Adolescent Substance Abuse: The Effects of Alcohol and Marijuana on Neuropsychological Performance

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Background: Adolescence is a period in which cognition and brain undergo dramatic parallel development. Whereas chronic use of alcohol and marijuana is known to cause cognitive impairments in adults, far less is known about the effect of these substances of abuse on adolescent cognition, including possible interactions with developmental processes.

Methods: Neuropsychological performance, alcohol use, and marijuana use were assessed in 48 adolescents (ages 12 to 18), recruited in 3 groups: a healthy control group (HC, $n = 15$), a group diagnosed with substance abuse or dependence (SUD, $n = 19$), and a group with a family history positive for alcohol use disorder (AUD) but no personal substance use disorder (FHP, $n = 14$). Age, drinks per drinking day (DPDD), percentage days drinking, and percentage days using marijuana were considered as covariates in a MANCOVA in which 6 neuropsychological composites (Verbal Reasoning, Visuospatial Ability, Executive Function, Memory, Attention, and Processing Speed) served as dependent variables.

Results: More DPDD predicted poorer performance on Attention and Executive Function composites, and more frequent use of marijuana was associated with poorer Memory performance. In separate analyses, adolescents in the SUD group had lower scores on Attention, Memory, and Processing Speed composites, and FHP adolescents had poorer Visuospatial Ability.

Conclusions: In combination, these analyses suggest that heavy alcohol use in adolescence leads to reduction in attention and executive functioning and that marijuana use exerts an independent deleterious effect on memory. At the same time, premorbid deficits associated with family history of AUD appeared to be specific to visuospatial ability.

Key Words: Adolescence, Alcohol Abuse, Alcohol Dependence, Alcohol Use Disorder, Marijuana, Neuropsychology, Cognition, Children of Alcoholics.

ADOLESCENCE IS A time of rapid brain development and associated dramatic changes in cognitive functioning. Decision-making ability, social skills, foresight, and abstract reasoning are developing during this period (Yurgelun-Todd, 2007). However, these same domains of executive functioning, attention, and social cognition are precisely those most consistently implicated in chronic alcohol dependence and drug abuse in adults (Chen et al., 2007; Crews and Boettiger, 2009; Fein et al., 2006; Oscar-Berman and Marinkovic, 2007; Oscar-Berman et al., 2004; Uekermann and Daum, 2008). Alcohol and marijuana are common substances of abuse among adolescents. In a recent epidemiologic study, approximately one-fifth of 10th graders and one-quarter of 12th graders were found to have engaged in recent binge drinking (i.e., 5 or more drinks on 1 occasion) and 25% of 10th graders and 32% of 12th graders used marijuana in the prior 12 months (Johnston et al., 2007).

In adolescents who met substance abuse criteria at baseline or another time point during an 8-year longitudinal investigation, alcohol and marijuana use separately predicted decrements in attention scores, and substance withdrawal symptoms predicted deficits in visuospatial performance (Tapert et al., 2002). Furthermore, in alcohol-naïve adolescents who transitioned to either moderate or heavy alcohol use during a 2-year period, greater percentage of drinking days was associated with decline in visuospatial functioning in girls, and greater endorsement of hangover symptoms was linked with poorer attention in boys (Squeglia et al., 2009b). More generally, after controlling for demographic factors, childhood behavior, and adolescent drug use, initiation of binge drinking early in adolescence predicted poor rates of high school completion, prosocial activity involvement,

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and family bonding, while a sharp increase in binge drinking from 13 to 18 independently predicted alcohol abuse or dependence at age 21 (Hill et al., 2000).

A confounding factor in studies of the effect of alcohol and marijuana use on cognition is that adolescents at high risk of developing substance use disorders may also have premorbid cognitive abnormalities. Deficits in visuospatial learning, verbal ability, executive function, and attention are among the liabilities conferred by family history of alcohol dependence (Corral et al., 1999; Garland et al., 1993; Harden and Pihl, 1995; Najam et al., 1997; Nigg et al., 2004, 2006; Ozkaragoz et al., 1997; Poon et al., 2000; Tapert and Brown, 2000). However, specific deficits reported in studies of adolescents with positive family histories are often inconsistent. Lack of agreement in findings may be due in part to differences in sample characteristics, such as density of family alcohol dependence, single-sex inclusion, or psychiatric comorbidity. In addition, many earlier studies either did not assess the alcohol and drug use of high-risk participants themselves (e.g., Najam et al., 1997) or did not account for alcohol and drug use in analyses of cognitive functioning (e.g., Sher et al., 1991). Of note, 2 studies on the effects of adolescent substance use have compared adolescents with alcohol use disorders (AUD) to a non-AUD sample matched on parental alcohol dependence (Brown et al., 2000; Tapert et al., 2002). These studies found that attention (Tapert et al., 2002) and verbal and visual retention (Brown et al., 2000) were impaired in the AUD adolescents relative to the nonabusing, positive family history group.

The primary goal of the current study was to assess the neuropsychological effects of substance use in adolescence. The high concordance of alcohol and marijuana in community samples precluded a "pure" AUD group, and in the current study, marijuana use was included as an additional predictor of neuropsychological functioning. Several recent studies have focused attention on both short-term and long-term cognitive ramifications of marijuana use initiated in adolescence. Reviews of the effects of marijuana on adolescent cognition have highlighted selective decrements in memory, learning, and attention in marijuana-dependent adolescents, even after several weeks of abstinence (Jacobus et al., 2009; Schweinsburg et al., 2008; Squeglia et al., 2009a). Further, some evidence suggests that adult marijuana users who began using marijuana prior to age 17 may be at higher risk of neuropsychological deficits later in life (Pope et al., 2003), making analysis of marijuana frequency and intensity data particularly salient.

Hence, our aim was to evaluate the independent effects of alcohol and marijuana consumption on adolescent neuropsychological functioning. A comprehensive battery of neuropsychological tests was administered to a community sample of adolescent alcohol and marijuana users. To detect neuropsychological abnormality that may be ascribed to familial risk, data were also collected from an additional group consisting of non-SUD adolescents with parental history of AUD. Neuropsychological composite scores were created to represent major neuropsychological domains as follows: Verbal Reasoning, Visuospatial Ability, Memory, Processing Speed, Attention, and Executive Function. Based on the established literature, we hypothesized that alcohol might reasonably be expected to affect any of these domains and that marijuana would exert an independent effect on Memory. Any neuropsychological abnormality identified in the non-SUD, family history positive (FHP) group would be construed as a predisposing factor.

METHODS

Participants

Forty-eight adolescents were recruited in 3 groups. The healthy control (HC) group comprised 15 adolescents with no substance abuse or dependence and no parental history of AUD. The FHP group included 14 adolescents with no substance abuse or dependence and with parental AUD. The 19 adolescents in the SUD group all carried a diagnosis of alcohol abuse ($n = 2$) or dependence ($n = 17$) as determined by the Structured Clinical Interview for DSM-IV, Childhood Diagnoses (KID-SCID; Hien et al., 2004). Twelve participants in the SUD group also met KID-SCID criteria for marijuana dependence.

Most participants were recruited from the community, but a minority of the adolescents with SUD was first contacted by study personnel via communication with their treatment programs. General inclusion criteria were as follows: (i) aged 12 to 18; (ii) ability and willingness to participate in all study components; (iii) functional facility with English language; (iv) either adolescent's ability to provide assent and parent's willingness to provide consent or adolescent's ability to provide consent for participation; (v) no overt physiological markers (e.g., facial characteristics) of fetal alcohol syndrome; (vi) no drinking in the prior 48 hours; (vii) urine sample negative for presence of cocaine, opiates, hallucinogens, barbiturates, benzodiazepines, and amphetamines; (viii) no history of neurological disorder or disease; (ix) no history of head injury with loss of consciousness > 5 minutes; (x) no evidence of psychotic disorder or bipolar disorder, as determined by the KID-SCID; (xi) no diagnosis of mental retardation or learning disability; (xii) no evidence of sensory disorder.

All participants were paid a total of $60 for their participation in this portion of the study. All data were collected under the auspices of the University of New Mexico Institutional Review Board/Human Subjects Research Review Committee. Participants also completed neuroimaging studies, the results of which will be reported separately.

Procedures

Diagnostic Procedures. All diagnostic testing and procedures were performed by research assistants trained by Dr. Thoma or by Roberta Chavez of the University of New Mexico, Center on Alcoholism, Substance Abuse, and Addictions (CASAA), Program Evaluation Service. Diagnoses of substance abuse or dependence were established with the KID-SCID. Consumption data for alcohol and other substances were collected using the Form-90 (Miller and Del Boca, 1994), a time-line follow-back interview in which the participant reports his or her use of alcohol and other substances starting at 90 days preceding the most recent drink (or the current date, if the participant has never drunk) to the present. Drinks per drinking day (DPDD) and percentage days drinking (PDD) were chosen as the alcohol variables of interest to capture both the intensity and frequency of drinking. In addition, percentage days using marijuana (PDM) for the total period of time recorded on the Form-90 was included to represent the frequency of marijuana use. Previous

studies of the effect of marijuana on cognition have pinpointed heaviness of use, chronicity, and age of onset as influential factors (e.g., Pope et al., 2003; Schweinsburg et al., 2008; Villares, 2007). In a teenaged sample, chronicity and age of onset will necessarily show restricted range, thereby limiting their predictive power. Although some investigators have quantified marijuana use with, for example, number of hits or joints, no standard unit of marijuana intake currently exists. Thus, we chose to focus on frequency rather than quantity to index severity of use.

For participants who responded to advertisements seeking adolescents with parental history of AUD, a parent was interviewed using DSM-IV criteria for alcohol abuse and dependence to establish AUD diagnosis.

Neuropsychological Testing Procedures. The neuropsychological test battery included the following: (i) Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999), (ii) Conners' Continuous Performance Test (CPT; Conners, 1994), (iii) Trail Making Test, Parts A and B (Trails A/B; Reitan and Wolfson, 1985), (iv) Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph, 1998), (v) Controlled Oral Word Association Test (COWAT; Benton et al., 1994), (vi) Wisconsin Card Sorting Test (WCST, Computerized Version; Heaton et al., 1993), (vii) Auditory Consonant Trigrams Test (ACT; Spreen and Strauss, 1998), (viii) Delis–Kaplan Executive Function System (D-KEFS) Tower Test (Delis et al., 2001), and (ix) Digit Span subtest from the Weschsler Adult Intelligence Scale-III (Wechsler, 1997).

Neuropsychological Composites. Age-standardized scores were used when available; otherwise, raw scores were used. Neuropsychological composites were constructed along generally accepted cognitive domains as follows: (i) Verbal Reasoning: WASI Vocabulary *t*-score, WASI Similarities *t*-score, RBANS Picture Naming raw score, COWAT FAS raw score, and COWAT Animals raw score; (ii) Visuospatial Ability: WASI Block Design *t*-score, WASI Matrix Reasoning *t*-score, RBANS Line Orientation raw score, and RBANS Figure Copy raw score; (iii) Memory: RBANS List Learning (immediate) raw score, RBANS Story Memory (immediate) raw score, RBANS List Recall (delayed) raw score, RBANS Story Recall (delayed) raw score, and RBANS Figure Recall (delayed) raw score; (iv) Processing Speed: RBANS Coding raw score, Trails A time, and Trails B time; (v) Attention: WAIS Digit Span Forward raw score, WAIS Digit Span Backward raw score, ACT total raw score, CPT omissions raw score, CPT variability raw score, and CPT hit reaction time standard error raw score; (vi) Executive Function: D-KEFS Tower scaled score, WCST perseverative errors raw score, and WCST failures to maintain set raw score. For each composite, individual neuropsychological scores were converted to *z*-scores, reverse-scored where necessary (i.e., so that a higher score was indicative of better performance in all instances) and then averaged.

RESULTS

Table 1 presents demographic characteristics of participants as well as substance use variables of interest. Groups were balanced in terms of sex composition, but the SUD group ($n = 19$) was approximately 2 years older on average than HC ($n = 15$) or FHP ($n = 14$) groups, which closely resembled each other. Because age-adjusted norms were not available for all tests in the neuropsychological battery, age was included as a predictor in MANCOVA analyses.

Total number of standard drinks reported on the Form-90 is also reported to give a sense of the overall level of consumption in the SUD group. One SUD participant reported an implausibly high number of total drinks and DPDD (2440.10 and 56.75, respectively); therefore, his data were winsorized to the maximum of the remainder of his group to avoid the loss of power associated with an erroneous predictor value (Stevens, 2009).

As composites, our dependent variables followed normal distributions, and, with a single exception, skewness and kurtosis values were below ± 2.0. Because our substance abuse predictors demonstrated positive skew and/or a floor effect at zero, these distributions required transformation. Consistent with the prevailing literature (e.g., Project MATCH, 1997), a square root transformation was applied to DPDD, and a square root followed by an arcsine transformation was applied to PDD and PDM (Stevens, 2009). Table 2 shows descriptive statistics of these variables' distributions before and after transformation, and Table 3 gives intercorrelations among

Table 1. Participant Demographics and Substance Use Variables

	HC ($n = 15$)	FHP($n = 14$)	SUD ($n = 19$)
Age[a,b]	14.67 ± 1.95	14.36 ± 1.98	16.58 ± 1.54
Sex	6 m, 9 f	5 m, 9 f	9 m, 10 f
Number of standard drinks in 90 days[a,b]	0.32 ± 1.24	1.30 ± 3.11	538.50 ± 515.96
DPDD[a,b]	0.16 ± 0.62	1.00 ± 2.55	13.12 ± 7.33
PDD[a,b]	0.00 ± 0.00	0.00 ± 0.00	0.37 ± 0.30
PDM[a,b]	0.05 ± 0.17	0.02 ± 0.08	0.41 ± 0.40

HC, healthy control group; FHP, family history positive group; SUD, substance use disorder group; DPDD, drinks per drinking day; PDD, percent days drinking; PDM, percent days using marijuana.
[a]HC ≠ SUD, $p < 0.05$.
[b]FHP ≠ SUD, $p < 0.05$.

Table 2. Skewness and Kurtosis of Substance Abuse Variables Before and After Transformation

	DPDD	PDD	PDM
Skewness before transformation	1.402	1.909	1.747
Skewness after transformation	0.625	1.470	1.593
Kurtosis before transformation	1.029	2.647	1.692
Kurtosis after transformation	−1.117	1.296	1.381

DPDD, drinks per drinking day; PDD, percent days drinking; PDM, percent days using marijuana.

Table 3. Intercorrelations Among Variables Used to Predict Neuropsychological Composites

	Age	DPDD	PDD	PDM
Age	–	0.466** (0.382**)	0.476** (0.422**)	0.332* (0.313*)
DPDD		–	0.754** (0.568**)	0.479** (0.277)
PDD			–	0.636** (0.575**)
PDM				–

Figures in parentheses represent Pearson intercorrelations for untransformed variables.
DPDD, drinks per drinking day; PDD, percent days drinking; PDM, percent days using marijuana.
**$p < 0.01$, *$p < 0.05$.

predictors before and after transformation. Additionally, regression residuals were checked, and systematic violations of the regression assumptions did not appear to be present.

Additional diagnoses of interest in the study of adolescent SUD are noted here. One participant in the HC group and 4 in the SUD group met KID-SCID diagnostic criteria for attention deficit hyperactive disorder (ADHD). The 4 SUD participants with ADHD did not differ significantly from the rest of the SUD group on DPDD, PDD, or PDM (p's > 0.15). One control group member and 10 SUD group members met KID-SCID criteria for conduct disorder. Independent t-tests comparing SUD participants with and without conduct disorder on the 4 predictor variables (age, DPDD, PDD, PDM) and the 6 neuropsychological composites were also performed. None of these tests approached significance (all p's > 0.15).

Prediction of Neuropsychological Composites With Substance Use Variables

A one-way, single-cell MANCOVA was tested with age and the transformed DPDD, PDD, and PDM variables as covariates and the 6 neuropsychological composites as dependent variables. The overall multivariate regression was significant ($F_{24,133.78} = 2.301$, $p = 0.001$) as were the covariates age ($F_{6,38} = 2.637$, $p = 0.031$, partial $\eta^2 = 0.294$), DPDD ($F_{6,38} = 2.544$, $p = 0.036$, partial $\eta^2 = 0.287$), and PDM ($F_{6,38} = 2.844$, $p = 0.022$, partial $\eta^2 = 0.310$).

Univariate follow-up analyses indicated significant regressions for Memory ($F_{4,43} = 4.78$, $p = 0.003$, partial $\eta^2 = 0.308$), Processing Speed ($F_{4,43} = 3.36$, $p = 0.018$, partial $\eta^2 = 0.238$), Executive Function ($F_{4,43} = 2.81$, $p = 0.037$, partial $\eta^2 = 0.207$), and Attention ($F_{4,43} = 2.67$, $p = 0.044$, partial $\eta^2 = 0.200$). Memory performance was positively associated with age ($p = 0.042$) and negatively associated with PDM ($p = 0.004$). Processing Speed performance improved with age ($p = 0.002$). Executive Function ($p = 0.004$) and Attention ($p = 0.006$) were negatively associated with DPDD. (See Fig. 1.) PDD was not a significant predictor of any neuropsychological composite.

When the above MANCOVA was rerun excluding the 5 subjects with ADHD, significance of the overall multivariate regression was lost, although a trend remained ($F_{24,116.33} = 1.55$, $p = 0.065$). DPDD remained a significant covariate ($F_{6,33} = 2.86$, $p = 0.024$). Executive Function retained its univariate significance ($F_{4,38} = 3.33$, $p = 0.020$, partial $\eta^2 = 0.206$) and continued to be negatively associated with DPDD ($p = 0.003$). DPDD continued to show an inverse relationship with Attention as well ($p = 0.015$), although the univariate effect of the regression was nonsignificant.

Excluding only the 2 SUD subjects diagnosed with alcohol abuse as opposed to dependence, the initial pattern of results remained, with the exception that the univariate effect on Attention was reduced to a trend ($F_{4,41} = 2.53$, $p = 0.055$).

Finally, the MANCOVA was modified by the removal of PDM as a covariate and the addition of a between-subjects factor reflecting the presence or absence of marijuana in a urinalysis for all subjects for whom this information was available ($n = 47$; 36 negative, 11 positive). The pattern of results remained largely unchanged, with the overall multivariate regression as well as the univariate regressions for Processing Speed, Executive Function, and Attention showing significance. As expected, the univariate regression on Memory was no longer significant. The multivariate effect of the urinalysis factor was nonsignificant, but the between-subjects univariate effect on Memory was significant ($F_{1,42} = 2.19$, $p = 0.033$), with the marijuana-negative group outperforming the marijuana-positive group. The pattern of association for the remaining covariates on the dependent variables was otherwise unchanged. No subject with a positive urinalysis failed to report the use of marijuana.

Prediction of Neuropsychological Composites With SUD Status

To determine the usefulness of the SUD categorical variable as a predictor of neuropsychological performance, a MANCOVA was run with age as a covariate and SUD status as a between-subjects factor (i.e., collapsing HC and FHP groups into a single "no SUD" group). The overall multivariate regression for age was significant ($F_{6,40} = 3.57$, $p = 0.006$, partial $\eta^2 = 0.348$) as was the effect of age on Verbal Reasoning ($F_{1,45} = 4.12$, $p = 0.046$, partial $\eta^2 = 0.085$) and Processing Speed ($F_{1,45} = 17.84$, $p = 0.000$, partial $\eta^2 = 0.284$), with a trend toward significance for Memory as well ($F_{1,45} = 3.89$, $p = 0.055$, partial $\eta^2 = 0.080$). The

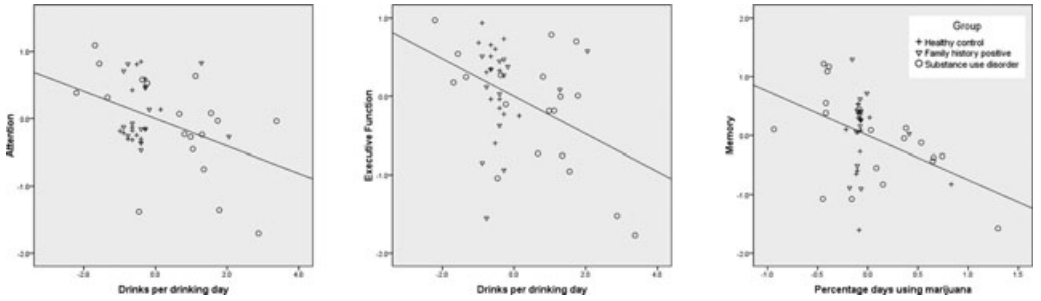

Fig. 1. Scatterplots of unstandardized residuals, regressing out the effects of age and other substance use variables, for relationships between (from left) Attention and Drinks per drinking day, Executive Function and Drinks per drinking day, and Memory and Percentage days using marijuana.

multivariate effect of SUD status was significant ($F_{6,40} = 3.21$, $p = 0.012$, partial $\eta^2 = 0.325$) as was the univariate effect on Memory ($F_{1,45} = 10.00$, $p = 0.003$, partial $\eta^2 = 0.182$), Processing Speed ($F_{1,45} = 4.95$, $p = 0.031$, partial $\eta^2 = 0.099$), and Attention ($F_{1,45} = 4.99$, $p = 0.031$, partial $\eta^2 = 0.100$). Trends toward significance were seen for Visuospatial Ability ($F_{1,45} = 3.30$, $p = 0.076$, partial $\eta^2 = 0.068$) and Executive Function ($F_{1,45} = 3.64$, $p = 0.063$, partial $\eta^2 = 0.075$). The group of participants with no SUD outperformed the SUD group in all cases.

Neuropsychological Performance According to Family History of AUD

A test of the possible contribution of high-risk status to neuropsychological scores was performed on the subset of participants for whom parental AUD status was available (i.e., HC and FHP groups). In a MANCOVA with age as a covariate and parental AUD as a between-subjects factor, the multivariate effect of group membership was significant ($F_{6,21} = 2.80$, $p = 0.037$, partial $\eta^2 = 0.445$), as was the univariate effect of group on Visuospatial Ability ($F_{1,26} = 10.37$, $p = 0.003$, partial $\eta^2 = 0.285$), where the HC group outperformed the FHP group.

DISCUSSION

In this sample of adolescents with and without substance use disorders, poorer Attention and Executive Function were associated with higher intensity of drinking (DPDD), and poorer Memory was associated with higher frequency of marijuana use (PDM). Frequency of drinking (PDD) did not have a significant relationship with any neuropsychological outcome. In a separate analysis, SUD diagnosis predicted Memory, Processing Speed, and Attention. Overall, effect sizes were larger for the model using substance abuse variables rather than group membership to predict neuropsychological outcome.

Deficits in Attention and Executive Function are among the most consistent neuropsychological findings in samples of both adults and adolescents who abuse alcohol (Crews and Boettiger, 2009; Giancola and Moss, 1998). In the current analyses, drinking intensity, but not age or frequency of alcohol or marijuana use, significantly predicted performance on Attention and Executive Function composites. The current results are consistent with those of Tapert and colleagues (2002), who found that adolescents' cumulative alcohol use over an 8-year period predicted attention scores, even after controlling for demographic factors and baseline performance. Moreover, although other studies have reported Executive Function deficits in adolescent substance users (e.g., Giancola et al., 2001), the current study is the first to establish an association between the quantity of alcohol typically consumed on a drinking day and Executive Function.

Two possibilities suggested by this finding are that adolescents with less developed Executive Function tend to drink more intensely and/or that higher quantity of drinks per occasion impairs Executive Function. Consistent with the latter contention, Crews and Boettiger (2009) pointed out that the frontal lobes are the "most insulted region" in adults with alcoholism. Therefore, it may not be surprising that Attention and Executive Function, the neuropsychological domains specifically associated with the frontal lobes (Fuster, 2002; Norman and Shallice, 1986), are most affected by the intensity of adolescent alcohol use. Also consistent with the current results, smaller prefrontal cortical and white matter volumes have been noted in adolescents with AUD compared with control subjects (De Bellis et al., 2005), and binge-pattern drinking specifically affects prefrontally mediated cognitive functions in young adult binge drinkers, particularly in women (Scaife and Duka, 2009).

Studies utilizing rodent models of binge drinking provide corroborating evidence of disruption in normal cognition and neurodevelopment. A predominant paradigm of adolescent drinking is the binge model developed by Crews and colleagues (2000), in which animals are exposed to high doses of alcohol for a single 4-day period. The self-reported consumption of our adolescent sample (11.6 ± 7.6 DPDD for all participants who ever drank; 13.1 ± 7.3 DPDD for participants with SUD) is roughly equivalent on a per-day basis to the toxic dosage administered by Crews and colleagues (2000) in this binge model, if one applies the formula provided by Reagan-Shaw and colleagues (2008) for converting a drug quantity administered in an animal study to its human equivalent dosage. Comparison of brain damage following binge exposure in adolescent and adult rats revealed that the former experienced a greater extent of damage to frontal cortical regions (Crews et al., 2000). Binge-exposed rats performing the Morris Water Maze Task exhibited impaired learning compared to control animals and a perseverative tendency to enter previously trained quadrants (Obernier et al., 2002), roughly consistent with the human results presented here.

Alcohol exposure in adolescent rats has also been linked to long-term behavioral deficits in adulthood. In an intermittent exposure paradigm of adolescent drinking, moderate doses of alcohol were administered for 2 days, with 2 intervening days of no alcohol, for 2 weeks (Pascual et al., 2007, 2009). This pattern of exposure during the adolescent period resulted in increases in inflammatory mediators and cell death in hippocampus, cerebellum, and prefrontal cortex (Pascual et al., 2007). Behavioral deficits on motor coordination and conditional discrimination learning tasks in alcohol-exposed animals persisted into adulthood (Pascual et al., 2007). Enduring alterations in dopaminergic and glutamatergic neurotransmitter systems critical to regulation of reward-seeking behavior were more pronounced in adolescent rats intermittently exposed to alcohol compared to adults (Pascual et al., 2009). In parallel with these changes in brain systems underlying reinforcement, adolescent exposure yielded increases in voluntary alcohol consumption during adulthood (Pascual et al., 2009). A study on chronic, voluntary alcohol intake during adolescence in rats substantiated a link to impaired

decision-making in adulthood, with alcohol-exposed animals displaying a disadvantageous preference for risk in the face of suboptimal returns (Nasrallah et al., 2009).

A significant relationship was also observed between greater frequency of marijuana use and poorer performance on the Memory composite. Including the results of the drug screen did not appreciably change this finding, suggesting that it did not exclusively reflect the effects of recent drug exposure. This finding is consistent with those of Medina and colleagues (2007), in which neuropsychological deficits were found after 1 month of abstinence in adolescent marijuana users, although a broader spectrum of abilities was implicated in that study. Across recent studies, memory difficulties are perhaps the most widely reported and most persistent cognitive deficit associated with extensive marijuana use in adolescents (Schweinsburg et al., 2008). Our results are also consistent with a meta-analysis of studies in adults examining the effects of long-term marijuana use that reported impaired learning and memory, but intact skills in other cognitive domains (Grant et al., 2003).

Contrary to previous studies, an effect of substance abuse on visuospatial functioning was not found. Tapert and colleagues (2002) determined that withdrawal from alcohol and other drugs over an 8-year period accounted for a significant proportion of variance in visuospatial performance, after controlling for baseline performance, quantity of alcohol and drug use, and demographic variables. Another longitudinal study found that adolescent girls who initiated moderate to heavy drinking over a 3-year period manifested a decrement in Visuospatial Ability that was predicted by frequency of drinking (Squeglia et al., 2009b). Absence of comparable relationships between alcohol abuse and visuospatial functioning in our small sample may have been due to lack of power to detect an effect or to the fact that the current study did not quantify withdrawal symptoms as did Tapert and colleagues (2002). It may be helpful for future studies to test a variety of alcohol use variables to compare specificity of effects on neuropsychological variables.

Studies of the effects of alcohol on cognition have often failed to find a direct relationship between measures of alcohol intake and subsequent impairment. DPDD over 90 days preceding the most recent drink may constitute a sensitive alternative to other consumption variables. The DPDD variable provides an index of the severity of the individual's drinking without requiring an estimation of intake over years, for which reliability is unknown. Further, DPDD may be especially relevant to an adolescent population. According to a national survey, approximately one-quarter of 12th graders and one-fifth of 10th graders had engaged in binge drinking (5 or more drinks on 1 occasion) in the past 2 weeks (Johnston et al., 2007). Considering this statistic along with the finding that the typical drinking pattern of adolescents with AUD favors binge drinking over steady-state intoxication (Miller et al., 2007), it is perhaps not surprising that DPDD demonstrated a stronger relationship with cognitive composites than PDD.

In a subanalysis of adolescents without SUD, parental history of AUD was associated with lower scores on tests of Visuospatial Ability. Although neuropsychological deficits in children of alcoholics have been posited by some investigators to be strongly verbal in nature (e.g., Najam et al., 1997), parental history of AUD in non-SUD adolescents was not related to performance across standard tests of verbal ability in this sample of adolescents. Visuospatial deficits in the offspring of alcoholics have been previously reported. For example, Garland and colleagues (1993) reported a main effect of family history on visuospatial learning in adults with a positive family history but without drinking problems. Corral and colleagues (1999) identified deficits in visuospatial ability and attention, but not in executive tasks, in children with high but not low family density of alcohol dependence. One comparison of sons of alcoholic fathers to sons of social drinkers revealed decrements in visuospatial functioning, memory, and attention, but only for the offspring whose fathers were currently drinking and thus presumed to have more severe alcohol dependence (Ozkaragoz et al., 1997).

In hindsight, we regret that this study did not include detailed information on family density of alcohol dependence. In particular, information on parental AUD in the SUD group would have been useful. However, previous studies have reported rates of parental alcohol dependence in adolescents with SUD ranging from 62 to 67% (Brown et al., 2000; Tapert et al., 2002). If those figures are extrapolated to the current sample, SUD and non-SUD adolescents would have roughly equal rates of parental AUD, rendering parental AUD less of a potential confound. Further limitations of this study include low power to detect effects because of small sample size, lack of comprehensive screening for prenatal exposure to alcohol or drugs, and lack of control over other psychiatric comorbidities. These limitations should be kept in mind when attempting to generalize current findings to adolescent SUD or at-risk populations.

The current results reinforce the findings of previous studies in human adolescents, which suggest that the presence of clinically significant binge drinking and marijuana use diverts the course of normal cognitive development. Although longitudinal assessment is necessary to test this proposed relationship rigorously, the current cross-sectional data suggest that abuse of these substances has lingering and independent effects upon cognition. To the extent that learning and honing of executive abilities are primary neurodevelopmental tasks during late adolescence, and given the prevalence of SUD in this population, it may be prudent to invest greater resources in the prevention and treatment of adolescent SUD.

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REFERENCES

Benton AL, Hamsher K, Sivan AB (1994) Multilingual Aphasia Examination. 3rd ed. AJA Associates, Iowa City, IA.

Brown SA, Tapert SF, Granholm E, Delis DC (2000) Neurocognitive functioning of adolescents: effects of protracted alcohol use. Alcohol Clin Exp Res 24:164–171.

Chen AC, Porjesz B, Rangaswamy M, Kamarajan C, Tang Y, Jones KA, Chorlian DB, Stimus AT, Begleiter H (2007) Reduced frontal lobe activity in subjects with high impulsivity and alcoholism. Alcohol Clin Exp Res 31:156–165.

Conners CK (1994) The Conners Continuous Performance Test. Multi-Health Systems, Toronto, Canada.

Corral MM, Holguin SR, Cadaveira F (1999) Neuropsychological characteristics in children of alcoholics: familial density. J Stud Alcohol 60:509–513.

Crews FT, Boettiger CA (2009) Impulsivity, frontal lobes and risk for addiction. Pharmacol Biochem Behav 93:237–247.

Crews FT, Braun CJ, Hoplight B, Switzer RC III, Knapp DJ (2000) Binge ethanol consumption causes differential brain damage in young adolescent rats compared with adult rats. Alcohol Clin Exp Res 24:1712–1723.

De Bellis MD, Narasimhan A, Thatcher DL, Keshavan MS, Soloff P, Clark DB (2005) Prefrontal cortex, thalamus, and cerebellar volumes in adolescents and young adults with adolescent-onset alcohol use disorders and comorbid mental disorders. Alcohol Clin Exp Res 29:1590–1600.

Delis DC, Kaplan E, Kramer J (2001) Delis Kaplan Executive Function System. Psychological Corporation, San Antonio, TX.

Fein G, Torres J, Price LJ, Di Sclafani V (2006) Cognitive performance in long-term abstinent alcoholic individuals. Alcohol Clin Exp Res 30:1538–1544.

Fuster JM (2002) Frontal lobe and cognitive development. J Neurocytol 31:373–385.

Garland MA, Parsons OA, Nixon SJ (1993) Visual-spatial learning in non-alcoholic young adults with and those without a family history of alcoholism. J Stud Alcohol 54:219–224.

Giancola PR, Moss HB (1998) Executive cognitive functioning in alcohol use disorders. Recent Dev Alcohol 14:227–251.

Giancola PR, Shoal GD, Mezzich AC (2001) Constructive thinking, executive functioning, antisocial behavior, and drug use involvement in adolescent females with a substance use disorder. Exp Clin Psychopharmacol 9:215–227.

Grant I, Gonzalez R, Carey CL, Natarajan L, Wolfson T (2003) Non-acute (residual) neurocognitive effects of cannabis use: a meta-analytic study. J Int Neuropsychol Soc 9:679–689.

Harden PW, Pihl RO (1995) Cognitive function, cardiovascular reactivity, and behavior in boys at high risk for alcoholism. J Abnorm Psychol 104:94–103.

Heaton RK, Chelune GJ, Talley JL, Kay GG, Curtiss G (1993) Wisconsin Card Sorting Test Manual: Revised and Expanded. Psychological Assessment Resources, Odessa, FL.

Hien D, Matzner F, First M, Spitzer R, Williams J, Gibbon M (2004) Structured Clinical Interview for DSM-IV Childhood Diagnoses (KID-SCID). Biometrics Research, New York.

Hill KG, White HR, Chung IJ, Hawkins JD, Catalano RF (2000) Early adult outcomes of adolescent binge drinking: person- and variable-centered analyses of binge drinking trajectories. Alcohol Clin Exp Res 24:892–901.

Jacobus J, Bava S, Cohen-Zion M, Mahmood O, Tapert SF (2009) Functional consequences of marijuana use in adolescents. Pharmacol Biochem Behav 92:559–565.

Johnston LD, O'Malley PM, Bachman JG, Schulenberg JE (2007) Monitoring the Future: National Results on Adolescent Drug Use, Overview of Key Findings. National Institute on Drug Abuse, Bethesda, MD.

Medina KL, Hanson KL, Schweinsburg AD, Cohen-Zion M, Nagel BJ, Tapert SF (2007) Neuropsychological functioning in adolescent marijuana users: subtle deficits detectable after a month of abstinence. J Int Neuropsychol Soc 13:807–820.

Miller WR, Del Boca FK (1994) Measurement of drinking behavior using the Form 90 family of instruments. J Stud Alcohol Suppl 12:112–118.

Miller JW, Naimi TS, Brewer RD, Jones SE (2007) Binge drinking and associated health risk behaviors among high school students. Pediatrics 119: 76–85.

Najam N, Tarter RE, Kiriscki L (1997) Language deficits in children at high risk for drug abuse. J Child Adolesc Subst Abuse 6:69–80.

Nasrallah NA, Yang TWH, Bernstein IL (2009) Long-term risk preference and suboptimal decision making following adolescent alcohol use. PNAS 106:17600–17604.

Nigg JT, Glass JM, Wong MM, Poon E, Jester JM, Fitzgerald HE, Puttler LI, Adams KM, Zucker RA (2004) Neuropsychological executive functioning in children at elevated risk for alcoholism: findings in early adolescence. J Abnorm Psychol 113:302–314.

Nigg JT, Wong MM, Martel MM, Jester JM, Puttler LI, Glass JM, Adams KM, Fitzgerald HE, Zucker RA (2006) Poor response inhibition as a predictor of problem drinking and illicit drug use in adolescents at risk for alcoholism and other substance use disorders. J Am Acad Child Adolesc Psychiatry 45:468–475.

Norman DA, Shallice T (1986) Attention to action: willed and automatic control of behavior, in *Consciousness and Self-regulation: Advances in Research and Theory* (Davidson RJ, Swartz GE, Shapiro D eds), pp. 1–18. Plenum, New York.

Obernier JA, White AM, Swartzwelder HS, Crews FT (2002) Cognitive deficits and CNS damage after a 4-day binge ethanol exposure in rats. Pharmacol Biochem Behav 72:521–532.

Oscar-Berman M, Kirkley SM, Gansler DA, Couture A (2004) Comparisons of Korsakoff and non-Korsakoff alcoholics on neuropsychological tests of prefrontal brain functioning. Alcohol Clin Exp Res 28:667–675.

Oscar-Berman M, Marinkovic K (2007) Alcohol: effects on neurobehavioral functions and the brain. Neuropsychol Rev 17:239–257.

Ozkaragoz T, Satz P, Noble EP (1997) Neuropsychological functioning in sons of active alcoholic, recovering alcoholic, and social drinking fathers. Alcohol 14:31–37.

Pascual M, Blanco AM, Cauli O, Minarro J, Guerri C (2007) Intermittent ethanol exposure induces inflammatory brain damage and causes long-term behavioural alterations in adolescent rats. Eur J Neurosci 25:541–550.

Pascual M, Boix J, Felipo V, Guerri C (2009) Repeated alcohol administration during adolescence causes changes in the mesolimbic dopaminergic and glutamatergic systems and promotes alcohol intake in the adult rat. J Neurochem 108:920–931.

Poon E, Ellis DA, Fitzgerald HE, Zucker RA (2000) Intellectual, cognitive, and academic performance among sons of alcoholics, during the early school years: differences related to subtypes of familial alcoholism. Alcohol Clin Exp Res 24:1020–1027.

Pope HG Jr, Gruber AJ, Hudson JI, Cohane G, Huestis MA, Yurgelun-Todd D (2003) Early-onset cannabis use and cognitive deficits: what is the nature of the association? Drug Alcohol Depend 69:303–310.

Project MATCH Research Group (1997) Matching Alcoholism Treatments to Client Heterogeneity: Project MATCH posttreatment drinking outcomes. J Stud Alcohol 58:7–29.

Randolph C (1998) Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). Psychological Corporation, San Antonio, TX.

Reagan-Shaw S, Nihal M, Ahmad N (2008) Dose translation from animal to human studies revisited. FASEB J 22:659–661.

Reitan RM, Wolfson D (1985) The Halstead-Reitan Neuropsychological Test Battery. Neuropsychology Press, Tucson, AZ.

Scaife JC, Duka T (2009) Behavioural measures of frontal lobe function in a population of young social drinkers with binge drinking pattern. Pharmacol Biochem Behav 93:354–362.

Schweinsburg AD, Brown SA, Tapert SF (2008) The influence of marijuana use on neurocognitive functioning in adolescents. Curr Drug Abuse Rev 1:99–111.

Sher KJ, Walitzer KS, Wood PK, Brent EE (1991) Characteristics of children of alcoholics: putative risk factors, substance use and abuse, and psychopathology. J Abnorm Psychol 100:427–448.

Spreen O, Strauss E (1998) A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary. Oxford University Press, NY.

Squeglia LM, Jacobus J, Tapert SF (2009a) The influence of substance use on adolescent brain development. Clin EEG Neurosci 40:31–38.

Squeglia LM, Spadoni AD, Infante MA, Myers MG, Tapert SF (2009b) Initiating moderate to heavy alcohol use predicts changes in neuropsychological functioning for adolescent girls and boys. Psychol Addict Behav 23:715–722.

Stevens JP (2009) Applied Multivariate Statistics for the Social Sciences. 5th ed. Routledge, New York.

Tapert SF, Brown SA (2000) Substance dependence, family history of alcohol dependence and neuropsychological functioning in adolescence. Addiction 95:1043–1053.

Tapert SF, Granholm E, Leedy NG, Brown SA (2002) Substance use and withdrawal: neuropsychological functioning over 8 years in youth. J Int Neuropsychol Soc 8:873–883.

Uekermann J, Daum I (2008) Social cognition in alcoholism: a link to prefrontal cortex dysfunction? Addiction 103:726–735.

Villares J (2007) Chronic use of marijuana decreases cannabinoid receptor binding and mRNA expression in the human brain. Neuroscience 145:323–334.

Wechsler D (1997) Wechsler Adult Intelligence Scale, 3rd ed. Psychological Corporation, San Antonio, TX.

Wechsler D (1999) Wechsler Abbreviated Scale of Intelligence Manual. Psychological Corporation, San Antonio, TX.

Yurgelun-Todd D (2007) Emotional and cognitive changes during adolescence. Curr Opin Neurobiol 17:251–257.