Striatal Dysfunction Marks Preexisting Risk and Medial Prefrontal Dysfunction Is Related to Problem Drinking in Children of Alcoholics

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Background: Parental alcoholism substantially raises risk for offspring alcoholism, an effect thought to be mediated by a dysregulation in impulse control. Adult alcoholics have alterations in the frontostriatal system involved in regulating impulsive responses. However, it remains controversial whether these alterations reflect preexisting traits predisposing to problem alcohol use or are secondary to alcohol involvement.

Methods: Sixty-one 16 to 22 year olds were tested using a go/no-go task during functional magnetic resonance imaging. Forty-one were family history positive (FH+), having at least one parent with a diagnosis of alcohol use disorder (AUD), and 20 were family history negative (FH−). Two FH+ subgroups were created to disentangle alcohol involvement from preexisting risk: the FH+ control group ($n = 20$) had low alcohol problems, differing from the FH– group only by family history. The FH+ problem group ($n = 21$) had high alcohol problems.

Results: The ventral caudate deactivated during successful inhibition in the FH– but not the FH+ groups, regardless of problem alcohol involvement. Regression analyses showed that ventral caudate deactivation was related to fewer externalizing problems as well as to family history. Orbital and left medial prefrontal regions were deactivated in both the FH– and FH+ control groups but not the FH+ problem group. Activation in these regions was associated with alcohol and other drug use.

Conclusions: These findings suggest a preexisting abnormality in ventral striatal function in youth at risk for AUD, which may lead to inappropriate motivational responding, and suggest that with alcohol use, the prefrontal "control" mechanism loses efficiency, further dysregulating the frontostriatal motivational circuitry.

Key Words: Adolescent, alcoholism, caudate, medial prefrontal, response inhibition, ventral striatum, vulnerability

Parental alcoholism significantly raises risk for offspring alcoholism (1,2), and some of this risk is mediated through intermediary behavioral traits (3–6). One of the core traits predicting alcohol use disorder (AUD) from early childhood onward is behavioral undercontrol (7,8), including externalizing behavior (aggression and delinquency), impulsivity, and sensation seeking. These variables share the characteristic of behavioral disinhibition, involving the inability, unwillingness, or failure to inhibit behavioral impulses even in the face of negative consequences (9). Weakness in response inhibition specifically has been found to be a general liability factor for a range of externalizing and substance use problems (10). A primarily right-hemisphere network including the prefrontal cortex, parietal cortex, and striatum is critical to response inhibition and the control of behavior more generally (11–13).

Few studies have investigated these neural systems directly in children of alcoholics (COA). One functional magnetic resonance imaging (fMRI) study found less activation in the left middle frontal gyrus during response inhibition in 12- to 14-year-old COA compared with non-COA, despite similar performance (14). Similarly, a dysregulation index of risk was negatively correlated with left frontal eye field activation during inhibition of eye movement, but not with performance in 12–19 year olds (15). These findings suggest that a weakness in frontal response inhibition circuitry may be related to risk.

Other studies have examined the neural correlates of familial risk using cognitive or emotional paradigms that do not specifically probe impulse control but recruit neural systems involved in behavioral regulation (16–18). A recent study of 12 to 14 year olds found family history was related to a failure of deactivation in medial prefrontal regions involved in the default mode network (DMN) (19) during spatial working memory compared with vigilance (18). This suggests familial risk may be related to less inhibition of task-irrelevant processing. Using a reward task known to activate the ventral striatum (20), familial risk was investigated in 12 to 16 years old COA and non-COA (16). Although ventral striatal activation did not differ between the groups in this sample, it correlated positively with a personality measure of impulsivity across groups, suggesting a possible relationship with risk.

One limitation of these studies is that the participants showed little evidence of behavior problems typically considered to lie on a developmental spectrum with AUD. Most were nondrinking youth with no behavioral or mood disorders, which may result in a diluted representation of risk. Furthermore, it is important to consider these neural systems in conjunction with the developmental transition from late adolescence to early adulthood, when there is major build up of alcohol use and alcohol use-related problem behavior (21).

A recent study investigated emotional processing during this developmental period in a design that accounted for both familial risk and behavioral risk (17). This study revealed increased dorsomedial prefrontal activation and decreased striatal activation to emotional versus neutral stimuli in COA showing risky drinking behavior compared with a control (nonrisky

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behavior) COA group and nonCOA. These findings suggest different neural activation in COA on a risky trajectory versus those who are not, highlighting the importance of capturing a range of behavior problems in studies designed to investigate risk. To date, these neural systems have not been studied during response inhibition in the context of familial risk during late adolescence/early adulthood.

Another important consideration is that drug and alcohol use undoubtedly alters the brain maturation processes, as reviewed by Spear and Varlinskaya (22). A recent fMRI study of impulse control found that adult abstinent alcoholics had altered neural processing, including decreases in left dorsolateral prefrontal cortex and increases in bilateral middle frontal gyrus (23). Evidence for altered functional networks has also been found during spatial working memory in adult (24,25) and adolescent (26) alcoholics.

This study was designed to build on prior work by investigating frontostriatal functioning during response inhibition in late adolescence/early adulthood and relate it to both familial risk and problem alcohol involvement. A go/no-go task (27,28) was used during fMRI acquisition. Participants with a family history of AUD (FH+) were divided into those with low alcohol problems (FH+ control), matched to a control group with no parental AUD (FH−), and those with high alcohol problems (FH+ problem). This allowed the following comparisons: 1) FH– vs. FH+ control isolates effects of family history and 2) FH+ control versus FH+ problem isolates effects of problem alcohol involvement. On the basis of prior work, we expected familial risk to be reflected in a weakness in frontal response inhibition circuitry. Evidence also exists for striatal differences based on risk; however, the direction this might take during impulse control is not clear considering there are reports of both striatal activation (29) and deactivation (30,31) during response suppression. We further expected evidence of additional recruitment of frontal regions because of problem alcohol involvement due to altered functional networks.

Given that alcohol problems can encompass both externalizing problem behavior (which includes both aggressive and conduct/antisocial problems) and level of alcohol consumption, we additionally conducted a series of supplemental analyses to take into account the contribution of each of these variables to the main findings. Other drug use was also considered because it tends to co-occur with externalizing problems and alcohol consumption and could contribute to differences in blood oxygen level–dependent (BOLD) activation. Marijuana use in particular has been shown to increase prefrontal activation during inhibitory processing (32,33).

Methods and Materials

Participants

Sixty-one (35 males) right-handed participants aged 16 to 22 (mean 19.1 ± 1.6) were recruited from the Michigan Longitudinal Study (MLS), an ongoing, prospective community study of families with high levels of parental AUD and a contrast sample of nonalcoholic families drawn from the same neighborhoods (34). Families in which the target child displayed evidence of fetal alcohol effects were excluded from the original ascertainment. Handedness was determined with the Edinburgh Handedness Inventory (35).

The FH– group (n = 20) had no parent history of AUD and low alcohol problems (operationalized below). The FH+ Control group (n = 20) had at least one parent with an AUD diagnosis and low alcohol problems. The FH+ Problem group (n = 21) had at least one parent with an AUD diagnosis and high alcohol problems. Parent diagnosis was based on DSM-IV criteria and established via multiple face-to-face assessments. Characteristics of these groups are summarized in Table 1.

Exclusionary criteria for the study were neurological, acute, uncorrected, or chronic medical illness; current or recent (within 6 months) treatment with centrally active medications; and history of psychosis or schizophrenia in first-degree relatives. In addition, participants were given a multidrug five-panel urine screen before scanning, and those with a positive drug screen were not included in this study. The presence of most Axis I psychiatric or developmental disorders was exclusionary, with the exception of conduct disorder, attention deficit/hyperactivity disorder (ADHD), or prior substance use disorder (SUD). These

Table 1. Subject Characteristics and Task Performance

	FH−	FH+ Control	FH+ Problem
n	20	20	21
Males:Females	11:9	12:8	12:9
Age (years)	19.2 (1.9)	19.0 (1.6)	19.3 (1.3)
IQ (WISC-III)[a]	112 (9)	109 (13)	110 (10)
Alcohol Abuse or Dependence	0	0	6
Mj Abuse or Dependence	0	0	5
Other Drug Abuse or Dependence	0	0	2
Any Substance Use Disorder Dx[b]	0	0	8
Conduct Disorder Dx	0	0	4
Attention Deficit Disorder Dx	0	0	1
Any Dx[c]	0	0	8
No. of Alcohol Problems from DDHx	.9 (1.4)	1.6 (1.7)	11.4 (4.8)[e]
Drinking Volume[d] from DDHx	19.0 (43.5)	26.7 (59.4)	55.2 (77.8)[e]
Mj Use—Past 12 Months from DDHx	1.1 (2.4)	.8 (1.8)	3.3 (2.8)[e]
Number Illicit Drugs Ever Used from DDHx	.45 (.83)	.55 (.89)	2.67 (2.4)[e]
Mother/Father/Both Dependence	0/0/0	2/9/7	3/10/7
Mother/Father/Both Abuse	0/0/0	2/4/0	1/1/0
Mother/Father/Both Dependence Or Abuse	0/0/0	0/9/11	3/10/8
Mother/Father/Both Abused Other Drugs	0/3/0	1/6/2	2/11/3
YSR Form *t* Scores			
Total internalizing	44 (12.8)	43 (12.1)	49 (7.8)
Total externalizing	46 (8.7)	49 (12.6)	57 (9.7)[e]
Go/No-Go Task Performance			
Reaction times (msec)	420 (55)	404 (52)	430 (44)
False alarm rate	.24 (.19)	.25 (.13)	.20 (.10)
Total error rate	.26 (.21)	.27 (.14)	.22 (.12)

DDHx, drinking and drug history form; Dx, diagnosis; FH+, at least one parent with a diagnosis of alcohol use disorder; FH–, no parent with alcohol use disorder; Mj, marijuana; YSR, Youth Self-Report.

[a]Wechsler Intelligence Scale for Children—3rd ed. These data were collected when participants were between the ages of 12 and 14 years as part of the ongoing Michigan Longitudinal Study.

[b]Includes alcohol abuse or dependence, marijuana abuse or dependence, and/or other drug abuse or dependence.

[c]Includes conduct disorder, attention-deficit disorder, and/or any substance use disorder.

[d]Drinking days over past year × usual number of drinks per day.

[e]Significant differences between groups (described fully in text).