are rephasing for at least 1-point in the image acquisition (Noll, 2002). A high resolution T1 scan was acquired to provide anatomical localization [3-dimensional spoiled gradient recalled echo (3-DSPGR), TR = 25 milliseconds, min TE, FOV = 24 cm, 256 × 256 matrix, slice thickness = 1.4 mm.). Stimuli were presented using the integrated functional imaging system (Psychology Software Tools, Inc., Pittsburg, PA), using an LCD video display in the bore of the MR scanner and a fiberoptic response collection device. Participant motion was minimized with the use of foam pads placed around the head along with a forehead strap. In addition, the importance of keeping as still as possible was emphasized during the Informed Consent process and before scanner entry.

Data Analysis

Behavioral Data. Recognition memory performance (p') for each word type was calculated by adjusting the percentage of correct responses to target stimuli (p) by the percentage of incorrect

responses to distractor stimuli (*fp*) using the formula: $p' = (p-fp)/(1-fp)$ (Epstein et al., 2006). Differences in valence ratings, arousal ratings, recognition memory and reaction times (RTs) between each word type were investigated within each group separately with repeated measures ANOVAS in SPSS. Differences in these measures and in YSR scores between groups were investigated with 1-way ANOVAS with age and IQ as covariates.

fMRI Data. Data were reconstructed off-line using an iterative image reconstruction procedure that allows for simultaneous estimation of the magnetic field distortion and the undistorted images (Sutton et al., 2002, 2003). This procedure has been shown to provide more accurate and complete corrections for magnetic susceptibility distortions. These data were slice time corrected (Oppenheim and Schafer, 1989) and realigned (SPM2; Wellcome Institute of Cognitive Neurology, London, UK). Because of the possibility of excessive subject movement (in excess of 2 mm) causing signal artifacts and increased noise, we examined the realignment parameters for each subject. No subjects were eliminated due to excessive motion. For group comparisons, the preprocessed images were co-registered into standard stereotactic space using the intercommissural line as the reference plane, and anatomically normalized by nonlinear warping to a standard stereotactic space as defined by the Montreal Neurological Institute (MNI). A 50-control-point warping algorithm was used for that purpose (Meyer et al., 1997, 1998a,b). The anatomical T1-weighted MR data were first warped, and the transformation matrix was then applied to the realigned functional images. After anatomical normalization, functional images were smoothed with a 6-mm Gaussian filter to reduce residual interindividual anatomical variability.

Statistical analysis was performed with MATLAB (Mathworks, Inc., Natick, MA, USA) and SPM2. For each subject, negative, neutral, positive, and rest blocks were modeled as epochs and planned comparisons (negative minus neutral; positive minus neutral) were computed as linear contrasts. The motion parameters collected during scanning were used in the individual analyses as regressors. Contrast *t*-maps for each subject were anatomically standardized, smoothed (3 mm FWHM), and entered into a second-level, random-effects ANOVA with group (control, vulnerable, resilient) as the

factor. Negative minus neutral and positive minus neutral activations differences between the vulnerable and resilient groups were the main outcomes of interest in the SPM analysis. Areas of activation were deemed significantly different between these 2 groups if they included at least 10 voxels and reached a statistical threshold of $p < 0.05$, corrected for multiple comparisons and spatial extent (Friston et al., 1994). In 5 a priori hypothesized regions (amygdala, ventral striatum, insula, prefrontal cortex, orbital frontal cortex), we accepted activation with a spatial extent greater than 10 voxels that reached a statistical threshold of $p < 0.001$, uncorrected for multiple comparisons.

The time-series data for the clusters showing a difference in BOLD response between the resilient and vulnerable groups were extracted for all participants using MarsBaR (Brett et al., 2002). From these data, the percent change in BOLD response for negative versus neutral and positive versus neutral was calculated for each region of interest (ROI). These extracted data were used to more fully characterize activation differences due to risk status of the COAs by comparing it with brain responses in these regions in the control subjects. To compare groups (control vs. resilient; control vs. vulnerable), ANCOVAs were performed with sex and IQ as covariates and each ROI as dependent variables.

RESULTS

Affect and Memory Data

Valence ratings, arousal ratings, memory scores, and RTs for the total sample and each group are shown in Table 2. All 3 groups rated the 3 word types as significantly different in valence, in the expected direction—i.e., negative words lowest and positive words highest—confirming that the task design worked as intended. The resilient and vulnerable groups showed differences across the 3 word types in arousal ratings whereas the control group did not. However, only the vulnerable group showed the expected pattern, with negative and positive words having higher arousal ratings than neutral

Table 2. Detection Memory, Valence, Arousal and Reaction Time for Negative, Neutral and Positive Words for Total Sample and Control, Resilient and Vulnerable Groups

| | | | Word valence | | | | | | |
| | | | Negative | | Neutral | | Positive | | ANOVA |
	Group	*n*	Mean	SD	Mean	SD	Mean	SD	Within-subject
Valence	Total	28	2.8	1.1	5.0	0.8	6.9	1.2	$F_{2,54} = 108.3, p < .0001$
	Controls	6	2.7	1.4	5.2	0.2	7.2	1.2	$F_{2,10} = 18.8, p < .0001$
	Resilient	11	2.6	1.1	5.1	0.5	7.3	1.0	$F_{2,20} = 57.9, p < .0001$
	Vulnerable	11	3.1	1.0	4.9	1.2	6.4	1.3	$F_{2,20} = 40.4, p < .0001$
	ANCOVA		$F_{4,23} = 1.1, p = 0.34$		$F_{4,23} = 0.6, p = 0.54$		$F_{4,23} = 1.8, p = 0.20$		
Arousal	Total	28	4.0	1.6	4.1	1.3	6.1	1.6	$F_{2,54} = 24.0, p < .0001$
	Controls	6	3.8	2.4	3.9	1.7	6.0	2.2	$F_{2,10} = 2.8, p = .11$
	Resilient	11	3.7	1.4	4.4	0.8	6.6	1.4	$F_{2,20} = 19.7, p < .0001$
	Vulnerable	11	4.3	1.4	3.9	1.5	5.6	1.3	$F_{2,20} = 8.0, p < .01$
	ANCOVA		$F_{4,23} = 0.4, p = 0.70$		$F_{4,23} = 0.1, p = 0.88$		$F_{4,23} = 0.9, p = 0.42$		
Memory	Total	28	0.64	0.28	0.47	0.37	0.63	0.29	$F_{2,54} = 5.9, p < .01$
	Controls	6	0.67	0.36	0.66	0.41	0.74	0.47	$F_{2,10} = 0.8, p = .41$
	Resilient	11	0.52	0.27	0.27	0.35	0.49	0.22	$F_{2,20} = 3.4, p < .05$
	Vulnerable	11	0.75	0.21	0.58	0.30	0.71	0.19	$F_{2,20} = 2.2, p = .13$
	ANCOVA		$F_{4,23} = 2.1, p = 0.14$		$F_{4,23} = 2.2, p = 0.14$		$F_{4,23} = 1.5, p = 0.23$		
Reaction time (milliseconds)	Total	28	959	403	931	386	974	397	$F_{2,54} = 5.2, p < .01$
	Controls	6	1122	436	1107	448	1155	456	$F_{2,10} = 1.4, p = .28$
	Resilient	11	855	180	810	173	864	210	$F_{2,20} = 4.0, p < .05$
	Vulnerable	11	973	533	955	488	984	494	$F_{2,20} = 0.7, p = .48$
	ANCOVA		$F_{4,23} = 0.5, p = 0.63$		$F_{4,23} = 0.4, p = 0.69$		$F_{4,23} = 0.2, p = 0.82$		$F_{4,23} = 0.5, p = .63$

words. Combined, the total sample showed the expected pattern of memory scores, with higher detection memory for negative and positive words than neutral words, although this was significant only in the resilient group. The total sample showed the expected pattern of RTs, with slower RTs to affective words than neutral words. Each group showed this pattern, although it was only significant in the resilient group. Results of the between-group ANCOVAs indicated no differences in RTs, valence and arousal ratings or detection memory for any of the word types.

Behavioral Adjustment

Group averages from the YSR are reported in Table 1. The between-group ANCOVAs revealed group differences in the externalizing broad-band scale ($F = 3.9$; df = 4,23; $p < 0.05$). The vulnerable group had more externalizing behavior than both the resilient and the low risk control groups, consistent with an antisocial pathway (Zucker, 2006), and with our earlier findings of externalizing differences between vulnerable and resilient groups in very early childhood and in early adolescence, as well as no differences between resilient and vulnerable groups in internalizing behavior in early adolescence (Zucker et al., 2003). We therefore examined the individual scales comprising the externalizing scale, identifying group differences on the aggression subscale (F = 3.6; df = 4,23; $p < 0.05$) due to more aggression in the vulnerable group than the resilient group. Group differences on the delinquent subscale approached significance (F = 3.0; df = 4,23; $p = 0.07$) due to more delinquent behavior in the vulnerable group than the control group.

Neuroimaging Results

Negative–Neutral Contrast. The vulnerable group had *greater* activation than the resilient group in the right dorsal medial prefrontal cortex (DMPFC; BA9/10; Table 3 and Fig. 1*A*). The extracted data revealed that this difference was due to *decreased* BOLD response with negative words compared with neutral words in the resilient group and *increased* BOLD response (i.e., more response to negative than neutral) in the vulnerable group (Fig. 1*C*).

Vulnerable subjects also had *less* activation compared with resilient subjects in the OFG bilaterally (BA11), the left insula/putamen, the extended amygdala, bilaterally and the ventral striatum including the nucleus accumbens bilaterally (Table 3 and Fig. 1b). These differences in BOLD activation were due to *increased* BOLD response with negative words versus neutral words in the resilient group and *decreased* BOLD response in the vulnerable group (Fig. 1*C*).

Positive–Neutral Contrast. Vulnerable subjects had *greater* activation than resilient subjects in the DMPFC extending from a peak in the superior frontal gyrus (BA8/9) to the medial frontal gyrus (9/10; Table 3 and Fig. 2*A*). This area encompassed the same region showing increased activation in this group for the negative versus neutral words contrast, above. The vulnerable group had an additional peak of increased activation in the medial prefrontal cortex ventrally (BA9/10) as well. These differences were due to *decreased* BOLD response with positive words versus neutral words in the resilient group and *increased* BOLD response in the vulnerable group (Fig. 2*C*).

No decreases in activation in the vulnerable group versus the resilient group were observed at the standard statistical threshold. However, at a more lenient threshold ($p < 0.005$) *lower* activation in the vulnerable group was observed in the left ventral striatum and right OFG (Table 3 and Fig. 2*B*). Both these areas coincided with those found to have lower activity for the negative versus neutral contrast in the vulnerable group. This difference in BOLD activation was again due to the groups having opposite patterns of response: *increased*

Table 3. SPM Results for Comparison Between Resilient and Vulnerable Groups

Brain region	Negative–neutral words				Positive–neutral words			
	MNI space x, y, z	Cluster size (mm³)	Peak t	Voxel level p (uncorr.)	MNI space x, y, z	Cluster size (mm³)	Peak t	Voxel level p (uncorr.)
				Resilient > Vulnerable				
R OFG (BA11)	24, 45, −12	1547	4.17	<0.0001	23, 46, −9	131	2.88	0.002 (n.s.)
L OFG (BA11)	−22, 40, −16	1942	4.16	<0.0001				
L insula/putamen	−29, 10, −11	2048	3.98	<0.0001				
L extended amygdala	−24, −4, −6		3.91	<0.0001				
L VS/NAcc	−19, 9, −9		3.85	<0.0001	−18, 11, −10	805	2.97	0.002 (n.s)
R VS/NAcc	18, 10, −10	904	3.51	<0.0001				
R extended amygdala	24, −7, −11		3.19	0.001				
				Vulnerable > Resilient				
DM PFC (BA8/9/10)	2, 52, 42	633	3.56	<0.0001	10, 41, 46	1788	4.24	<.0001
					0, 51, 41		4.15	<.0001
Medial PFC (BA9/10)					4, 52, 15	296	3.33	<.0001

L, left hemisphere; R, right hemisphere; OFG, orbital frontal gyrus; BA, Brodmann's Area; NAcc, nucleus accumbens; VS, ventral striatum; DM, dorsomedial; PFC, prefrontal cortex.
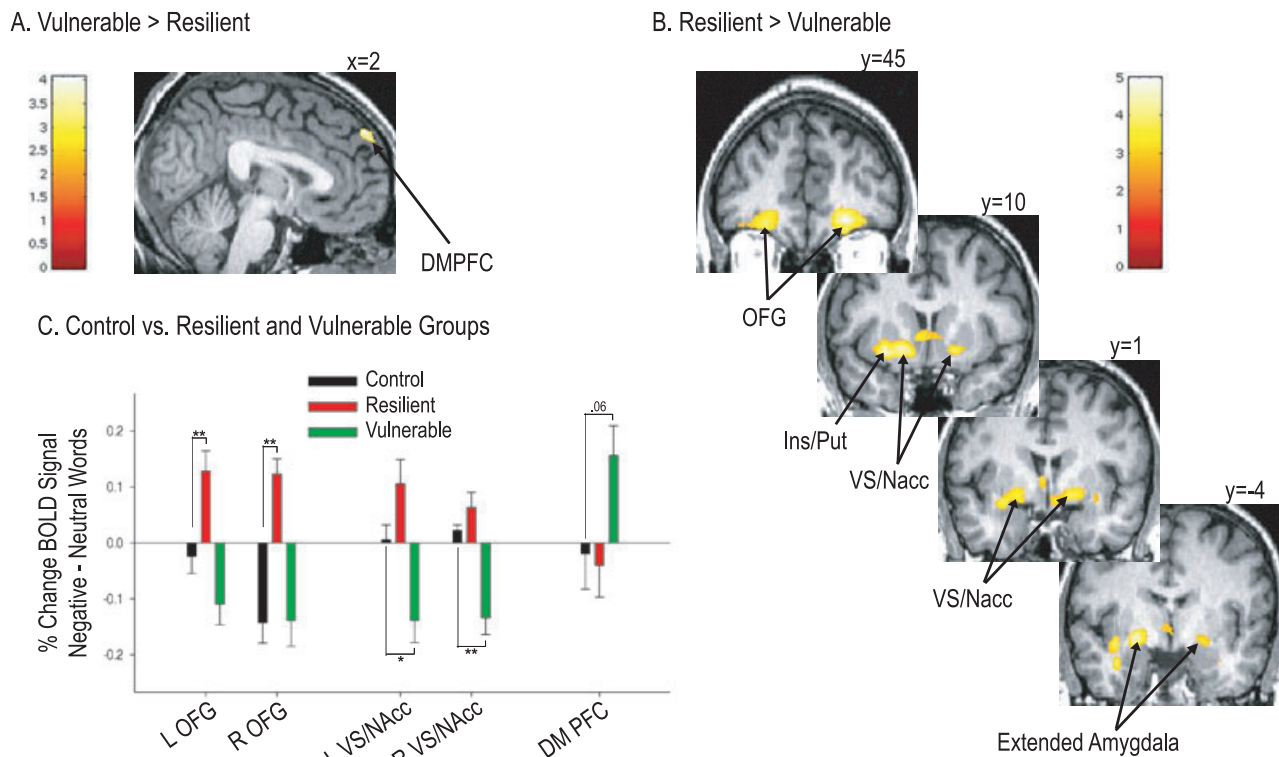
Fig. 1. Activation differences between groups for the negative minus neutral contrast. (**A**) Statistical parametric map showing regions where activation was greater in the vulnerable group than the resilient group. (**B**) Statistical parametric map showing regions where activation was greater in the resilient group than the vulnerable group. (**C**) Graph of extracted data showing percent signal change in control, resilient, and vulnerable groups. All differences between resilient and vulnerable groups are significant at $p < 0.001$. *Different from control group at $p < 0.05$; **different from control group at $p < 0.01$. L, left hemisphere; R, right hemisphere; OFG, orbital frontal gyrus; BA, Brodmann's Area; NAcc, nucleus accumbens; VS, ventral striatum; DM, dorsomedial; PFC, prefrontal cortex. Color bars represent *t*-values. Note: All differences between resilient and vulnerable groups are significant at $p < 0.001$.
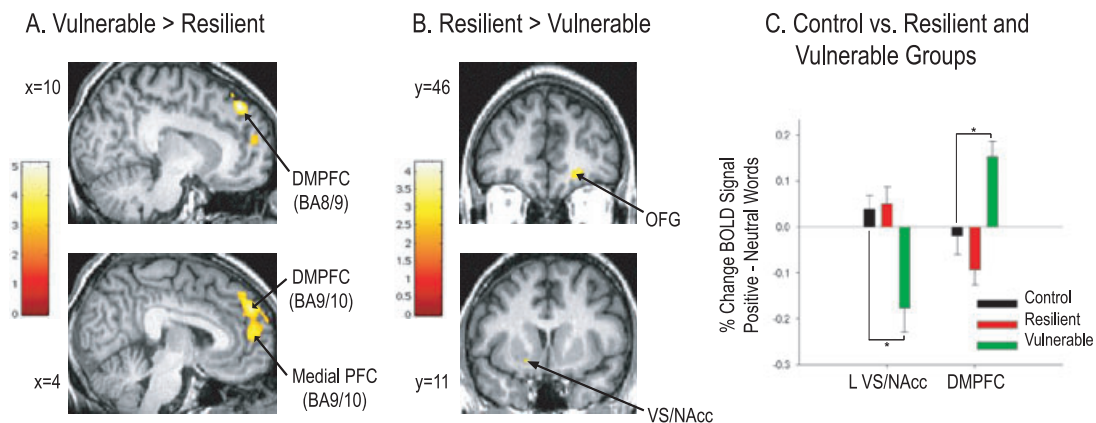

Fig. 2. Activation differences between groups for the positive minus neutral contrast. (**A**) Statistical parametric map showing regions where activation was greater in the vulnerable group than the resilient group. (**B**) Statistical parametric map showing regions where activation was greater in the resilient group than the vulnerable group. (**C**) Graph of extracted data showing percent signal change in control, resilient, and vulnerable groups. All differences between resilient and vulnerable groups are significant at $p < 0.01$. *Different from control group at $p < 0.05$; **different from control group at $p < 0.01$. L, left hemisphere; R, right hemisphere; OFG, orbital frontal gyrus; BA, Brodmann's Area; NAcc, nucleus accumbens; VS, ventral striatum; DM, dorsomedial; PFC, prefrontal cortex. Color bars represent t values. Note: All differences between resilient and vulnerable groups are significant at $p < 0.01$.

BOLD response with positive words versus neutral words in the resilient group, but *decreased* BOLD response in the vulnerable group (Fig. 2*C*).

Comparisons With Control Group. For each ROI showing a difference between resilient and vulnerable groups (Table 3), percent changes were calculated for the control

group and *t*-tests performed to determine differences between each risk/COA group and controls (Table 4). The resilient group showed significantly greater activation in the right and left OFG in the negative minus neutral contrast (Fig. 1*C*) and a trend for greater activation in the right OFG to positive versus neutral words compared with controls whereas the vulnerable group did not differ from controls in their activation of the OFG. In contrast, the vulnerable group showed significantly lower activation for negative minus neutral contrasts in the ventral striatum, bilaterally (Fig. 1*C*), and the right extended amygdala, as well as for positive minus neutral contrasts in the left ventral striatum (Fig. 2*C*) than controls. The resilient group did not differ from controls in these regions. In addition, the vulnerable group had greater activation of the DMPFC in the positive minus neutral contrast than the controls (Fig. 2*C*). In the negative minus neutral contrast this effect approached significance (Fig. 1; $p = 0.06$). DMPFC activation did not differ between the resilient and control groups.

Correlations With YSR. Nonorthogonal correlations were performed between percent changes in each ROI from Table 3 and YSR externalizing and aggression scores. For negative versus neutral words, YSR externalizing correlated negatively with percent change in the left extended amygdala and the right ventral striatum and positively with percent change in the DMPFC (Fig. 3). These regions also correlated with YSR aggression (left extended amygdala: $r = -0.58$, $p < 0.01$; right ventral striatum: $r = -0.56$, $p < 0.01$; DMPFC: $r = 0.46$, $p < 0.01$).

From the positive versus neutral contrast, externalizing correlated negatively with percent change in the left ventral striatum and positively with percent change in the DMPFC (Fig. 3). DMPFC activation also correlated with YSR aggression ($r = .39$, $p < 0.05$) and a correlation between the left

ventral striatum and YSR aggression approached significance ($r = -0.36$, $p = 0.06$).

DISCUSSION

The 2 primary aims of this study were to identify neural activation mechanisms that may mark protection or vulnerability to AUD in children of alcoholic fathers, and to map the same activation patterns in relation to risk behavior (here, externalizing behavior). The guiding conceptual framework was that the functioning of affective and behavioral regulation networks in the brain may serve as such mechanisms. Consistent with that framework, the resilient and vulnerable groups were distinguished from one another by remarkably consistent inverse patterns of activation in response to the processing of lexical emotional stimuli. These patterns were most apparent with regard to management of negative affective stimuli, with the vulnerable group—the group with the most externalizing behavior—displaying a pattern of greater control—i.e., more DMPFC activation, and lesser subcortical activation. Consistent with that group effect, across all groups, more externalizing behavior and aggression was associated with more activation in DMPFC and less activation subcortically.

These results suggest separate pathways of risk and resilience in the COAs. First, the COA group that was not prone to early problem drinking (the resilient group) had more activation of OFG than controls in response particularly to negative affect stimuli, but also to some extent in response to positive affect stimuli. The OFG is involved in the monitoring and evaluation of the affective value of stimuli, allowing for appropriate behavioral responses (Kringelbach and Rolls, 2004; Rolls, 2004). The resilient group also had increased left insula activation to negative words. The insula is involved in evaluating internally

Table 4. BOLD Activations in Vulnerable and Resilient Groups Compared to Control Group

| Brain region | Resilient versus control | | | | | Vulnerable versus control | | | | |
| | Direction | Negative | | Positive | | Direction | Negative | | Positive | |
		F	*p*	*F*	*p*		*F*	*p*	*F*	*p*
L OFG (BA11)	+	14.1	0.002			=				
R OFG (BA11)	+	16.8	0.001	2.1	0.17	=				
L insula/putamen	+	6.1	0.03			=				
L extended amygdala	=					=				
R extended amygdala	=					−	4.9	0.04		
L VS/NAcc	=					−	5.8	0.03	7.4	0.02
R VS/NAcc	=					−	11.5	0.005		
DM PFC (BA8/9/10)	=					+	4.1	0.06	8.6	0.01
Medial PFC (BA10/32)	=					=				

L, left hemisphere; R, right hemisphere; OFG, orbital frontal gyrus; BA, Brodmann's Area; NAcc, nucleus accumbens; VS, ventral striatum; DM, dorsomedial; PFC, prefrontal cortex.

+ indicates an increase in percent signal change relative to the control group; − indicates a decrease in percent signal change relative to the control group; = indicates no significant difference from control group; Negative refers to the negative minus neutral contrast; positive refers to the positive minus neutral contrast.

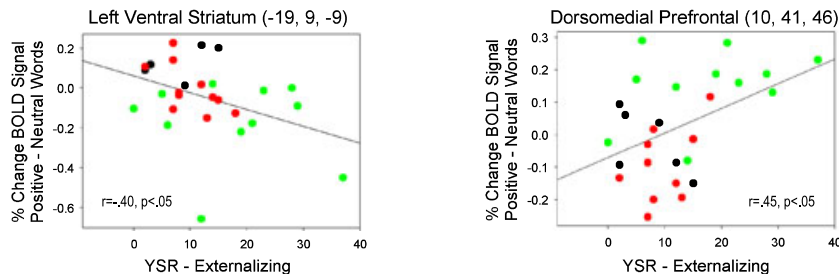## A. Negative vs. Neutral
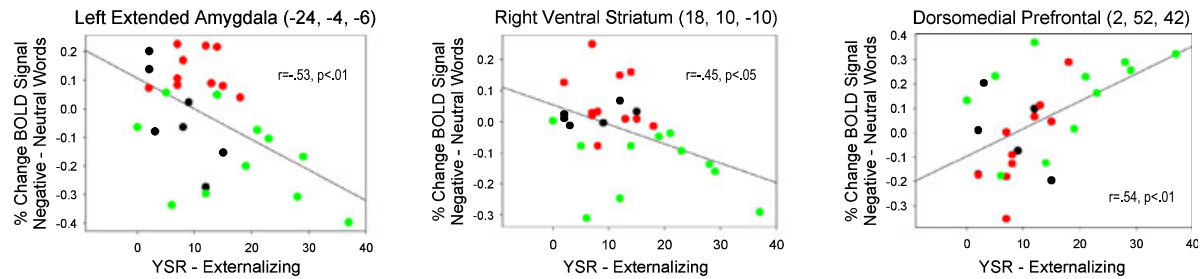
B. Positive vs. Neutral

Fig. 3. Correlations between YSR externalizing and ROI activations for total sample. (**A**) Correlations between YSR externalizing and percent signal change for negative minus neutral in left extended amygdala (left), right ventral striatum (middle) and dorsomedial prefrontal cortex (right). (**B**) Correlations between YSR externalizing and percent signal change for positive minus neutral in left ventral striatum (left) and dorsomedial prefrontal cortex. Black circles indicate the control group; red circles indicate the resilient group; green circles indicate the vulnerable group.

generated emotions and the monitoring of ongoing internal emotional state (Phan et al., 2002).

The present findings, then, are consistent with the hypothesis that resilient youth have enhanced monitoring of emotionally arousing stimuli, even compared with typically developing youth. Yet, in an important nuance, they did not suppress the emotional experience, as indicated by an activation of the subcortical emotional regions that paralleled that of the control group. Therefore, we suggest that they were prepared to modify behavioral response while maintaining affective response to these stimuli. This pattern of response in resilient youth may represent increased flexibility in emotional and social behavior. Barkley (1997) elaborated a theory suggesting that externalizing risk is rooted in failure to adequately delay response. These youth may be exhibiting precisely that ability to delay external response to arousing stimuli, while internally processing those stimuli. In short, this may be a "reflective" pattern of approach to the world, captured in neural activation pattern. It is not difficult to speculate how this pattern might protect these at risk youth from substance misuse: they are able to respond to the emotional stimuli, but demonstrate enhanced monitoring that may allow for the inhibition of inappropriate responding, buying time for flexible response options based on well-processed information.

Secondly, and in contrast, the vulnerable group displayed no differences from the control group in emotional monitoring and behavioral regulation systems (OFG and insula), suggesting that weakness in that system is not a risk factor.

Rather, they had a different pattern of risk that was not simply the inverse of the protective pattern seen in the resilient group. They demonstrated over-activation of DMPFC and an atypical under-activation of key emotion processing regions (particularly extended amygdala and ventral striatum). Although this pattern was more notable in regard to negative affect, it was also observed to a lesser extent with positive affect. Furthermore, this group showed higher externalizing behaviors, which correlated positively with DMPFC activation and negatively with extended amygdala and ventral striatal activation. All of this may be consistent with a reactive approach to the world, in which affect is not fully processed. Supporting this interpretation, neuroimaging studies have consistently shown the involvement of the DMPFC with conscious self-monitoring of emotional responses (Beauregard et al., 2001; Kuchinke et al., 2006; Levesque et al., 2003, 2004; Phan et al., 2005). For example, during the voluntary suppression of negative affect in healthy adults, activation in the dorsal medial and lateral prefrontal cortex increased and that in the nucleus accumbens and extended amygdala decreased (Phan et al., 2005). It has been suggested that emotional information is conveyed from limbic regions to the prefrontal cortex allowing conscious, voluntary emotional self-regulation (Levesque et al., 2003, 2004). Therefore, one interpretation of the present findings is that the vulnerable youth were recruiting an emotional control system that was suppressing emotional response.

One can question whether, because these youth have begun to drink, this pattern represents a failure of

emotional engagement that may influence the temptation to drink, or failure of maturation of emotional systems, perhaps secondary to early drinking, or both. Although the present data do not allow definitive differentiation between these possibilities, their pattern weighs against a neurotoxic effect of alcohol use driving the results. If the functional brain abnormalities observed in the vulnerable group were attributable to the neurotoxic effects of alcohol, one might expect a general deficiency in the brain responses in this group. Instead, the responses in the ventral striatum and prefrontal cortex were very similar between control and resilient groups and the vulnerable group, instead of showing less reactivity in these regions, displays the opposite pattern of responding than the other groups. This very specificity of response patterns, rather than a diffuse inefficiency of response in 1 group, weighs in favor of a basic difference in the pattern of adaptive organization in the brains of the vulnerable youth, as opposed to a generalized deficit in responding.

Furthermore, although adolescents with heavy alcohol use retain less verbal and nonverbal information (Brown and Tapert, 2004); in the present study, the vulnerable group did not show a deficit in memory and, in fact showed a trend for better recognition memory for all word types than the resilient group. This is probably because, even though they have begun to drink, the late-adolescent in our study have not yet engaged in years of heavy drinking. In all, then, it can be tentatively proposed that the fMRI effects observed here reflect preexisting vulnerability, rather than mainly effects of alcohol use.

Alterations in the functioning of the ventral striatum and prefrontal cortex have been proposed previously to underlie vulnerability to alcoholism (Piazza et al., 1991; Volkow et al., 2002). Specifically, receptor PET studies have found significant reductions in striatal dopamine D2 receptors (Heinz et al., 2004; Hietala et al., 1994; Martinez et al., 2005; Volkow et al., 1996, 2002) and blunted dopamine release (Martinez et al., 2005) in adult alcoholics. Volkow et al. (2002) have suggested that this may represent a predisposing factor in alcoholism. Furthermore, because D2 receptor availability is positively associated with OFG activity, individuals with decreased D2 receptor availability also have decreased OFG functioning (Goldstein and Volkow, 2002). However, those findings were based on subjects who had moved beyond risk into diagnosis. Therefore, effects due to alcohol could not be entirely disentangled from effects prior to serious alcohol use. In a recent study, however, nonalcoholic adult members of alcoholic families had higher dopamine D2 receptor availability in the caudate and ventral striatum than nonalcoholic controls, which was associated with increased resting glucose metabolism in the OFG and prefrontal cortex (BA8/9)—paralleling the regions observed in the present study (Volkow et al., 2006). Taken together, these studies in alcoholics and nonalcoholic members of alcoholic families suggest that low levels of striatal D2 receptors and prefrontal functioning confer vulnerability, whereas high levels of striatal D2 receptors and prefrontal functioning are protective (Volkow et al., 2004, 2006). The present study provides support for that hypothesis but adds nuance to it by pointing to dissociable circuits within these regions conferring protection and vulnerability.

Because of the small sample size in each group, these results should be considered preliminary. Although the differences did not reach significance, the vulnerable group had more individuals who had used marijuana and a higher rate of externalizing disorder diagnoses than the resilient group. These characteristics are consistent with the expectation driving this research that vulnerable individuals are more likely to move into AUD diagnosis and, in fact, some of them have. However, it also prevents the strict interpretation of the results as relating to AUD risk specifically as opposed to externalizing disorders more generally. Another potentially confounding factor is the greater parental loading of alcoholism in the vulnerable group despite our matching on family alcoholism risk— i.e., severity of father's alcoholism (abuse vs. dependence) and the presence of an alcoholic mother. Further studies with larger samples are necessary to tease apart possible contributions of these factors.

In conclusion, within the limitations noted, the findings suggest separable pathways through which resiliency and vulnerability are conferred in COAs. This is an important step toward understanding the neural circuitry which underlies the heterogeneity of risk in this population. A more nuanced understanding of how the functioning of different types of control mechanisms may influence outcome has the potential to lead to more efficacious prevention and intervention strategies. In addition, follow-up assessments will be done to determine whether individuals in the vulnerable group move into diagnosis and whether the resilient group was indeed resilient.

ACKNOWLEDGMENTS

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