

Development of Impulse Control Circuitry in Children of Alcoholics

Jillian E. Hardee, Barbara J. Weiland, Thomas E. Nichols, Robert C. Welsh, Mary E. Soules, Davia B. Steinberg, Jon-Kar Zubieta, Robert A. Zucker, and Mary M. Heitzeg

Background: Difficulty with impulse control is heightened in children with a family history of alcohol use disorders and is a risk factor for later substance problems. Cross-sectional functional magnetic resonance imaging studies have shown altered impulse control processing in adolescents with a positive family history, yet developmental trajectories have yet to be examined.

Methods: Longitudinal functional magnetic resonance imaging was conducted in children of alcoholic families (family history positive [FH+]; $n = 43$) and children of control families (family history negative [FH-]; $n = 30$) starting at ages 7–12 years. Participants performed a go/no-go task during functional magnetic resonance imaging at intervals of 1–2 years, with two to four scans performed per subject. We implemented a repeated-measures linear model fit across all subjects to conduct a whole-brain search for developmental differences between groups.

Results: Performance improved with age in both groups, and there were no performance differences between groups. Significant between-group differences in linear age-related activation changes were found in the right caudate, middle cingulate, and middle frontal gyrus. Post hoc analyses revealed significant activation decreases with age in the caudate and middle frontal gyrus for FH- subjects and a significant increase with age in middle cingulate activation for FH+ subjects. Group differences were evident at age 7–12 years, even in alcohol- and drug-naïve participants, with FH+ subjects showing significantly blunted activation at baseline compared with FH- subjects.

Conclusions: Differences in response inhibition circuitry are visible in FH+ individuals during childhood; these differences continue into adolescence, displaying trajectories that are inconsistent with development of normal response inhibition. These patterns precede problem drinking and may be a contributing factor for subsequent substance use problems.

Key Words: Adolescence, alcoholism, caudate, cingulate, development, response inhibition

Children of alcoholics are at heightened risk for alcohol use disorders (AUDs) and alcohol-related problems later in life (1,2). Emotional and behavioral traits can be identified in these children before the onset of drinking that are early predictors of later problem use. One such trait is behavioral undercontrol (3–5), or an inability, unwillingness, or failure to inhibit impulses or responses, even when faced with adverse repercussions.

Poor response inhibition is a key mechanism underlying behavioral undercontrol generally and vulnerability to disinhibitory psychopathology, such as substance abuse, more specifically (6). Response inhibition can be assessed using tasks that require a prepotent response to be withheld, such as the go/no-go paradigm, where individuals respond to frequent “go” stimuli, while inhibiting responses to infrequent “no-go” stimuli. Imaging studies have found that a right-hemisphere network, including cortical and subcortical regions known to be involved in

executive and motor control, supports response inhibition during this task (7–13).

Evidence suggests that weaknesses in this network may be a risk factor for substance problems. Heitzeg *et al.* (14) found abnormal caudate activation during response inhibition in individuals 16–22 years old with a family history of AUD compared with controls. Schweinsburg *et al.* (15) observed a decrease in left middle frontal gyrus activity during response inhibition in youth 12–14 years old with a positive family history. Silveri *et al.* (16) reported greater recruitment of frontal regions, including right middle frontal and cingulate gyri, in individuals 8–19 years old with a parent with an AUD. Further studies have used follow-up data to retrospectively classify participants (who were not recruited based on family history) by whether they began using substances after functional magnetic resonance imaging (fMRI) scanning to provide a more definitive connection between neural activation patterns and risk. Norman *et al.* (17) examined youth 12–14 years old with limited substance use histories and used subsequent interviews to categorize them later into heavy drinkers or controls. The youth who transitioned into heavy drinking showed blunted activation during no-go trials at baseline, before the onset of substance use, in the frontal cortices and striatum; this was the first demonstration of atypical activation patterns predicting future substance use. More recently, Mahmood *et al.* (18) investigated whether brain responses during no-go trials in subjects 16–19 years old predicted substance use 18 months later. Decreased activation in ventromedial prefrontal cortex and increased activation in regions such as the left angular gyrus were reported in participants who later became high-frequency substance users.

Although evidence indicates that abnormal response inhibition is a risk factor for later substance problems, no consistent picture has emerged with respect to overreactivity or underreactivity for regions within this network. One reason may be the variability in

From the Departments of Psychiatry (JEH, BJW, RCW, MES, DBS, J-KZ, RAZ, MMH) and Radiology (RCW), Addiction Research Center (JEH, BJW, MES, DBS, RAZ, MMH), and Molecular and Behavioral Neuroscience Institute (J-KZ), University of Michigan, Ann Arbor, Michigan; Department of Psychology and Neuroscience (BJW), University of Colorado, Boulder, Colorado; and Department of Statistics & Warwick Manufacturing Group (TEN), University of Warwick, Coventry, United Kingdom. Address correspondence to Mary M. Heitzeg, Ph.D., Department of Psychiatry, University of Michigan, 4250 Plymouth Road, Ann Arbor, MI 48109; E-mail: mheitzeg@umich.edu.

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developmental periods during which subjects were scanned in cross-sectional studies. The ability to inhibit a response successfully increases throughout youth and continues into early adulthood (19–24), concomitant with the maturation of inhibitory control (25,26). Cross-sectional fMRI studies of response inhibition have shown that prefrontal activation is bilateral in children but lateralizes to the right hemisphere and becomes more focal in adults, whereas striatal activation continues to increase with age (27–30). Other studies have found greater posterior activation in children compared with adults (31). Significant and diverse developmental changes are occurring in response inhibition circuitry during the time when risk for alcohol and drug initiation is sharply increasing. Identifying specific neural abnormalities in this circuitry represents a moving target when viewed from childhood to early adulthood because the neural differences representing risk are likely quite different at ages 12–14 years versus 16–19 years. Furthermore the use of broad age ranges may mask important developmental differences.

The present study was designed to identify differences in inhibition circuitry development from childhood to adolescence in subjects with and without a family history of alcoholism. A longitudinal study was conducted, with two to four scans performed per subject, with data collection at 1- to 2-year intervals starting at ages 7–12 years (age range, 7–16.9 years). Additionally, a repeated-measures linear model fit was implemented across all subjects to conduct a whole-brain search for developmental differences between groups. Based on prior cross-sectional work investigating familial risk, we expected to find developmental group differences in the prefrontal cortices and

striatum. Based on prior cross-sectional work investigating development, we tentatively hypothesized that emerging differences would represent either a delay or a failure in the specialization of inhibitory control in the right prefrontal cortex of subjects with a family history of alcoholism.

Methods and Materials

Participants

We recruited 73 right-handed participants (32) 7–12 years old from the Michigan Longitudinal Study, an ongoing, prospective study of families with high levels of parental AUD and a contrast sample of families without alcoholism (33). Families in which the target child displayed evidence of fetal alcohol effects were excluded. All participants and at least one parent gave written assent, as approved by the local institutional review board.

Participants performed a go/no-go task during fMRI at 1- to 2-year intervals. Included participants had at least two fMRI scans, covering the age range of 7–16.9 years. Participants were divided into two groups: subjects with at least one parent who had an AUD diagnosis during the child's lifetime (family history–positive [FH+]; $n = 43$; scans = 113) and subjects with no parental AUD history within 2 years of the child's birth or during the child's lifetime (family history–negative [FH–]; $n = 30$; scans = 85). Diagnosis of AUD was calculated by a clinical psychologist based on answers to Diagnostic Interview Schedule–Version 4 (34–36), Health History, and Drinking & Drug Use (Supplement 1). Characteristics of these groups are summarized in Table 1.

Table 1. Subject Characteristics and Task Performance

	All Participants	FH–	FH+
<i>n</i>	73	30	43
Males/Females	51/22 ^a	25/5	26/17
Total Scans	198	85	113
No. with at least two scans	73	30	43
No. with at least three scans	39	19	20
No. with four scans	14	6	8
Age Range (Minimum/Maximum)	7.58/16.83	7.58/16.83	7.85/16.74
IQ (Mean $\pm$ SD)	103.60 $\pm$ 14.45	105.36 $\pm$ 13.90	102.46 $\pm$ 14.86
Family History AUD: Father/Mother/Both	23/3/17	0/0/0	23/3/17
ADHD Diagnosis (No.)	6	2	4
CD Diagnosis (No.)	0	0	0
CBCL at Scan 1 (Mean $\pm$ SD)			
Aggressive behavior	5.13 $\pm$ 9.12 ^{a,b}	3.06 $\pm$ 6.01	6.90 $\pm$ 10.97
Delinquent behavior	1.07 $\pm$ 1.90 ^b	.53 $\pm$.90	1.52 $\pm$ 2.38
Externalizing total	6.19 $\pm$ 10.86 ^{a,b}	3.59 $\pm$ 6.73	8.43 $\pm$ 13.20
Alcohol/Drug Use			
Baseline (scan 1)			
Alcohol use	4	0	4
Marijuana use	2	0	2
Illicit drug use	1	0	1
Total subjects reporting any use	5	0	5
Follow-up (scans 2, 3, or 4) ^c			
Alcohol use	8 ^a	1	7
Marijuana use	8	3	5
Illicit drug use	5	0	5
Total subjects reporting any use	13	3	10

ADHD, attention-deficit/hyperactivity disorder; AUD, alcohol use disorder; CBCL, Child Behavior Checklist; CD, conduct disorder; FH–, family history–negative; FH+, family history–positive.

^a $p < .05$.

^b $p < .05$ with gender as a covariate.

^cFollow-up use was the report of alcohol or drug use at any time after the first scan was completed.

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