Neural Predictors of Initiating Alcohol Use During Adolescence

Lindsay M. Squeglia, Ph.D., Tali M. Ball, Ph.D., Joanna Jacobus, Ph.D., Ty Brumback, Ph.D., Benjamin S. McKenna, Ph.D., Tam T. Nguyen-Louie, M.S., Scott F. Sorg, Ph.D., Martin P. Paulus, M.D., Susan F. Tapert, Ph.D.

Objective: Underage drinking is widely recognized as a leading public health and social problem for adolescents in the United States. Being able to identify at-risk adolescents before they initiate heavy alcohol use could have important clinical and public health implications; however, few investigations have explored individual-level precursors of adolescent substance use. This prospective investigation used machine learning with demographic, neurocognitive, and neuroimaging data in substance-naive adolescents to identify predictors of alcohol use initiation by age 18.

Method: Participants (N=137) were healthy substance-naive adolescents (ages 12–14) who underwent neuropsychological testing and structural and functional magnetic resonance imaging (sMRI and fMRI), and then were followed annually. By age 18, 70 youths (51%) initiated moderate to heavy alcohol use, and 67 remained nonusers. Random forest classification models identified the most important predictors of alcohol use from a large set of demographic, neuropsychological, sMRI, and fMRI variables.

Results: Random forest models identified 34 predictors contributing to alcohol use by age 18, including several demographic and behavioral factors (being male, higher socioeconomic status, early dating, more externalizing behaviors, positive alcohol expectancies), worse executive functioning, and thinner cortices and less brain activation in diffusely distributed regions of the brain.

Conclusions: Incorporating a mix of demographic, behavioral, neuropsychological, and neuroimaging data may be the best strategy for identifying youths at risk for initiating alcohol use during adolescence. The identified risk factors will be useful for alcohol prevention efforts and in research to address brain mechanisms that may contribute to early drinking.

Am J Psychiatry 2017; 174:172–185; doi: 10.1176/appi.ajp.2016.15121587

Underage drinking is widely recognized as one of the leading public health and social problems for adolescents in the United States. Teenage drinking is common in the United States, with approximately 66% of 18-year-olds reporting alcohol use (1). Adverse consequences of adolescent drinking include higher rates of violence, missing school, drunk driving, riding with a drunk driver, suicide, and risky sexual behavior, and it accounts for more than 5,000 deaths per year (2). Thus, being able to identify at-risk children before they initiate heavy alcohol use could have immense clinical and public health implications. However, few investigations have been conducted to gain a greater understanding of individual differences that could lead to adolescent substance use.

Previous findings have suggested that a mix of social, psychological, and biological mechanisms contribute to alcohol use during adolescence (3–5). Demographic risk factors for alcohol initiation include being male, having higher levels of psychological problems and externalizing behaviors, and having positive expectations about the effects of alcohol (5). Neuropsychological and neuroimaging data may provide quantification of underlying behavioral mechanisms of risk for substance use. Several studies suggest that poorer performance on tests of executive functioning (6), as well as having less brain activation relative to comparison participants during tasks of working memory, inhibition, and reward processing, can be used to predict which youths will initiate alcohol use during adolescence (7–11). In addition, having less volume in brain regions involved in impulsivity, reward sensitivity, and decision making appear to influence initiation of alcohol and other substance use during adolescence (7, 11). Understanding factors involved in the initiation and escalation of alcohol use during adolescence could provide crucial information for prevention and intervention efforts.

Machine learning approaches (12–17) are increasingly being used to generate predictions based on complex data like brain imaging (18, 19). Random forests (20) is a machine

See related feature: **AJP Audio** *(online)*

learning tool that can be used for feature selection and/or robust predictive modeling and that has been suggested to be superior to other machine learning techniques (21). The random forest technique consists of a complex partitioning of the predictor variable space and can be used when the number of predictor variables is much larger than the number of study participants, as is typically the case with neuroimaging data. Moreover, the random forest model has a low tendency to overfit, and the stepwise partitioning of the predictor space can yield high-order interactions among many predictor variables that cannot be identified using other classification procedures (22). Random forest models have been successfully used to detect a number of clinical outcomes and to predict behaviors (23), but they have not been used to identify predictors of substance use initiation in adolescents.

The present study uses random forest models in combination with multimodal imaging and neuropsychological test data to identify the best predictors of initiation to moderate to heavy alcohol use by age 18 in substance-naive adolescents. Based on previous research, initiation of substance use was expected to be associated with key demographic factors (e.g., being male, endorsing more externalizing behaviors and psychopathology, having positive expectations about alcohol use), neuropsychological performance (e.g., poorer performance on executive function tasks), and thinner cortices and less brain activation in key brain regions involved in executive functioning and decision making. Unlike other studies that focused on initiation of any alcohol use (11), we were interested in factors that predicted a pattern of more frequent and intense alcohol use, as these have been most consistently associated with poorer cognitive (7, 24) and social (5) outcomes.

METHOD

Participants

Participants were 137 healthy children and adolescents ages 12–14 (44% female) from a larger ongoing neuroimaging study recruited through flyers sent to households of students attending local middle schools (Table 1). Extensive screening and background information was obtained from the youths, one biological parent, and one other parent or close relative. All primary informants lived with the youths. The study protocol was executed in accordance with the standards approved by the University of California, San Diego, Human Research Protections Program.

Strict exclusionary criteria for project entry included experience with alcohol or drugs, defined as ≥10 total days in their life in which drinking had occurred, or >2 drinks in a week (i.e., two drinks on one occasion or one drink on two occasions in the same week); ≥3 lifetime experiences with marijuana and any use in the past 3 months; ≥5 lifetime cigarette uses; any history of other intoxicant use; any suggestion of prenatal exposure to alcohol (>2 drinks during a given week) or any illicit drug; premature birth (i.e., born before the 35th gestational week); a history of any neurological or DSM-IV axis I disorder (determined by the National Institute of Mental Health Diagnostic Interview Schedule for Children, version 4.0), head trauma, or loss of consciousness >2 minutes; chronic medical illness, learning disability or mental retardation, or use of medications potentially affecting the brain; contraindication to MRI (e.g., braces); inadequate comprehension of English; and non-correctable sensory problems.

Measures

Substance use measures. At baseline and follow-up assessments, the Customary Drinking and Drug Use Record (25) was administered to obtain quantity and frequency of lifetime and recent (past year) alcohol, marijuana, and other drug use, withdrawal/hangover symptoms, and DSM-IV abuse and dependence criteria. Breath alcohol testing and urine toxicology screens confirmed self-report data at baseline. Substance use information was updated every 6 months by telephone or in person after the participant's baseline assessment. Parent and/or informant (sibling, friend, roommate) report of youth substance use was collected as collateral evidence.

Demographic information. The Structured Clinical Interview (26) was administered to youths to ascertain information about the child's sex, age, race, academic functioning (i.e., grade point average on a 4.0 scale), grade in school, family characteristics (i.e., birth order, living situation, parent's marital status), dating status (e.g., never dated or history of dating), involvement in extracurricular activities, and hours of video games played per week.

Socioeconomic status. Socioeconomic background information (i.e., educational attainment, occupation, and salary of each parent) was obtained from parents and converted to a Hollingshead Index of Social Position score (27).

Family background. At baseline, the Family History Assessment Module (28) was administered to parents and youths to ascertain familial density of alcohol and drug use disorders in first- and second-degree relatives. Family history density scores were calculated by adding 0.5 for each biological parent and 0.25 per biological grandparent endorsed by either youth or parent as having alcohol use disorder or substance use disorder (possible scores range from 0 to 4).

Pubertal development. The Pubertal Development Scale (29) determined the current level of pubertal development for girls and boys separately with five sex-specific items, with scores ranging from 1 (prepubertal) to 4 (postpubertal). Participants in this sample were, on average, early to midpubertal at baseline and were late to postpubertal at follow-up.

Psychopathology and mood. The parent-administered Child Behavior Checklist (30) provided age- and gender-normed continuous measures of externalizing and internalizing psychopathology. T scores from the following subscales of the Child Behavior Checklist were used in analyses: withdrawn, somatic complaints, anxious/depressed, social problems, thought

TABLE 1. Demographic, Psychological, and Neuropsychological Variables for Adolescents Who Remained Nonusers or Transitioned to Moderate to Heavy Substance Use Patterns by Approximately Age 18 (N=137)[a]

	Continuous Nonusers (N=67)			Moderate to Heavy Alcohol Initiators (N=70)						
Variable	Mean	SD	%	Mean	SD	%	t or χ^2	df	p	Cohen's d
Demographic and family variables										
Sex (female)			60			29	13.48	1, N=137	<0.001	0.661
Follow-up age (range=16–19)[b]	18.20	0.66		18.20	0.57		0.07	135	0.943	0.000
Race (Caucasian)			58			77	5.63	1, N=137	0.018	0.414
Baseline Hollingshead Index of Social Position score (socioeconomic status)	24.03	16.75		21.11	11.50		1.19	135	0.235	0.203
Family history density of alcohol or drug use disorder	0.17	0.28		0.18	0.31		0.14	135	0.887	0.034
Baseline Pubertal Development Scale score (girls only; N=60)	15.05	3.15		14.95	3.15		0.12	58	0.908	0.032
Baseline Pubertal Development Scale score (boys only; N=77)	10.81	3.33		11.20	3.37		0.48	75	0.632	0.116
Baseline grade in school	6.76	0.74		7.00	0.87		1.73	135	0.086	0.297
Birth order	1.52	0.79		1.64	0.76		0.91	135	0.364	0.155
Baseline % living with both parents			79			81	0.12	1, N=137	0.732	0.059
Baseline % youth with biological parents married to each other			78			77	0.00	1, N=137	0.948	0.000
Baseline youth behavior, mood, and cognition										
Initiated dating by age 14 (%)			22			61	21.37	1, N=137	<0.001	0.860
Involved in extracurricular activities (%)			82			89	1.15	1, N=137	0.283	0.184
Hours of video games played per week	3.10	4.95[c]		2.47	4.04[c]		0.72	106	0.472	0.139
Grade point average (4.0 scale)	3.65	0.45		3.47	0.55		2.14	135	0.034	0.358
CBCL externalizing disorder t score	41.09	7.12[d]		40.42	7.64[d]		0.52	128	0.606	0.091
CBCL internalizing t score	44.48	8.80[d]		42.11	7.65[d]		1.65	128	0.102	0.287
CBCL withdrawn t score	52.00	3.79[d]		51.42	2.69[d]		1.00	128	0.319	0.176
CBCL somatic complaints t score	52.45	4.13[d]		51.79	3.15[d]		1.04	128	0.302	0.180
CBCL anxious/depressed t score	51.61	3.60[d]		51.11	2.60[d]		0.92	128	0.361	0.159
CBCL social problems t score	51.33	3.62[d]		50.55	1.64[d]		1.60	128	0.113	0.278
CBCL thought problems t score	51.98	3.90[d]		51.03	2.31[d]		1.70	128	0.091	0.296
CBCL attention problems t score	51.05	2.16[d]		51.20	2.81[d]		0.34	128	0.734	0.060
CBCL delinquent behavior t score	50.59	1.84[d]		50.98	2.53[d]		1.01	128	0.317	0.176
CBCL aggressive behavior t score	50.75	2.06[d]		50.68	2.11[d]		0.19	128	0.852	0.034
CBCL total problem t score	39.83	9.75[d]		37.83	8.83[d]		1.22	128	0.223	0.215
Conduct Disorder Questionnaire total score	0.45	1.08		1.17	1.88		2.75	135	0.007	0.470
Beck Depression Inventory–II total score	1.39	2.75[e]		1.25	2.81[e]		0.30	132	0.765	0.050
State-Trait Anxiety Inventory total score	26.22	6.66[f]		26.68	6.48[f]		0.40	130	0.690	0.070
AEQ total score	79.14	32.23		92.45	29.75		2.51	135	0.013	0.429
AEQ global positive score	37.81	8.37		40.83	9.53		1.97	135	0.051	0.336
AEQ social behavior change score	36.92	7.41		41.23	7.94		3.28	135	0.001	0.561
AEQ improved performance score	16.55	4.57		16.96	4.98		0.50	135	0.621	0.086
AEQ sexual enhancement score	20.15	5.06		21.00	4.07		1.09	135	0.279	0.185
AEQ impaired performance score	98.41	10.08		96.39	10.28		1.16	135	0.247	0.198
AEQ increased arousal score	24.24	5.44		24.96	4.78		0.82	135	0.414	0.141
AEQ relaxation score	41.88	9.83		43.87	7.90		1.31	135	0.193	0.293

continued

TABLE 1, *continued*

Variable	Continuous Nonusers (N=67)			Moderate to Heavy Alcohol Initiators (N=70)			t or χ^2	df	p	Cohen's d
	Mean	SD	%	Mean	SD	%				
Baseline substance use										
CDDR baseline lifetime smoking days	0.03	0.17		0.11	0.65		1.03	135	0.305	0.168
CDDR baseline lifetime drinking days	0.00	0.00		0.31	1.50		1.72	135	0.089	0.292
CDDR baseline lifetime marijuana use days	0.00	0.00		0.09	0.44		1.59	135	0.115	0.289
Total number of repetitions excluded during functional magnetic resonance imaging	4.46	6.77		7.03	8.82		1.90	134	0.060	0.327
Follow-up substance use										
Age at first use of alcohol	16.54	1.27[g]		15.46	1.60		3.09	94	0.003	0.748
Lifetime alcohol use occasions	1.52	2.87[g]		69.01	110.58		4.99	135	0.000	0.863
Peak drinks on an occasion in past year	0.46	0.96[g]		9.30	4.60		15.41	135	0.000	2.66
Lifetime marijuana use occasions	0.06	0.38[h]		108.61	256.94		3.46	135	0.001	0.597
Reporting >30 lifetime marijuana use occasions (%)			0			29				
Lifetime other drug use	0.00	0.00		7.04	38.05		1.52	135	0.132	0.261

[a] CBCL=Child Behavior Checklist; AEQ=Alcohol Expectancy Questionnaire; CDDR=Customary Drinking and Drug Use Record.
[b] All controls in this sample were at least 17 years of age to allow sufficient time to transition to alcohol use. Sixteen-year-old substance users were included because it was clear that by age 16 they were already using a substance.
[c] N=108; continuous nonusers, N=55; alcohol initiators, N=53.
[d] N=130; continuous nonusers, N=64; alcohol initiators, N=66.
[e] N=134; continuous nonusers, N=66; alcohol initiators, N=68.
[f] N=132; continuous nonusers, N=64; alcohol initiators, N=68.
[g] N=26.
[h] N=2.

problems, attention problems, delinquent behavior, and aggressive behavior, as well as three summary scores representing externalizing, internalizing, and total problems. Youths completed the Conduct Disorder Questionnaire (31), which determined DSM-IV diagnostic criteria for conduct disorder; total symptom count was used in analyses. The Beck Depression Inventory–II (32) and the State-Trait Anxiety Inventory (33) assessed recent depressive and anxiety state symptoms in youths.

Alcohol Expectancy Questionnaire–Adolescent version. Youths completed the Alcohol Expectancy Questionnaire–Adolescent version (AEQ) (34), which was developed to assess beliefs about the anticipated effects of alcohol. This version yields a total score (AEQ total score) and seven empirically derived factor scores indicating expectations for the effects of drinking alcohol: global positive changes (AEQ global positive), enhancement/impedance of social behavior (AEQ social behavior change), improvement in cognitive/behavioral functioning (AEQ improved performance), enhancement of sexuality (AEQ sexual enhancement), deterioration in cognitive/behavioral functioning (AEQ impaired performance), increased arousal (AEQ increased arousal), and promotion of relaxation/tension reduction (AEQ relaxation).

Neurocognition. A comprehensive neuropsychological battery was completed by youths at baseline to assess cognitive functioning on several cognitive domains that could potentially affect initiation of alcohol and marijuana use during adolescence. (See Table 2 for neuropsychological tests and domains assessed, and see the supplementary references for neuropsychological testing materials found in the data supplement that accompanies the online edition of this article.)

Follow-up procedures. At baseline, 12- to 14-year-old youths underwent a baseline interview, neuropsychological testing, and a structural and functional neuroimaging session. Every 6 months, telephone or in-person interviews assessed current substance use and psychiatric functioning. At baseline, all participants were considered control participants and had never had more than 10 lifetime alcohol use occasions, with never more than one drink per occasion, and no more than three lifetime marijuana use episodes. Ninety-seven percent of the sample had never used alcohol, and 98% had never used marijuana. Rigorous follow-up procedures were used to ensure excellent follow-up rates (96%). At follow-up (approximately age 18), participants were classified as either continuous controls (baseline control who maintained abstinence during the follow-up, defined as 0–4 drinks on an occasion and <12 lifetime drinking occasions) or moderate to heavy drinking initiators (baseline controls who transitioned to moderate or heavy alcohol use, defined as 3–29 drinks on an occasion and 3–834 drinking occasions; see Figure 1 for

TABLE 2. Baseline Neuropsychological Test Variables in a Study of Neural Predictors of Alcohol Use Initiation During Adolescence

		Continuous Nonusers (N=67)		Moderate to Heavy Alcohol Initiators (N=70)					
Variable	Domain Assessed	Mean	SD	Mean	SD	t	df	p	Cohen's d
Digit vigilance total time to complete (sec)	Sustained attention	225.06	52.80[a]	219.59	41.46[a]	0.67	132	0.504	0.115
Wechsler Abbreviated Scale of Intelligence (WASI) block design raw score	Spatial perception, visual abstract processing, problem solving	47.27	13.81[a]	42.86	13.13[a]	1.89	132	0.060	0.327
WASI matrix reasoning raw score	Nonverbal abstract problem solving, inductive reasoning	27.80	3.62[b]	26.41	3.34[b]	2.31	131	0.023	0.399
WASI vocabulary raw score	Word knowledge, verbal concept formation	53.02	7.09[a]	51.96	7.06[a]	0.87	132	0.389	0.150
WASI similarities raw score	Abstract verbal reasoning	35.17	4.24[a]	34.31	5.07[a]	1.06	132	0.292	0.184
Delis-Kaplan Executive Function System (D-KEFS) trails number-letter switching time to complete (sec)	Flexibility of thinking on a visual-motor task	70.60	19.45	77.46	28.75	1.63	135	0.106	0.279
D-KEFS towers total achievement score (raw)	Spatial planning, rule learning	17.04	2.68	17.24	2.73	0.43	135	0.669	0.074
D-KEFS color word interference inhibition time to complete (sec)	Inhibitory functioning	57.39	14.25	59.60	13.12	0.95	135	0.346	0.161
D-KEFS color word interference inhibition/ switching time to complete (sec)	Inhibition/cognitive flexibility	65.81	15.81	63.91	14.39	0.73	135	0.465	0.126
Rey-Osterrieth Complex Figure (ROCF) copy accuracy score	Visuospatial functioning; organization	29.35	3.02[a]	28.63	3.01[a]	1.39	132	0.168	0.239
ROCF delay accuracy score	Spatial memory	18.09	4.12[c]	17.77	4.26[c]	0.43	130	0.665	0.076
Wechsler Intelligence Scale for Children, 3rd edition (WISC-III), digits forward raw score	Attention	9.91	1.84[a]	10.17	1.94[a]	0.81	132	0.421	0.138
WISC-III digits backward raw score	Short-term memory, attention	6.44	1.74[a]	6.19	2.05[a]	0.76	132	0.447	0.131
WISC-III arithmetic raw score	Computational skills, auditory memory, attention, problem solving	22.23	3.36[a]	22.46	3.34[a]	0.39	132	0.701	0.069
WISC-III coding raw score	Visual motor speed, visual memory, sustained effort and attention	61.20	10.88[a]	59.37	10.75[a]	0.98	132	0.329	0.169
WISC-III mazes raw score	Planning, perceptual organization, visual-motor coordination and speed, nonverbal reasoning	23.48	3.71[a]	22.77	3.20[a]	1.19	132	0.235	0.205
Wechsler Adult Intelligence Scale (WAIS-IV) letter-number sequence raw score	Attention, auditory short-term memory, sequencing ability	10.69	1.94[d]	10.09	1.88[d]	1.65	108	0.103	0.314
Hooper Visual Organization Test total raw score	Visuospatial functioning and spatial integration	25.32	2.26[d]	24.94	2.40[d]	0.86	108	0.392	0.163
California Verbal Learning Test (CVLT) list A total 1 to 5 raw score	Verbal learning and memory	55.91	8.01[a]	54.51	6.29[a]	1.12	132	0.263	0.194
CVLT list A trial 1 raw score	Verbal learning and memory	7.72	1.93[a]	7.37	1.64[a]	1.13	132	0.262	0.195
CVLT list A trial 5 raw score	Verbal learning and memory	12.92	1.68[a]	12.74	1.57[a]	0.64	132	0.525	0.111
CVLT short delay free raw score	Verbal learning and memory	11.87	2.07[a]	11.74	2.29[a]	0.33	132	0.743	0.060
CVLT short delay cued raw score	Verbal learning and memory	12.15	1.94[e]	12.19	1.70[e]	0.12	129	0.907	0.022

continued

TABLE 2, *continued*

Variable	Domain Assessed	Continuous Nonusers (N=67)		Moderate to Heavy Alcohol Initiators (N=70)		t	df	p	Cohen's d
		Mean	SD	Mean	SD				
CVLT long delay free raw score	Verbal learning and memory	12.11	1.91[f]	12.30	1.79[f]	0.60	130	0.550	0.103
CVLT long delay cued raw score	Verbal learning and memory	12.52	1.80[f]	12.54	1.75[f]	0.04	130	0.968	0.011
Wide Range Achievement Test–3 Reading raw score	Premorbid functioning and intellectual capacity	45.44	4.14[a]	44.67	4.04[a]	1.08	132	0.280	0.188

[a] N=134; continuous nonusers, N=64; alcohol initiators, N=70.
[b] N=133; continuous nonusers, N=64; alcohol initiators, N=69.
[c] N=132; continuous nonusers, N=62; alcohol initiators, N=70.
[d] N=110; continuous nonusers, N=55; alcohol initiators, N=55.
[e] N=131; continuous nonusers, N=63; alcohol initiators, N=68.
[f] N=132; continuous nonusers, N=63; alcohol initiators, N=69.

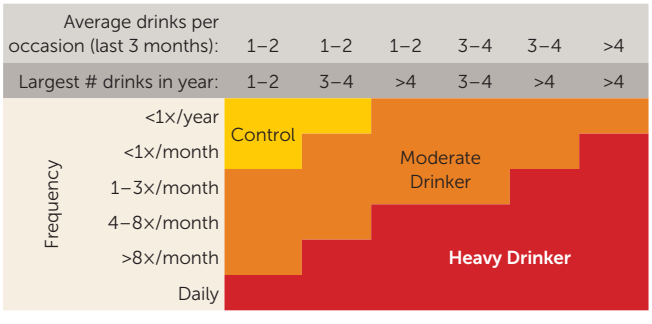
classification). Participants who had fewer drinking days but drank significantly on those occasions (e.g., three lifetime occasions, 15 drinks per occasion) were classified as moderate to heavy drinkers to capture the fact that they had initiated significant levels of alcohol use. Sixty-seven participants (49%) were classified as continuous controls (of whom 61% continued to remain completely alcohol-naive at follow-up) and 70 (51%) as moderate to heavy drinking initiators (see Table 1; of the alcohol initiators, 27% met criteria for moderate drinking, and 73% met criteria for heavy drinking). Continuous nonusers were at least 17 years of age at follow-up to allow sufficient time to transition to alcohol use. Sixteen-year-old substance users were included because it was clear that onset of substance use had occurred by that age. For this sample, rates of alcohol initiation were consistent with those of the general U.S. adolescent population (1).

Procedures

Image acquisition. High-resolution anatomical and functional MRI (fMRI) images were collected at the University of California, San Diego, Center for Functional MRI on a 3-T CXK4 short-bore Excite-2 MR system (General Electric, Milwaukee) with an eight-channel phase-array head coil. Participants were placed on the scanner table, and the head was stabilized within the head coil using foam cushions (NoMoCo, La Jolla, Calif.). Scan sessions involved a 10-second scout scan to ensure good head placement and slice selection covering the whole brain, followed by a high-resolution T_1-weighted sequence using a sagittally acquired spoiled gradient recalled sequence (field of view=24 cm, 256×256×192 matrix, 0.94×0.94×1 mm voxels, 176 slices, TR=20 ms, TE=4.8 ms, flip angle=12°, acquisition time=7 minutes and 26 seconds). Blood-oxygen-level-dependent (BOLD) response contrast was measured with T_2*-weighted axially acquired echo-planar images (field of view=24 cm, 64×64 matrix, 3.75×3.75×3.8 mm voxels, 32 slices, TE=30 ms, TR=2,000 ms, flip angle=90°, ramped bandwidth=250 KHz). Field maps were acquired to minimize warping and signal dropout (~4 minutes total) and employed two different echo times to assess field inhomogeneities and signal distortions using the same grid parameters under which echo-planar images were acquired.

Visual working memory task. All participants were administered the same fast event-related visual working memory task (35) during fMRI acquisition, which has been shown to predict future initiation of alcohol use (8). Participants were instructed to indicate whether dot arrays presented with a 2,000 ms interstimulus interval were identical or different (i.e., one dot was of a different color). Each participant completed 30 trials of each level of complexity (two, four, or six dots) presented randomly, in addition to 69 null trials of 2,000 ms each interspersed to provide an optimized fast event-related sequence (256 repetitions in all; 8 minutes and 32 seconds). The six-dot condition is considered supra-span (i.e., higher than most people's working memory span), and the two-dot condition is subspan (i.e., well within most people's working memory load capacity) (36). None of the 137 total runs used during analysis had performance at or below chance level (50%) on the two-dot condition (i.e., low-capacity/easy condition). A greater BOLD response contrast

FIGURE 1. Substance Use Classification Chart for a Study of Neural Predictors of Alcohol Use Initiation During Adolescence[a]



[a] "Control" indicates continuously nondrinking participants. "Largest # drinks in year" refers to the largest number of alcoholic drinks consumed on one occasion in the past year. Reprinted with permission from American Psychiatric Association Publishing, Squeglia et al., Brain Development in Heavy-Drinking Adolescents. Am J Psychiatry 2015; 172:531–542.

TABLE 3. List of Variables Selected as Important in Each Model in a Study of Neural Predictors of Alcohol Use Initiation During Adolescence[a]

Variable	Model 1	Model 2	Model 3
Demographic and family variables			
1. Sex	X	X	X
2. Baseline age			
3. Follow-up age	X	X	X
4. Race			
5. Hollingshead Index of Social Position score (socioeconomic status)	X	X	X
6. Family history density of alcohol or drug use disorder			
7. Pubertal Development Scale score	X		
8. Grade in school			
9. Birth order			
10. Living with both parents			
11. Parents' marital status			
Youth behavior, mood, and cognition			
12. Dating status	X	X	X
13. Child involvement in extracurricular activities			
14. Hours of video games per week			
15. Grade point average	X		
16. CBCL externalizing t score			
17. CBCL internalizing t score			
18. CBCL withdrawn t score			
19. CBCL somatic complaints t score			
20. CBCL anxious/depressed t score			
21. CBCL social problems t score			
22. CBCL thought problems t score			
23. CBCL attention problems t score			
24. CBCL delinquent behavior t score			
25. CBCL aggressive behavior t score			
26. CBCL total problem t score	X		
27. Conduct Disorders Questionnaire total score	X	X	X
28. Beck Depression Inventory-II total score			
29. State-Trait Anxiety Inventory total score			
30. AEQ total score	X	X	X
31. AEQ global positive score	X	X	X
32. AEQ social behavior change score	X	X	X
33. AEQ improved performance score			
34. AEQ sexual enhancement score			
35. AEQ impaired performance score			
36. AEQ increased arousal score			
37. AEQ relaxation total score			
38. CDDR baseline lifetime smoking days (<5 for all participants)			
39. CDDR baseline lifetime drinking days (<10)			
40. CDDR baseline lifetime marijuana use days (<3)			
41. Repetitions excluded from functional magnetic resonance imaging (fMRI) series due to motion			X
Neuropsychological testing variables			
1. Digit vigilance total time to complete (sec)		X	X
2. WASI block design raw score		X	X
3. WASI matrix reasoning raw score		X	X
4. WASI vocabulary raw score		X	

continued

(i.e., a larger fit coefficient) to the six-dot (supra-span) relative to the two-dot (subspan) condition was interpreted as having more cognitive energy expended to complete the challenging supra-span trials.

Data Analysis

Structural image processing. FreeSurfer, version 5.0 (surfer.nmr.mgh.harvard.edu) was used for cortical surface reconstruction and cortical thickness estimation (37, 38) of the high-resolution T_1-weighted MR data. The FreeSurfer program uses a series of automated imaging algorithms to produce measures of cortical thickness. One rater (L.M.S.), blind to participant characteristics, followed the reconstruction procedures (http://surfer.nmr.mgh.harvard.edu/fswiki/RecommendedReconstruction) to identify and correct any errors made during the cortical reconstruction. After inspection, an automated parcellation procedure divided each hemisphere into 34 independent cortical regions based on gyral and sulcal features (39; see Table 3 for a list of parcellated brain regions). Cortical thickness estimates of each region were extracted for subsequent statistical analyses.

Functional image processing. AFNI (40) was used to process functional images. Artifact and aberrant signal levels were examined in each repetition of each slice using an automated program developed by the University of California, San Diego, Laboratory of Cognitive Neuroimaging. Motion in time-series data was corrected by registering each acquisition to the maximally stable base volume with an iterated least squares algorithm (41) to estimate three rotational and three displacement parameters for each participant. An output file specifying adjustments made controlled for spin history effects in analyses if no significant task-correlated motion was found. To evaluate task-related motion, the reference vector was correlated with the six motion parameters for each data set. Data sets with significant task-correlated or bulk motion (>2 mm) were excluded from analyses. Two trained raters then scanned the time series to omit any remaining repetitions with visually discernible motion; if more than 15% of repetitions in a task were discarded, the run was not used (N=10, not described in this article).

Raw time-series data were standardized to percent signal change from baseline, and deconvolution was conducted with a reference

function that convolved the behavioral stimuli with a hemodynamic response model while covarying for linear trends and motion correction, ignoring the first three repetitions (42). This resulted in a functional image in which every voxel contains a fit coefficient representing the change in signal across behavioral conditions, as well as the signal change percentage and threshold statistics. Standardized Talairach transformations were made for each high-resolution anatomical image, and functional data sets were warped in accordance to manage individual anatomical variability. Functional data were resampled into isotropic voxels (3 mm^3), and a spatial smoothing Gaussian filter (full-width, half maximum, 5 mm) was applied to minimize the influence of individual anatomic variability. Coregistration of structural images to functional images was performed with a mutual information registration program (41) that robustly handles images with different signal characteristics and different spatial resolutions.

Volumetric and functional image alignment. The AFNI Surface Mapper (SUMA) program (43) was used to align segmented volumetric and functional data sets to the same template space. SUMA programs allow for fine control over the mapping between volume and surface domains produced by the FreeSurfer segmentation process while maintaining a direct link to volumetric data from which surface models and data originated. Combining functional and structural neuroimaging data using SUMA has been described in detail elsewhere (44). BOLD response values, averaged across the parcellation regions derived from FreeSurfer (39), were imported from AFNI to SPSS (IBM, Armonk, N.Y.).

Statistical Analysis

Independent-sample t tests or chi-square tests (for dichotomous variables) compared differences between groups (Table 1). Random forest classification was implemented in the R statistics package (http://cran.r-project.org; randomForest library) to predict alcohol initiator status, with missing data handled using the rfimpute function (see Table 1 for sample sizes per variable). Default parameters for the randomForest function were used, with the exception of expanding the number of trees to 2,000 (45).

Random forest classification has been described in detail elsewhere (20, 23). Briefly, random forest classification has two primary

TABLE 3, *continued*

Variable	Model 1	Model 2	Model 3
5. WASI similarities raw score			
6. D-KEFS trails condition 4 (number-letter switching) time to complete (sec)		X	
7. D-KEFS towers total achievement raw score			
8. D-KEFS color word interference inhibition time to complete (sec)			
9. D-KEFS color word interference inhibition/switching time to complete (sec)			
10. ROCF copy accuracy score			
11. ROCF delay accuracy score			
12. WISC-III digits forward raw score			
13. WISC-III digits backward raw score			
14. WISC-III arithmetic raw score			
15. WISC-III coding raw score			
16. WISC-III mazes raw score			
17. WAIS-IV letter-number sequence raw score			
18. Hooper Visual Organization Test total raw score			
19. CVLT list A total 1 to 5 raw score			
20. CVLT list A trial 1 raw score			
21. CVLT list A trial 5 raw score			
22. CVLT short delay free raw score			
23. CVLT short delay cued raw score			
24. CVLT long delay free raw score			
25. CVLT long delay cued raw score			
26. WRAT–3 reading raw score			
Cortical thickness and BOLD regions[b]			
1. Banks of superior temporal sulcus			L-CT
2. Caudal anterior cingulate			R-BOLD
3. Caudal middle frontal			
4. Cuneus			
5. Entorhinal			
6. Fusiform			
7. Inferior parietal			
8. Inferior temporal			
9. Isthmus cingulate			
10. Lateral occipital			L-CT
11. Lateral orbitofrontal			
12. Lingual			L-CT
13. Medial orbitofrontal			
14. Middle temporal			R-CT, L-BOLD
15. Parahippocampal			
16. Paracentral			
17. Pars opercularis			
18. Pars orbitalis			R-CT
19. Pars triangularis			
20. Pericalcarine			
21. Postcentral			
22. Posterior cingulate			R-BOLD
23. Precentral			
24. Precuneus			R-CT, L-BOLD, R-BOLD
25. Rostral anterior cingulate			L-CT
26. Rostral middle frontal			R-CT
27. Superior frontal			R-CT
28. Superior parietal			L-CT, R-CT
29. Superior temporal			R-BOLD
30. Supramarginal			L-CT

continued

TABLE 3, *continued*

Variable	Model 1	Model 2	Model 3
31. Frontal pole			R-CT, R-BOLD
32. Temporal pole			R-CT
33. Transverse temporal			L-CT
34. Insula			

[a] CBCL=Child Behavior Checklist; AEQ=Alcohol Expectancy Questionnaire; CDDR=Customary Drinking and Drug Use Record; WASI=Wechsler Abbreviated Scale of Intelligence; D-KEFS=Delis-Kaplan Executive Function System; ROCF=Rey-Osterrieth Complex Figure; WISC-III=Wechsler Intelligence Scale for Children, 3rd edition; WAIS-IV=Wechsler Adult Intelligence Scale; CVLT=California Verbal Learning Test; WRAT–3=Wide Range Achievement Test–3 Reading. Model 1 initially included demographic and family and youth behavior, mood, and cognition variables. Model 2 initially included all of the variables from model 1 plus neuropsychological testing variables. Model 3 initially included all of the variables from models 1 and 2 plus neuroimaging variables (cortical thickness and blood-oxygen-level-dependent [BOLD] response during a visual working memory task). Demographic and neuropsychological variables predicting initiation into alcohol use by age 18 are marked with X. For neuroimaging data in model 3, Desikan (39) brain region location is specified using the following: R=right hemisphere; L=left hemisphere. The neuroimaging index is specified using the following: CT=cortical thickness; BOLD=BOLD response contrast during a visual working memory task (six-dot supra-span relative to the two-dot subspan condition).

[b] Based on the Desikan atlas (39); 34 regions per hemisphere, cortical thickness and fMRI measures for each region listed; 34×2×2=136 total variables.

parameters: the number of trees (2,000 were used in these analyses) and the number of variables tried at each node (as recommended [20], the square root of the total number of variables). In addition, trees were grown to the highest possible number of nodes such that all participants in the bootstrap training sample were accurately classified. Variable selection was accomplished using permutation importance scores, defined as the mean decrease in model accuracy when a predictor variable's values are randomly permuted. Specifically, the random forest algorithm was run 500 times on the entire set of possible predictors to generate stable importance scores for each predictor (based on the median score across the 500 repetitions). Because negative permutation importance scores arise from random variation around zero of the poor predictor variables (22), only variables with an importance score greater than the magnitude of the most negative score were selected as important predictors (22, 23). Notably, this technique utilizes bootstrapped cross-validation to reduce overfitting when generating permutation importance scores.

This approach is consistent with the first steps executed in Ball et al. (23). However, we do not generate and evaluate a final model using the select predictors because this results in "double dipping," or selecting and evaluating variables from the same sample (46). Although a holdout sample could be used to circumvent this issue (i.e., splitting the sample into variable selection and final model testing subsamples), this requires a sample size of greater than 200 for sufficient power in the subsamples. Therefore, analyses are focused exclusively on variable selection to identify potentially important risk factors for adolescent alcohol use.

Three sequential models were built to compare the following sets of variables (see Table 3): demographic and behavioral variables only; demographic and behavioral and neuropsychological test variables; and demographic and behavioral, neuropsychological, and neuroimaging variables. (See the data supplement for models that were run on 26 neuropsychological and 136 neuroimaging variables separately.) The relatively wide range in baseline age (12–14 years) could have biased findings because those enrolled at age 14 survived 2 more years without initiating alcohol use; this was accounted for by including baseline and follow-up age in the models.

RESULTS

Demographic Model

The initial variable set comprised 41 demographic and psychological variables (see Table 3) as predictors of moderate to heavy alcohol initiation. Eleven of these were identified as important: sex, age at follow-up, socioeconomic status, pubertal development, dating status, grade point average, Child Behavior Checklist total problems, Conduct Disorder Questionnaire total problems count, AEQ total score, AEQ global positive score, and AEQ social behavior change score.

Demographic and Neuropsychological Performance Model

After adding neuropsychological test variables (26 additional variables; see Table 3) to the variable set, 13 of the 67 total variables were identified as important: eight of 11 from the previous model (sex, age at follow-up, socioeconomic status, dating status, Conduct Disorder Questionnaire total problems count, AEQ total score, AEQ global positive score, and AEQ social behavior change score), and five additional variables (Digit Vigilance Test total time; the Wechsler Abbreviated Scale of Intelligence (WASI) block design, matrix reasoning, and vocabulary total raw scores; and the D-KEFS trails condition 4 [number-letter switching] time to complete).

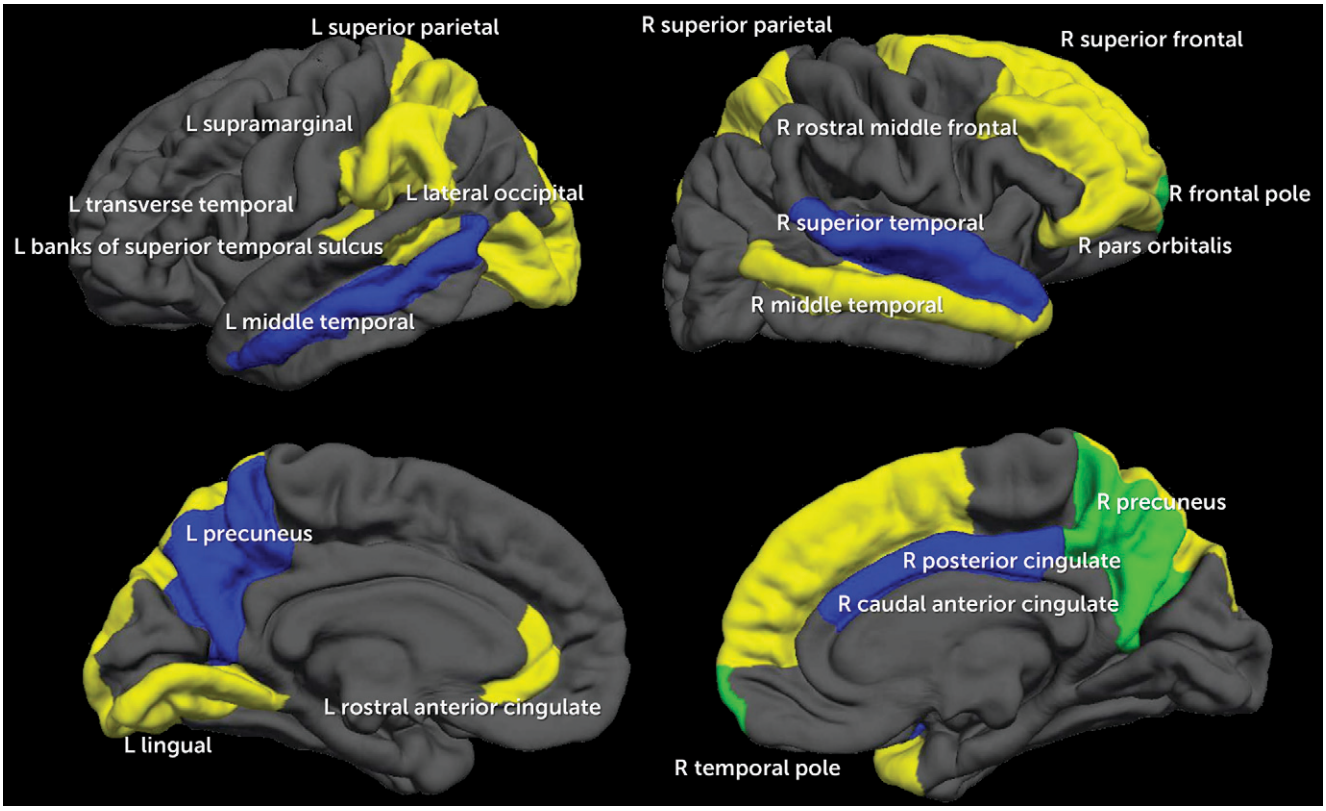
Demographic, Neuropsychological Performance, and Neuroimaging Model

After including the neuroimaging data (cortical thickness and BOLD response for each of the 68 brain regions; see Table 3), 34 of the 203 total variables were identified as important (see Table 3 and Figure 2).

Further Investigation of Model 3

The precise contribution of each variable to the outcome prediction is complex, owing to the high-order interactions critical to the success of random forests. However, main effects can be investigated straightforwardly. As shown in Table 4, alcohol initiators had less brain activation contrast between supra- and subspan conditions than continuous nonusing control participants in all seven brain regions and had thinner cortices in 13 of the 15 brain regions in the final model. The lingual gyrus and lateral occipital gyrus were thicker in future alcohol initiators. Neuropsychological test variables that contributed to predicting future initiation of

FIGURE 2. Twenty Brain Regions That Predicted Alcohol Initiation by Approximately Age 18 in a Study of Neural Predictors of Alcohol Use Initiation During Adolescence[a]



[a] Yellow indicates cortical thickness regions identified as important in model 3. Blue indicates blood-oxygen-level-dependent (BOLD) response regions included in the final model. Green (overlapping of yellow and blue regions) indicates cortical thickness and BOLD response in the same brain region. With regard to neuroimaging data, thinner cortices (in 13 of the 15 regions) and less BOLD response contrast (in all seven regions) predicted initiation of moderate to heavy drinking by approximately age 18.

drinking included faster Digit Vigilance Test time and poorer performance on the WASI block design and matrix reasoning tests. Demographic predictors of initiating alcohol use included being male, having a higher socioeconomic status, starting to date at an earlier age (by age 14), having a greater endorsement of conduct disorder–related behaviors, having higher positive alcohol expectancies (i.e., higher AEQ global positive, social behavior change, and total scores), and having more motion during the fMRI task. Table 4 lists the variables in the third model, in order of importance, and indicates which variables were statistically different between continuous nonusers and moderate to heavy alcohol initiators. Notably, while each variable by itself may not differentiate continuous controls from drinkers (as shown by the p values in Table 4), selected variables can contribute to prediction via interaction effects, supporting the importance of using statistical techniques such as random forests that can model these complex, high-order interaction terms.

DISCUSSION

This study aimed to address an important public health issue by identifying variables that can generate individual-level predictions of initiating alcohol use during adolescence. This multimodal variable identification will be crucial to inform ongoing longitudinal adolescent studies (47; see also https://addictionresearch.nih.gov/abcd-study), which will have sufficient power to provide predictive accuracy estimates. The findings show that a mix of demographic, neuropsychological, and brain imaging indices are important in predicting which 12- to 14-year-olds would initiate moderate to heavy alcohol use by approximately age 18.

Specifically, being male and coming from higher socioeconomic backgrounds appear to be risk factors for initiation of drinking by age 18. Dating by age 14, reporting more externalizing behaviors, and having more positive expectations about how alcohol would affect behaviors and cognitions (particularly in social settings) appear to be risk factors for adolescent-onset alcohol initiation. In terms of neuropsychological functioning, adolescents who showed poorer performance on executive function tests and were faster on sustained attention tests (perhaps indicating impulsivity) during early adolescence had higher rates of alcohol initiation, consistent with previous findings (48). The neuroimaging features of thinner cortices and less BOLD response contrast to a cognitive challenge by age 14 also

TABLE 4. Variables, in Order of Importance, in Model 3 (Including Demographic, Neuropsychological, and Structural and Functional Neuroimaging Data) in a Study of Neural Predictors of Alcohol Use Initiation During Adolescence[a]

	Continuous Nonusers (N=67)			Moderate to Heavy Alcohol Initiators (N=70)					
Measure	Mean	SD	%	Mean	SD	%	p	Variable Importance	Cohen's d
1. L supramarginal cortical thickness	2.96	0.14		2.89	0.13		0.002	10.01	0.518
2. Sex (female)[b]			60			29	>0.001	9.99	0.661
3. R posterior cingulate BOLD	−0.63	3.90		−2.19	3.60		0.016	8.84	0.416
4. R superior temporal BOLD	−1.17	3.60		−1.89	2.83		0.194	8.45	0.222
5. Dating at baseline[b]			22			61	>0.001	8.08	0.860
6. Socioeconomic status	24.03	16.75		21.11	11.50		0.235	7.44	0.203
7. L transverse temporal cortical thickness	2.78	0.21		2.68	0.21		0.006	7.37	0.476
8. R pars orbitalis cortical thickness	3.02	0.22		2.92	0.19		0.005	7.28	0.487
9. WASI matrix reasoning raw score	27.80	3.62		26.41	3.34		0.023	7.11	0.399
10. WASI block design raw score	47.27	13.81		42.86	13.13		0.060	6.43	0.327
11. R rostral middle frontal cortical thickness	2.53	0.10		2.49	0.11		0.058	6.06	0.381
12. L middle temporal BOLD	−1.11	2.56		−1.62	2.47		0.238	5.83	0.203
13. R superior parietal cortical thickness	2.60	0.12		2.55	0.10		0.016	5.76	0.453
14. L lingual cortical thickness	2.26	0.16		2.28	0.13		0.367	5.62	0.137
15. R precuneus cortical thickness	2.82	0.11		2.78	0.11		0.049	5.42	0.364
16. R caudal anterior cingulate BOLD	2.40	4.90		0.43	4.66		0.017	5.24	0.412
17. AEQ social behavior change total score[b]	36.92	7.41		41.23	7.94		0.001	5.23	0.561
18. R temporal pole cortical thickness	3.88	0.30		3.76	0.37		0.041	5.18	0.356
19. R precuneus BOLD	−1.46	5.64		−3.06	4.90		0.078	4.81	0.303
20. Repetitions excluded from functional magnetic resonance imaging series due to motion	4.46	6.77		7.03	8.82		0.060	4.44	0.327
21. L lateral occipital cortical thickness	2.45	0.16		2.46	0.14		0.774	4.41	0.067
22. Conduct Disorder Questionnaire total score	0.45	1.08		1.17	1.88		0.007	4.04	0.470
23. R frontal pole BOLD	2.02	4.74		0.50	7.54		0.161	3.91	0.241
24. R frontal pole cortical thickness	3.10	0.28		2.99	0.33		0.038	3.80	0.360
25. L rostral anterior cingulate cortical thickness	3.20	0.30		3.12	0.26		0.107	3.71	0.285
26. AEQ total score	79.14	32.23		92.45	29.75		0.013	2.88	0.429
27. R middle temporal cortical thickness	3.26	0.14		3.22	0.18		0.192	2.85	0.248
28. L banks superior temporal sulcus cortical thickness	2.85	0.19		2.80	0.16		0.104	2.67	0.285
29. L precuneus BOLD	−2.03	5.85		−3.46	5.17		0.130	2.63	0.260
30. L superior parietal cortical thickness	2.60	0.12		2.5	0.11		0.015	2.55	0.869
31. AEQ global positive total score	37.81	8.37		40.83	9.53		0.051	2.42	0.336
32. Digit vigilance completion time (seconds)	225.06	52.80		219.59	41.46		0.504	2.36	0.115
33. Right superior frontal cortical thickness	3.05	0.15		3.01	0.13		0.076	2.19	0.285
34. Follow-up age	18.20	0.66		18.20	0.57		0.943	1.22	0.000

[a] Importance was defined as the mean decrease in model accuracy when the variable was permuted. In random forest analyses, the contribution of each variable to the outcome prediction is complex given the high-order interactions critical to the success of this technique. While some group differences on individual variables are statistically nonsignificant or would not survive control for multiple comparisons, each variable contributes significantly to the overall success of the predictive model when allowed to interact with other variables. The group differences and effect sizes are presented to better understand the direction and magnitude of the relationship. Cortical thickness is measured in millimeters. AEQ=Alcohol Expectancy Questionnaire; WASI=Wechsler Abbreviated Scale of Intelligence; R=right hemisphere; L=left hemisphere; BOLD=blood-oxygen-level-dependent response during a visual working memory task (% signal change during six-dot versus two-dot condition).

[b] Group differences that survive Bonferroni correction ($p \leq 0.001$).

contribute to risk of moderate to heavy drinking by age 18, consistent with previous findings (5, 8, 11). Interestingly, more head movement (yet still within the acceptable limits to be included in analyses) while in the scanner was selected as an important variable, perhaps representing a phenotypic marker of impulsivity. While current substance use is highly predictive of future use (11), baseline alcohol, cigarette, and marijuana use was not selected as an important variable in our model; however, this is not surprising given that our sample was almost completely substance naive at baseline (97% had

never tried alcohol). These findings build on previous reports (11) and focus on predicting patterns of more frequent and intense alcohol use as opposed to initiation alone.

Five of the 10 most important predictors were MRI and fMRI variables, suggesting that the inclusion of neuroimaging improves the accuracy of predicting future alcohol use (see Table 4). Morphometry or activation of 20 diffusely distributed brain regions substantially contributed to alcohol initiation (see Figure 1). Cortical thickness and BOLD response regions did not overlap, except in the right precuneus and right frontal pole, similar to previous studies showing that structural and functional maturation tend to show distinct developmental trajectories during early adolescence (44). More "mature" neural functioning (i.e., thinner cortices and less BOLD response contrast) was related to greater rates of transitioning to substance use, which is consistent with previous findings (8–10, 49). This "pseudomaturity" in at-risk youths has also been observed in other behavioral studies, including a 33-year longitudinal study that found that more mature behavior during childhood (based on psychiatrist ratings) predicted greater nicotine dependence in adulthood (F.X. Castellanos, personal communication, 2015). Early maturation of neural features could be considered a vulnerability for youths, increasing the likelihood of engaging in sensation-seeking behaviors at an earlier age. Neurodevelopmentally precocious youths may have a greater tendency to initiate and escalate risk-taking behaviors (e.g., early dating, substance use), relative to peers. Longitudinal studies with three or more time points will be needed to elucidate the trajectory of youths with these different outcomes.

Consistent with epidemiological data, alcohol was the most commonly used substance in this sample (1). However, significant marijuana use was reported among the moderate to heavy alcohol initiators. We chose to focus specifically on alcohol initiation because only 15% of our overall sample (29% of alcohol initiators) endorsed more than 30 lifetime occasions of marijuana use, and most alcohol initiators (80%) used alcohol before trying marijuana. However, it is likely that the reported risk factors confer risk not only to use of alcohol but also to use of marijuana and other illicit substances, and potentially to additional risky behaviors. Larger studies and additional years of follow-up will indicate the extent to which these predictive features are replicated, are predictive of substance use or problem behavior more broadly, and, as participants age, are predictive of addiction.

Strengths of this study include its extensive neuropsychological and multimodal neuroimaging data and utilization of a robust machine learning technique to identify potential risk factors for adolescent alcohol use. Limitations of this study include the lack of an independent replication sample. Nevertheless, random forests is a robust statistical technique that has been suggested to be superior to other machine learning techniques (21), and it includes bootstrapped cross-validation, with permutation importance determined based on an out-of-bag sample to reduce overfitting. Regardless, future work should seek to replicate these predictors. To this end, we are publishing the random forest script (see the online data supplement) that we used here so that other groups can try to replicate our findings using their own data sets. In random forest analyses, the contribution of each variable to the outcome prediction is complex given the high-order interactions critical to the success of this technique. While some group differences on individual variables are statistically nonsignificant or would not survive control for multiple comparisons (Table 4), each variable contributes significantly to the overall success of the model when allowed to interact with other variables. The group differences are presented to better understand the direction of the relationship. Genotyping was not included in this study. While previous findings suggest a nominal role of genetics in adolescent alcohol initiation compared with other personality and environmental factors (11), future studies should explore potential genetic risk factors associated with alcohol use and risk-taking generally. The participants in this sample came from a relatively high socioeconomic status, which may limit generalizability to low socioeconomic status youths; published scripts will allow for replication in more diverse samples (see the data supplement). A limitation inherent to fMRI is that the BOLD findings are task dependent and have sensitivity only to detect regions engaged by the task. Therefore, it is possible that functional activity in different regions would be predictive of future alcohol use if a different task were used. There is a large quantity and frequency range covered across the moderate to heavy alcohol initiator category, and predictors may vary across the severity of this continuum. While most alcohol users in this study were not drinking frequently, they tended to drink in large quantities (an average of >9 drinks on peak occasion in the past year), suggesting that we were capturing risky drinking behaviors in this group. Continued follow-up of this sample as some youths transition to alcohol use disorders will help clarify which predictors are most important in identifying problematic drinking.

The results provide evidence that interactions between multimodal neuroimaging data, neuropsychological testing, and demographic and clinical information can best predict future behaviors such as initiation of alcohol use. Understanding neurocognitive factors that predate substance use initiation is crucial to specifying the consequences of substance use on brain development, as well as identifying at-risk youths and potential targets of preventive efforts. The random forest script used in this study is now published to allow other groups to replicate findings, in the hope that a final, validated model can be used clinically to predict adolescent alcohol use.

AUTHOR AND ARTICLE INFORMATION

From the Addiction Sciences Division, Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston; the Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, Calif.; the Department of Psychiatry, University of California, San Diego, La Jolla; the VA San Diego Healthcare System, San Diego; the

San Diego State University and University of California, San Diego, Joint Doctoral Program in Clinical Psychology, San Diego; and the Laureate Institute for Brain Research, Tulsa, Okla.

Address correspondence to Dr. Tapert (stapert@ucsd.edu).

Supported by National Institute on Alcohol Abuse and Alcoholism (NIAAA) grants R01 AA13419 and U01 AA021692 and National Institute on Drug Abuse (NIDA) grant U01 DA041089 to Dr. Tapert; by NIDA grant K12 DA031794 and NIAAA grant K23 AA025399 to Dr. Squeglia; by NIDA grant T32 DA031098 to Dr. McKenna; by NIAAA grant T32 AA013525 to Ms. Nguyen-Louie; and by NIDA grants R01 DA016663 and P20 DA027843 to Dr. Paulus.

The authors thank the Adolescent Brain Imaging Project laboratory and the participating schools in the San Diego Unified School District and their families, as well as Lindsay Meredith for assistance with preparation of this article. The authors acknowledge Matthias Guggenmos for bringing the issue of "double dipping" to their attention.

The authors report no financial relationships with commercial interests.

Received Dec. 21, 2015; revisions received April 4 and May 13, 2016; accepted May 20, 2016; published online Aug. 19, 2016.

REFERENCES

1. Johnston LD, O'Malley PM, Miech RA, et al: Monitoring the Future: National Survey Results on Drug Use: 1975–2014: Overview, Key Findings on Adolescent Drug Use. Ann Arbor, University of Michigan, Institute for Social Research, 2015
2. Miller JW, Naimi TS, Brewer RD, et al: Binge drinking and associated health risk behaviors among high school students. Pediatrics 2007; 119:76–85
3. Squeglia LM, Jacobus J, Tapert SF: The effect of alcohol use on human adolescent brain structures and systems. Handb Clin Neurol 2014; 125:501–510
4. Squeglia LM, Gray KM: Alcohol and drug use and the developing brain. Curr Psychiatry Rep 2016; 18:46
5. Brown SA, McGue M, Maggs J, et al: A developmental perspective on alcohol and youths 16 to 20 years of age. Pediatrics 2008; 121(suppl 4): S290–S310
6. Squeglia LM, Jacobus J, Nguyen-Louie TT, et al: Inhibition during early adolescence predicts alcohol and marijuana use by late adolescence. Neuropsychology 2014; 28:782–790
7. Squeglia LM, Tapert SF, Sullivan EV, et al: Brain development in heavy-drinking adolescents. Am J Psychiatry 2015; 172:531–542
8. Squeglia LM, Pulido C, Wetherill RR, et al: Brain response to working memory over three years of adolescence: influence of initiating heavy drinking. J Stud Alcohol Drugs 2012; 73:749–760
9. Wetherill RR, Squeglia LM, Yang TT, et al: A longitudinal examination of adolescent response inhibition: neural differences before and after the initiation of heavy drinking. Psychopharmacology (Berl) 2013; 230:663–671
10. Heitzeg MM, Nigg JT, Hardee JE, et al: Left middle frontal gyrus response to inhibitory errors in children prospectively predicts early problem substance use. Drug Alcohol Depend 2014; 141:51–57
11. Whelan R, Watts R, Orr CA, et al: Neuropsychosocial profiles of current and future adolescent alcohol misusers. Nature 2014; 512:185–189
12. Passos IC, Mwangi B, Kapczinski F: Big data analytics and machine learning: 2015 and beyond. Lancet Psychiatry 2016; 3:13–15
13. Patel MJ, Andreescu C, Price JC, et al: Machine learning approaches for integrating clinical and imaging features in late-life depression classification and response prediction. Int J Geriatr Psychiatry 2015; 30:1056–1067
14. Lavagnino L, Amianto F, Mwangi B, et al: Identifying neuroanatomical signatures of anorexia nervosa: a multivariate machine learning approach. Psychol Med 2015; 45:2805–2812
15. Hajek T, Cooke C, Kopecek M, et al: Using structural MRI to identify individuals at genetic risk for bipolar disorders: a 2-cohort, machine learning study. J Psychiatry Neurosci 2015; 40:316–324
16. Sato JR, Moll J, Green S, et al: Machine learning algorithm accurately detects fMRI signature of vulnerability to major depression. Psychiatry Res 2015; 233:289–291
17. Shouval R, Bondi O, Mishan H, et al: Application of machine learning algorithms for clinical predictive modeling: a data-mining approach in SCT. Bone Marrow Transplant 2014; 49:332–337
18. Pariyadath V, Stein EA, Ross TJ: Machine learning classification of resting state functional connectivity predicts smoking status. Front Hum Neurosci 2014; 8:425
19. Brodersen KH, Deserno L, Schlagenhauf F, et al: Dissecting psychiatric spectrum disorders by generative embedding. Neuroimage Clin 2013; 4:98–111
20. Breiman L: Random forests. Mach Learn 2001; 45:5–32
21. Qi Y, Bar-Joseph Z, Klein-Seetharaman J: Evaluation of different biological data and computational classification methods for use in protein interaction prediction. Proteins 2006; 63:490–500
22. Strobl C, Malley J, Tutz G: An introduction to recursive partitioning: rationale, application, and characteristics of classification and regression trees, bagging, and random forests. Psychol Methods 2009; 14:323–348
23. Ball TM, Stein MB, Ramsawh HJ, et al: Single-subject anxiety treatment outcome prediction using functional neuroimaging. Neuropsychopharmacology 2014; 39:1254–1261
24. Squeglia LM, Spadoni AD, Infante MA, et al: Initiating moderate to heavy alcohol use predicts changes in neuropsychological functioning for adolescent girls and boys. Psychol Addict Behav 2009; 23:715–722
25. Brown SA, Myers MG, Lippke L, et al: Psychometric evaluation of the Customary Drinking and Drug Use Record (CDDR): a measure of adolescent alcohol and drug involvement. J Stud Alcohol 1998; 59:427–438
26. Brown SA, Myers MG, Mott MA, et al: Correlates of success following treatment for adolescent substance abuse. Appl Prev Psychol 1994; 3:61–73
27. Hollingshead AB: Two-factor index of social position. New Haven, Conn, Yale University Press, 1965
28. Rice JP, Reich T, Bucholz KK, et al: Comparison of direct interview and family history diagnoses of alcohol dependence. Alcohol Clin Exp Res 1995; 19:1018–1023
29. Petersen AC, Crockett L, Richards M, et al: A self-report measure of pubertal status: reliability, validity, and initial norms. J Youth Adolesc 1988; 17:117–133
30. Achenbach TM, Rescorla LA: Manual for the ASEBA School-Age Forms & Profiles. Burlington, Vt, University of Vermont, Research Center for Children, Youth, & Families, 2001
31. Brown SA, Gleghorn A, Schuckit MA, et al: Conduct disorder among adolescent alcohol and drug abusers. J Stud Alcohol 1996; 57:314–324
32. Beck AT, Steer RA, Brown GK: Manual for the Beck Depression Inventory-2. San Antonio, Tex, Psychological Corporation, 1996
33. Spielberger CD, Gorsuch RL, Lushene RE: Manual for the State-Trait Anxiety Inventory. Palo Alto, Calif, Consulting Psychologists Press, 1970
34. Brown SA, Christiansen BA, Goldman MS: The Alcohol Expectancy Questionnaire: an instrument for the assessment of adolescent and adult alcohol expectancies. J Stud Alcohol 1987; 48:483–491
35. Tapert SF, Pulido C, Paulus MP, et al: Level of response to alcohol and brain response during visual working memory. J Stud Alcohol 2004; 65:692–700
36. Luck SJ, Vogel EK: The capacity of visual working memory for features and conjunctions. Nature 1997; 390:279–281
37. Dale AM, Fischl B, Sereno MI: Cortical surface-based analysis. I. Segmentation and surface reconstruction. Neuroimage 1999; 9:179–194
38. Fischl B, Sereno MI, Dale AM: Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. Neuroimage 1999; 9:195–207
39. Desikan RS, Ségonne F, Fischl B, et al: An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 2006; 31:968–980

40. Cox RW: AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. Comput Biomed Res 1996; 29:162–173
41. Cox RW, Jesmanowicz A: Real-time 3D image registration for functional MRI. Magn Reson Med 1999; 42:1014–1018
42. Cohen JD, Perlstein WM, Braver TS, et al: Temporal dynamics of brain activation during a working memory task. Nature 1997; 386:604–608
43. Saad ZS, Reynolds RC: SUMA. Neuroimage 2012; 62:768–773
44. Squeglia LM, McKenna BS, Jacobus J, et al: BOLD response to working memory not related to cortical thickness during early adolescence. Brain Res 2013; 1537:59–68
45. Genuer R, Poggi JM, Tuleau-Malot C: Variable selection using random forests. Pattern Recognit Lett 2010; 31:2225–2236
46. Kriegeskorte N, Simmons WK, Bellgowan PS, et al: Circular analysis in systems neuroscience: the dangers of double dipping. Nat Neurosci 2009; 12:535–540
47. Brown SA, Brumback T, Tomlinson K, et al: The National Consortium on Alcohol and NeuroDevelopment in Adolescence (NCANDA): a multisite study of adolescent development and substance use. J Stud Alcohol Drugs 2015; 76:895–908
48. Peeters M, Janssen T, Monshouwer K, et al: Weaknesses in executive functioning predict the initiating of adolescents' alcohol use. Dev Cogn Neurosci 2015; 16:139–146
49. Squeglia LM, Rinker DA, Bartsch H, et al: Brain volume reductions in adolescent heavy drinkers. Dev Cogn Neurosci 2014; 9:117–125

EDITOR'S NOTE

In the January 2017 issue, *The American Journal of Psychiatry* published a correction stating that the article "Neural Predictors of Initiating Alcohol Use During Adolescence" by Lindsay M. Squeglia, Ph.D., et al. (doi:10.1176/appi.ajp.2016.15121587) was being extensively revised from the version initially published online August 19, 2016. Subsequent to that online publication, the authors presented their findings at a conference, where Dr. Matthias Guggenmos (Department of Psychiatry and Psychotherapy, Charité–Universitätsmedizin Berlin) brought to their attention that this strategy yields a biased estimate of predictive power. The authors determined that while their feature selection process was sound, the validation scheme in their original analytic pathway indeed resulted in an overestimation of the predictive accuracy of the models. The revised version that omits the claim of validation appears in this February 2017 issue. Included in the online edition as a data supplement is the previously published version marked to show the changes from that article to what appears in this issue.