

Effects of reward sensitivity and regional brain volumes on substance use initiation in adolescence

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This longitudinal study examines associations between baseline individual differences and developmental changes in reward [i.e. behavioral approach system (BAS)] sensitivity and relevant brain structures' volumes to prospective substance use initiation during adolescence. A community sample of adolescents ages 15–18 with no prior substance use was assessed for substance use initiation (i.e. initiation of regular alcohol use and/or any use of other substances) during a 2-year follow-up period and for alcohol use frequency in the last year of the follow-up. Longitudinal 'increases' in BAS sensitivity were associated with substance use initiation and increased alcohol use frequency during the follow-up. Moreover, adolescents with smaller left nucleus accumbens at baseline were more likely to initiate substance use during the follow-up period. This study provides support for the link between developmental increases in reward sensitivity and substance use initiation in adolescence. The study also emphasizes the potential importance of individual differences in volumes of subcortical regions and their structural development for substance use initiation during adolescence.

Keywords: adolescence; behavioral approach system (BAS); reward sensitivity; substance use initiation

INTRODUCTION

Adolescence is characterized by increased substance use (Eaton *et al.*, 2006) and risk for related disorders (Kessler *et al.*, 2005). Approximately 18% of eighth graders and 55% of 12th graders report ever being drunk; use of illicit drugs is also common (Johnston *et al.*, 2009). Adolescent substance use is linked to suicidal ideation (Windle *et al.*, 1992), sexual risk-taking (Hingson *et al.*, 2003) and later substance dependence (King and Chassin, 2007). We have suggested that adolescents experience an increased sensitivity of the behavioral-activation/approach system (BAS: Fowles, 1987; Gray, 1991; Depue and Collins, 1999) that mediates approach to rewards (Luciana *et al.*, 2012; Urošević *et al.*, 2012), including substances of abuse. Longitudinal studies are needed to clarify whether developmental increases, *vs* stable individual difference factors, in reward sensitivity and its neural substrates, predict adolescents' substance use initiation. This study addresses this question.

Studies support adolescents' reward hypersensitivity. Adolescents show stronger effects of monetary incentives on cognitive task performance (Jazbec *et al.*, 2006; Hardin *et al.*, 2007) and increased positive affect (Ernst *et al.*, 2005) relative to adults. They are relatively more sensitive to positive feedback (Cauffman *et al.*, 2010). In functional magnetic resonance imaging (fMRI) paradigms, adolescents exhibit greater ventral striatal/nucleus accumbens (Nacc) activity in response to rewards compared with other ages (Ernst *et al.*, 2005; Galvan *et al.*, 2006; Cohen *et al.*, 2010; Somerville *et al.*, 2011 but see Bjork *et al.*, 2004, 2010). During risk-taking, adolescents' ventral striatal activity is greater when peers are present, suggesting that social context serves as a potent source of reward (Chein *et al.*, 2011). The BAS system that underlies reward sensitivity is facilitated by dopamine (DA)

projections from the ventral tegmental area to Nacc and dorsal striatum, as well as the amygdala and prefrontal cortex (Depue and Collins, 1999; Wahlstrom *et al.*, 2010). This DA-modulated network is implicated in adolescent brain development (Ernst *et al.*, 2006b; Wahlstrom *et al.*, 2010) and it contributes to rewarding aspects of abused substances (Koob and Volkow, 2010). Thus, increased reward sensitivity and associated Nacc activity may promote adolescent substance use (Galvan *et al.*, 2006).

In a recent longitudinal study, self-reported reward/BAS sensitivity peaked from early to late adolescence and declined thereafter, a pattern also observed for Nacc volumes (Urošević *et al.*, 2012). Individuals with greater Nacc and medial orbitofrontal cortex (OFC) volumes at baseline exhibited greater longitudinal increases in self-reported BAS. This pattern was not found for threat [behavioral inhibition system (BIS)] sensitivity (Urošević *et al.*, 2012).

Cross-sectional studies link BAS hypersensitivity to substance misuse (e.g. Franken and Muris, 2006). In adults, BAS hypersensitivity predicts substance use disorders (Johnson *et al.*, 2003), heightened craving responses to conditioned substance-related cues (Kambooropoulos and Staiger, 2001, 2004) and cravings for alcohol among residential patients (Franken, 2002). In a large adolescent sample, increased BAS sensitivity predicted a composite measure that combined frequency and onset age of substance use (Knyazev *et al.*, 2004). Similarly, BAS hypersensitivity is linked to alcohol abuse in adolescent females (Loxton and Dawe, 2001). The relationship between BAS hypersensitivity and substance use remains significant when controlling for extraversion, neuroticism and psychoticism (Knyazev, 2004; Knyazev *et al.*, 2004).

Links between BAS hypersensitivity and substance use are also evident in individuals transitioning from adolescence into young adulthood. In undergraduates, BAS hypersensitivity predicts alcohol and tobacco use (O'Connor *et al.*, 2009), infrequent, impairing heavy alcohol use (O'Connor and Colder, 2005), illicit drug use (Simons *et al.*, 2008) and lifetime number of substances used (Franken and Muris, 2006). These associations may be moderated by working memory and inhibitory control (Patrick *et al.*, 2008).

Most of the above cross-sectional studies of links between BAS hypersensitivity and substance use rely on the BIS/BAS scales'

Received 25 March 2013; Revised 14 January 2014; Accepted 10 February 2014
Advance Access publication 12 February 2014

Data collection and analysis were supported by National Institute on Drug Abuse Grant R01 DA 017843 and National Institute of Alcohol Abuse and Alcoholism grant AA020033 to M.L. S.U.'s work on the manuscript was supported by National Institute of Mental Health Grants T32 MH 017069 and K01 MH 093621. This work was also supported by BTRC grants awarded to the CMRR, P41 RR008079, P41 EB015894 and 1P30 NS076408, and the University of Minnesota's Supercomputing Institute and Center for Neurobehavioral Development.

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(Carver and White, 1994) assessment of BAS/reward sensitivity. The BIS/BAS scores correlate with electroencephalography (EEG) indices of approach and withdrawal (Harmon-Jones and Allen, 1997; Sutton and Davidson, 1997), responses to reward and punishment (Carver and White, 1994) and clinical symptomatology (Meyer *et al.*, 2001; Alloy *et al.*, 2006). Twin data suggest a moderate genetic effect on variance in BIS/BAS scores (Takahashi *et al.*, 2007).

There are no longitudinal studies examining effects of reward sensitivity on substance use and no studies of associations with substance use 'initiation'. Cross-sectional approaches cannot determine whether it is the normative 'increase' in reward sensitivity during adolescence that predicts substance use, or whether individuals with reward hypersensitivity exhibit greater substance use regardless of developmental stage. The few existing longitudinal studies on prospective risk factors of substance use initiation have examined other predictors, such as aggression and impulsivity (Ernst *et al.*, 2006a). Another longitudinal study failed to find a significant relationship between preferences for high risk/high reward task choices and substance use initiation in a mixed sample of adolescents with and without psychopathology (Ernst *et al.*, 2010). Longitudinal studies focusing on reward sensitivity as a predictor of substance use initiation in otherwise healthy adolescents are needed.

Similarly, little research has examined individual differences in brain structures involved in reward processing and their associations with adolescent substance use. Cheetham *et al.* (2012) found individual differences in OFC, but not amygdala, hippocampus, or anterior cingulate volumes to predict prospective cannabis use initiation. Whether these associations extend to other substances or other brain regions is unknown.

Based on the prior studies described earlier, we hypothesize that both baseline individual differences and 'longitudinal increases' in reward/BAS sensitivity will predict prospective substance use initiation and alcohol use frequency in adolescents. Furthermore, we predict that baseline individual differences in volumes of brain structures relevant for reward processing (i.e. Nacc and medial OFC) will predict prospective substance use initiation and alcohol use frequency. Longitudinal changes in these structures' volumes have been observed in the course of typical adolescent development, coincident with similar changes in BAS sensitivity (Urošević *et al.*, 2012). Thus, we hypothesize that longitudinal increases in Nacc volumes will predict substance use initiation and frequency of use. Finally, we will determine the specificity of reward sensitivity and relevant brain structures volumes' effects by also examining threat (BIS) sensitivity as well as amygdala and lateral OFC volumes. The BIS responds to threat/punishment and inhibits approach in situations of risk/reward conflict (Gray and McNaughton, 2000).

METHOD

Participants

The sample is part of a larger longitudinal study of normative adolescent brain development (see below). This report focuses on adolescents [15- to 18-year-old at Time 1 (T1)] who completed two data collection waves with a mean follow-up interval of 2.25 ± 0.34 years. This baseline age range was targeted, because substance use initiation is common between ages 15 and 20 (Eaton *et al.*, 2006). At T1, minor participants were recruited through a University-sponsored database of metro community families that agreed, at their child's birth, to be contacted about research participation or by postcards mailed to the University's non-academic employees. Adult participants were recruited through flyers and mass mailings.

At T1, eligibility was determined with a phone screening and in-person clinical interview (Kaufman *et al.*, 1996). Exclusions included histories of neurological or Diagnostic and Statistical Manual of

Mental Disorders, 4th edition Text Revision, (DSM-IV-TR) Axis I disorders (including substance use disorders), birth complications, loss of consciousness, learning disabilities, psychoactive medication use, non-native English speaking, uncorrected vision/hearing, non-right-handedness (Oldfield, 1971) and MRI contraindications. More stringent exclusion criteria for the present analyses included endorsement of any substance use screens in the clinical interview at T1. That is, participants were substance naïve at T1.

This procedure yielded 34 participants (15 female, 19 male) aged 15.33–18.94 years at T1 ($M = 16.88$, $s.d. = 1.19$) and from 17.22 to 21.95 years at Time 2 (T2) ($M = 19.13$, $s.d. = 1.30$). Participants self-identified predominantly as Caucasian (97.1%) and Asian/Pacific Islander (2.9%), overall consistent with Minnesota's demographics (2010 US Census, published by the U.S. Census Bureau: <http://factfinder.census.gov>). Socio-economic status (SES) was determined by participants' parental education and occupation (A.B. Hollingshead, unpublished data), yielding a mean SES of 52.29 ($s.d. = 10.07$) and a range from 17 to 66, largely representing middle to upper-middle SES.

Procedure

At T1 and T2, participants completed diagnostic and demographics interviews, questionnaires, behavioral tasks and structural brain imaging (see Olson *et al.*, 2007, 2009; Muetzel *et al.*, 2008; Luciana *et al.*, 2009; Porter *et al.*, 2011; Schissel *et al.*, 2011; Urošević *et al.*, 2012). The present analyses focus on measures of age, sex, IQ as measured by Matrix Reasoning and Vocabulary subtests (Wechsler Abbreviated Scale of Intelligence: Wechsler, 1999), reward and threat sensitivities as measured by the BIS/BAS scales, interview and questionnaire assessments of substance use, and structural MRI data. Participants received monetary compensation. Prior to data collection, consistent with the Declaration of Helsinki, minors provided written assent; parents/legal guardians and adult participants provided written consent. The local Institutional Review Board approved the protocol.

Measures

Magnetic resonance imaging

Volumetric measures were derived for the left and right hemisphere in the following regions of interest (ROIs): lateral OFC, medial OFC, amygdala, and Nacc at T1 and T2. MRI images were acquired on a 3 Tesla Siemens Trio (Siemens Medical Systems, Erlangen, Germany) at the University of Minnesota's Center for Magnetic Resonance Research. Three-dimensional images were obtained with a coronal T1-weighted magnetization prepared rapid gradient echo sequence (repetition time (TR) = 2530 ms, echo time (TE) = 3.65 ms, inversion time (TI) = 1100 ms, 240 slices, voxel size = 1.0 mm × 1.0 mm × 1.0 mm, flip angle = 7°, field of view (FOV) = 256 mm).

Cortical and subcortical volume estimates were obtained by processing the high-resolution anatomical images in the FreeSurfer v.4.5.0 image analysis suite (<http://surfer.nmr.mgh.harvard.edu/>). During T2 data collection, the 3 T system was upgraded to a Siemens TIM Trio. To minimize upgrade-related variability, T1-weighted images were corrected for distortions resulting from gradient nonlinearity (Jovicich *et al.*, 2006) before processing. After this correction, the standard FreeSurfer's longitudinal data processing pipeline was followed (<http://surfer.nmr.mgh.harvard.edu/fswiki/LongitudinalProcessing>; Fischl *et al.*, 2002; Reuter *et al.*, 2010, 2012; see Supplementary Data).

Reward and threat sensitivities

Reward/BAS and threat/BIS sensitivities were assessed by the BIS/BAS scales (Carver and White, 1994), with BAS Reward Responsiveness, BAS Drive, BAS Fun Seeking, and BAS Total assessing reward sensitivity and the BIS scale assessing threat sensitivity. The same

four-factor structure characterizes adolescent and adult samples. Thus, the measure yields comparable indices across development (Cooper et al., 2007) (see [Supplementary Data](#) for additional information).

Substance use measures

At T1 and T2, participants completed the Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version (K-SADS-PL) semi-structured diagnostic interview (Kaufman et al., 1996), including all substance use screen questions. For minors, a parent simultaneously completed the interview (reporting on the participant) with a different interviewer. Consensus ratings for each interview item were derived.

At T1, due to exclusion criteria, no participants endorsed any substance use screens. This lack of endorsement at T1 indicated lifetime absence of tobacco and illicit substances use. The K-SADS-PL alcohol screen requires two alcoholic beverages per week on four occasions for endorsement. No participant endorsed this level of alcohol use at T1. Participants endorsed either never having a whole alcoholic beverage (84.9%) or consuming minimal amounts of alcohol at family functions, such as a holiday celebration or wedding (15.1%).

At T2, participants completed age-appropriate versions of the Personal Experiences Inventory (PEI; Winters, 1999; Winters et al., 2004), which assess substance use severity and use-related motivations. 'Alcohol use frequency' at T2 was assessed by one item [How many times have you had alcoholic beverages (including beer, wine and liquor) to drink during the last 12 months?]. Ratings across versions were coded into a common scale of alcohol use frequency for the last 12 months: 0 (never), 1 (1–5 times), 2 (6–20 times), 3 (21–49 times) and 4 (50+ times). This variable was square-root transformed for subsequent analyses.

At T2, K-SADS-PL screen questions assessed whether participants used tobacco, alcohol or illicit substances (i.e. cannabis, stimulants, cocaine, barbiturates/anxiolytics/narcotics, opioids, phencyclidine (PCP), hallucinogens, inhalants or other substances) during the follow-up. Participants were rated using a binary variable of 'clinical-level substance use initiation' with scores of '1' indicating positive responses to any K-SADS-PL substance use screen item and scores of '0' indicating no substance use initiation. The K-SADS-PL's alcohol screen required two alcoholic beverages per week on four occasions for endorsement, whereas the screens for other substances are less stringent and required any use (i.e. once or more) during the follow-up for endorsement. Lack of K-SADS-PL-determined clinical-level alcohol use initiation at T2 did not preclude subclinical levels of alcohol use during the follow-up as captured by the PEI (e.g. a participant could have one drink per week on multiple occasions and still be considered subthreshold by the K-SADS-PL assessment).

Statistical analyses

Effects of age, sex, IQ, SES and follow-up interval length on clinical-level substance use initiation and alcohol use frequency at T2 were examined first by calculating bivariate correlations and binary logistic regressions to determine which variables were significantly associated with outcomes. There were no significant effects of sex or IQ. Older age, Wald's $\chi^2(1) = 4.53$, $P = 0.033$, OR = 2.04, 95% CI = 1.06–3.92 significantly predicted clinical-level substance use initiation. Lower SES marginally predicted clinical-level substance use initiation, Wald's $\chi^2(1) = 2.81$, $P = 0.094$, OR = 0.93, 95% CI = 0.86–1.01. Older age, $r = 0.43$, $P = 0.012$, and longer follow-up length, $r = 0.39$, $P = 0.025$, significantly predicted greater alcohol use frequency at T2. There were no significant correlations between age, SES and follow-up interval length. All subsequent analyses controlled for age, SES and follow-up interval length, and when appropriate, total brain volumes

and scanner upgrade. Covariates were kept constant across all analyses to enhance interpretability and comparability of findings in relation to the two outcome variables of interest. [Table 1](#) provides a summary of all covariates and predictors, as well as outcome variables, for binary logistic and hierarchical regression analyses.

Binary logistic regressions examined effects of individual differences (i.e. baseline measures) and developmental changes (i.e. residual change) in the BIS/BAS scales and ROI brain volumes on prospective clinical-level substance use initiation. Age, follow-up interval and SES were covariates with a dichotomous outcome variable (1/0) of substance use initiation. Similar hierarchical regressions were conducted with age, follow-up interval and SES as covariates and a continuous outcome variable of alcohol use frequency during the last 12 months at T2.

The developmental/longitudinal changes in predictors were indexed by unstandardized residuals from each T2 predictor regression on its T1 value. In regression analyses involving brain ROI variables, left and right hemisphere estimates for each ROI were entered together, yielding four regression models (i.e. one per ROI), in analyses of baseline ROI individual differences' effects and four regressions (i.e. one per ROI) in analyses of developmental changes in ROI volumes' effects. [Table 1](#) and the [Supplementary Data](#) summarize relevant regression models.

RESULTS

Descriptive analyses

[Table 2](#) includes means and standard deviations of the BIS/BAS scales and brain ROI volumes at T1 and T2. The BIS/BAS scales at T1 and T2 were examined for associations with ROI brain volumes at each relevant time point. There were no significant associations at T1, except for a trend between BAS Drive and right Nacc volume, $r = 0.29$, $P = 0.096$. At T2, BAS Reward Responsiveness was significantly related to left medial OFC volume, $r = 0.37$, $P = 0.03$, and at a trend-level to right lateral OFC volume, $r = 0.34$, $P = 0.051$. T2 BIS was also related to left medial OFC volume, $r = 0.44$, $P = 0.009$ and inversely related to left Nacc volume, $r = -0.37$, $P = 0.032$. No other associations between the BIS/BAS scales and ROI volumes at T2 were significant.

Based on the T2 K-SADS, [Table 3](#) describes substance use for 14 participants (41.2%) who initiated clinical-level use of 1–3 substances ($M = 1.50$, $s.d. = 0.65$; median = 1.00) during the follow-up interval. Two of these met alcohol abuse criteria, in partial remission, at T2. Based on the T2 PEI-item assessment of alcohol use frequency, an additional 11 (32.4%) participants reported drinking 1–5 times and one participant (2.9%) 6–20 times in the last year of the follow-up, but did not meet the K-SADS criteria for clinically significant use initiation. Finally, eight (23.5%) participants reported no substance use during the follow-up.

Baseline predictors of T2 alcohol use frequency

There were no significant effects of BIS/BAS scores at T1 on T2 alcohol use frequency. In hierarchical regression analyses of the baseline ROI volumes' effects on prospective alcohol use frequency, there were no significant effects.

Developmental predictors of T2 alcohol use frequency

In five hierarchical regressions examining effects of developmental changes in the BIS/BAS scales' scores from T1 to T2 on prospective alcohol use frequency, there were significant effects for increases in BAS Total, partial $r = 0.40$, $t = 2.32$, $P = 0.028$, and BAS Drive, partial $r = 0.39$, $t = 2.25$, $P = 0.032$, after controlling for age, SES and follow-up interval significant effects (covariates' Step 1 $R^2 = 0.31$, $P = 0.010$). There were no other significant BIS/BAS effects.

Table 1 Statistical analytic approach for predicting prospective substance use

Regression analyses' predictors of substance use ^a				
Regression step	Regression model/analyses			
	Individual difference in the BIS/BAS	Individual differences in ROI volumes	Developmental change in the BIS/BAS	Developmental change in the ROI volumes
1	Age, SES, follow-up length	Age, SES, follow-up length, total brain volume ^b	Age, SES, follow-up length	Age, SES, follow-up length
2	BIS/BAS subscale score at T1	L and R ROI volumes at T1	Unstandardized Residual for BIS/BAS T2 score ^c	Unstandardized Residuals for L and R ROI volumes at T2 ^d

^aThere were two types of outcome variables for two different types of regressions: a binary clinical-level substance use initiation (yes/no) in binary logistic regression analyses and continuous alcohol use frequency in hierarchical regression analyses; however, the set and order of predictors were the same in both regressions types. ^bAs recommended by the FreeSurfer group, the 'brainsegnonvent' variable yielded by standard processing was used as a measure of total brain volume excluding the ventricles. ^cRegressions with the relevant BAS or BIS subscale at T1 predicting the same subscale at T2 yielded these unstandardized residual scores. ^dRegressions with relevant ROI volume at T1 predicting the same ROI volume at T2, controlling for total brain volume and scanner upgrade, yielded these unstandardized residuals.

Table 2 Means and standard deviations for BIS/BAS scales and ROI brain volumes

Measures	T1	T2
BAS Total	38.76 (4.83)	39.21 (4.46)
BAS Drive	10.12 (2.10)	10.35 (2.21)
BAS Fun Seeking	11.35 (2.17)	11.62 (2.03)
BAS Reward Responsiveness	17.29 (1.78)	17.24 (2.06)
BIS scale	20.32 (3.29)	20.03 (3.55)
R amygdala	1733.50 (188.98)	1724.71 (193.03)
L amygdala	1567.68 (143.47)	1575.15 (144.98)
R Nacc	720.79 (104.60)	715.85 (104.27)
L Nacc	716.50 (111.90)	686.44 (110.14)
R medial OFC	5733.44 (737.34)	5501.32 (652.63)
L medial OFC	5448.50 (888.36)	5235.47 (829.33)
R lateral OFC	8879.74 (1111.70)	8510.26 (867.63)
L lateral OFC	9012.74 (836.73)	8678.35 (805.09)

L, left hemisphere; R, right hemisphere. All brain volumes are presented in mm³ and not corrected for total brain volume, but in all reported statistical analyses, total brain volume is controlled.

When developmental changes in structural brain ROIs' volumes from T1 to T2 on alcohol use frequency during the follow-up were similarly examined, there were no significant effects.

Baseline predictors of clinical-level substance use initiation during the follow-up

When individual differences in T1 (baseline) BIS/BAS were examined, there were no significant effects of the BIS/BAS scales on clinical-level substance use initiation.

In binary logistic regressions examining effects of ROIs' volumes at T1 on prospective substance use initiation, there was a significant effect for the left Nacc, Wald's $\chi^2(1) = 4.13$, $P = 0.042$, OR = 0.985, 95% CI = 0.971–0.999, after controlling for age, SES and total brain volume. This effect remained after potential influential cases and an outlier were excluded from the analyses (see [Supplementary Data](#)).

To address the specificity of this effect within the striatum, *post hoc* analyses were conducted to examine whether baseline volumes of the caudate, putamen and pallidum were similarly associated with prospective substance use initiation. There were no significant effects.

Developmental predictors of T2 clinical-level substance use initiation

In five logistic regressions examining effects of developmental changes in the BIS/BAS scale scores from T1 to T2 on prospective substance use

initiation, there was a significant effect for increases in BAS Total, Wald's $\chi^2(1) = 3.88$, $P = 0.049$, OR = 1.34, 95% CI = 1.002–1.789 and increases in BAS Reward Responsiveness, Wald's $\chi^2(1) = 4.20$, $P = 0.040$, OR = 2.59, 95% CI = 1.043–6.435, controlling for the covariates. Again, these significant effects remained after potential influential cases and outliers were excluded from analyses (see [Supplementary Data](#)). Other effects were not significant.

When effects of the changes in ROI volumes from T1 to T2 on prospective substance use initiation were similarly examined, there were no significant effects.

DISCUSSION

Substance misuse is a significant public health problem in the United States and other regions. When substances (e.g. alcohol) are introduced during periods of rapid neural development (e.g. the prenatal period), negative consequences are evident (Streissguth *et al.*, 1980). Whether similar consequences are evident during periods of more subtle brain development, such as adolescence, is an active area of investigation (for reviews, see Elofson *et al.*, 2013; Jacobus and Tapert, 2013). An interpretive dilemma in discerning the behavioral and neural impacts of adolescent substance use is that premorbid vulnerabilities cannot be reliably distinguished from the direct effects of substances. This is largely due to most existing studies either not involving adolescents who were free of substance use at baseline or not following adolescents from periods of no use into active substance use initiation. This study is unique in that the prospective predictors and subsequent impacts of substance use initiation can both be examined.

Using a theoretically guided analytic strategy, we found evidence of baseline vulnerabilities for substance use initiation during adolescence. Individuals in the mid-adolescent period who were most likely to initiate substance use were identified prior to the use initiation on the basis of their premorbid Nacc volumes. Adolescents who initiated clinical-level of substance use exhibited significantly smaller Nacc volumes at baseline, after controlling for potential confounds, compared with their peers. At baseline, participants were ages 15–18, a period associated with peak levels of Nacc volume, followed by a decrease from age 18 into early 20s in our larger longitudinal study (Urošević *et al.*, 2012). Based on the present findings, adolescents aged 15–18 with non-optimal timing of these normative Nacc volume changes may be at increased risk for substance use. In other words, adolescent who are either lagging (i.e. not reaching peak) or accelerating (i.e. already peaked and moving into pruning usually seen into early 20s), compared with their peers, may be more likely to initiate clinical-levels of substance use.

Table 3 Adolescents with substance use initiation during the 2-year follow-up

	Sex	Ages T1, T2	K-SADS-PL assessment				PEI assessment ^a	
			Alcohol use frequency	Maximum alcohol quantity in 24 h	Tobacco use frequency	Cannabis use frequency	Other drug use frequency	Alcohol use in last 12 months
1	M	17.63, 19.96	2–3×/month	12–13 beers	—	—	—	6–20×
2	M	17.71, 19.92	1×/semester	3 beers	—	—	—	1–5×
3	M	17.51, 19.67	1×/week	0.5 l of 80-proof vodka	<10 cigarettes ever	6×/summer	—	21–49×
4	M	15.70, 17.97	1×/3 months	6–8 drinks	—	—	—	1–5×
5	M	18.59, 21.95	1×/week	6 beers	—	>10× ever	—	21–49×
6	M	18.94, 20.88	1×/week	5 drinks	—	—	—	≥50×
7	F	18.55, 20.96	1×/week	4 drinks	—	—	—	6–20×
8	F	15.63, 17.59	4–5× ever	3–4 drinks	—	—	1× ever, inhaler	1–5×
9	F	16.49, 19.07	<1×/month	3 drinks	—	—	—	6–20×
10	M	17.76, 19.79	1×/2–3 weeks	8 shots	—	1× ever	—	6–20×
11	M	18.20, 20.77	1×/week	2/3 of rum bottle	—	2× ever	—	≥50×
12	F	17.70, 20.10	1×/month	5–6 drinks	—	5× ever	—	6–20×
13	M	17.69, 20.02	1×/2 weeks	75-proof whiskey ^b	—	—	—	≥50×
14	F	15.76, 17.93	(2× ever) ^c	4 drinks	—	1× ever	—	6–20×

M, male; F, female. ^aK-SADS-PL assessed for frequency of use for any period of time that a participant drank alcohol, whereas the PEI item assessed frequency of alcohol use for the last 12 months; given this and other differences in assessment, it is important to report both frequencies. ^bThis participant was not certain of the exact amount of whiskey consumed, but medical attention was required. ^cThis participant did not meet the K-SADS-PL alcohol screen criteria due to drinking two drinks in a week on only two occasions.

In another longitudinal study of adolescents ages 11–13, left Nacc volumes exhibited similar increases during a 3- to 4-year follow-up (Dennison *et al.*, 2013). Other recent studies have reported different developmental trajectories for Nacc volumes, such as decreases with greater pubertal development compared with peers (Goddings *et al.*, 2014) and mean annual decreases in Nacc volumes from ages 8 to 22 (Tamnes *et al.*, 2013). These longitudinal studies differ on a number of methodological issues, such as use of 3 T MRI scanners and modeling of hemisphere-specific trajectories (Urošević *et al.*, 2012; Dennison *et al.*, 2013) vs reliance on 1.5 T MRI scanners and averages of volumes between hemispheres (Tamnes *et al.*, 2013; Goddings *et al.*, 2014) and statistical approaches to modeling age effects. Differences in samples' age ranges may also influence results when modeling developmental age effects (Fjell *et al.*, 2010). Furthermore, Goddings *et al.*' (2014) findings of pubertal effects on Nacc volumes suggest a complex set of influences on developmental changes. Findings might be clarified in future longitudinal studies by modeling the full range of adolescence, hemisphere-specific trajectories, and the effects of both pubertal development and chronological age. These discrepancies regarding the nature of typical developmental changes in Nacc volumes during adolescence do not detract from the potential significance of the present finding that adolescents with smaller Nacc volumes at ages 15–18 are at greater risk for substance use initiation.

Possible explanations for the association of smaller baseline Nacc volumes and prospective substance use initiation in adolescence require consideration of the larger neural circuitry involving the Nacc. The Nacc is part of a broad network that promotes approach toward potential sources of rewards and engagement with positively reinforcing stimuli once they are encountered (Koob and Volkow, 2010). Through its efferent connections with the ventral pallidum, which further relays information through the thalamus to the prefrontal cortex and back to the striatum, the Nacc is positioned to facilitate the translation of approach motivation to behavioral action (Depue and Collins, 1999). Afferents from the medial prefrontal cortex, insula, extended amygdala, hippocampus and ventral tegmental area modulate neuronal responses to rewarding stimuli within the Nacc. Together, these afferent and efferent pathways serve to guide reward-related motivations and behaviors. In particular, interconnections between the ventral striatum and prefrontal cortex enable a cost–benefit

analysis that weighs a potential reward's value against positive and negative potential consequences of pursuing the reward.

The interconnections between prefrontal cortex and ventral striatum are complex and feature topographically segregated projections, e.g. ventromedial prefrontal cortex projections terminate primarily in patches within the shell region of the Nacc whereas dorsolateral prefrontal cortex projections terminate primarily in the head of the caudate nucleus. In addition, the ventral striatum contains zones where the prefrontal projections overlap, forming the basis for integration of information from different prefrontal areas (e.g. involved in reward pursuit vs cognitive control) prior to sending efferent signals to the ventral pallidum as information is processed throughout the striatal–thalamocortical circuit (Ferry *et al.*, 2000; Haber *et al.*, 2006). The integration of competing forms of prefrontal input within the ventral striatum may play a unique role in selecting potential rewards to pursue (or not) under conditions of strong incentive–reward motivation. In this context, smaller Nacc volumes may set a structural limit on the capacity for weighing potential reward values vs potential consequences, both pleasant and aversive, during risk–reward decision-making. Additional empirical support for this hypothesis includes a finding from a large multi-site study that smaller left Nacc volumes predicted a greater risk-taking bias in adolescents (Schneider *et al.*, 2012). Moreover, smaller Nacc volumes mediated the association between risk-taking and Nacc's functional activity as measured using fMRI (Schneider *et al.*, 2012). Together, these findings suggest that smaller Nacc volumes during adolescence render individuals vulnerable to risk-taking behaviors, including substance use and potential misuse.

Like Cheetham *et al.* (2012), the present findings indicate that a priori differences in regional brain volumes predict substance use patterns in adolescence. However, Cheetham *et al.* (2012) found that smaller baseline OFC volumes (not Nacc volumes) predicted cannabis use initiation. Differences across studies may reflect unique neurobiological markers for cannabis initiation, or differences in the two studies' sample characteristics. Notably, both studies implicate structures that are important nodes within the reward processing network and point to structural limits on integration of information related to reward pursuit.

In addition to premorbid vulnerabilities, this study supports certain longitudinal predictors of substance use in adolescence. We have

reported that self-reported engagement with rewards normatively increases over time in the mid-adolescent period (Urošević *et al.*, 2012). Within the present subsample, relative increases in reward sensitivity from baseline to follow-up were associated with a greater likelihood of substance use initiation and a relatively greater self-reported frequency of alcohol use. This patterning provides longitudinal support for the hypothesized associations between normative increases in reward sensitivity and substance use risk (Bjork *et al.*, 2004, 2010; Ernst *et al.*, 2005; Galvan *et al.*, 2006; Geier *et al.*, 2010; Urošević *et al.*, 2012). There were no such effects for threat sensitivity. This pattern coheres with cross-sectional studies showing that BAS hypersensitivity is associated with heightened craving responses to substance cues (Kambouropoulos and Staiger, 2001, 2004) and greater substance use (e.g. Knyazev, 2004) in adolescents and young adults.

Moreover, this study adds novel nuances to the nature of the reward/BAS hypersensitivity and adolescent substance use relationship. Relative increases in different aspects of reward sensitivity were associated with different substance use outcomes. Increases in emotional responses to rewards, indexed by BAS Reward Responsiveness, were linked to greater substance use initiation risk, whereas increases in persistence of reward pursuits, indexed by BAS Drive, were linked to greater alcohol use frequency. This patterning is intriguing in light of findings suggesting that the three components of the BAS total score are empirically dissociable (Ross *et al.*, 2002), with specific neural, behavioral and clinical correlates that extend to social decision-making (Scheres and Sanfey, 2006). BAS Reward Responsiveness reflects positive affect and excitability in the presence of rewards, whereas BAS Drive is associated with behavioral action, approach motivation and the tendency to prioritize one's individual goals over those of others (Smits and De Boeck, 2006). Our observation that adolescents who increase in their relative levels of approach motivation (BAS Drive) use alcohol with relatively greater frequency most likely reflects their tendency to seek situations where rewards, such as alcohol, are likely to be present. Approach motivation is distinct from one's experience when a reward is actually encountered. Those who endorse high levels of positive affect or excitability when encountering rewards, otherwise construed as sensitivity to the 'magnitude of reward' and as indexed by BAS Reward Responsiveness, are likely to initiate clinical-level use of substances in general (e.g. alcohol, cannabis).

Despite potential for overlap, it is notable that BAS Fun Seeking did not emerge as an independent predictor of either outcome. BAS Fun Seeking has been more specifically associated with reward-related impulsivity (Smillie *et al.*, 2006) and is elevated in individuals likely to advance to addiction (O'Connor *et al.*, 2009; Park *et al.*, 2013). Its lack of association with outcomes in this sample suggests that approach motivation and enjoyment of rewarding pursuits, rather than impulsivity, may represent the most salient vulnerability factors for adolescent substance use. Future studies of adolescent substance use will need to further examine whether the link between prospective increases in reward pursuit and greater frequency of use holds for substances other than alcohol. Future studies will also need to examine whether increases in positive affect in presence of rewards predict risk not just for initiation of clinical-level of substance use, but risk for development of full syndromes of substance use disorders.

Limitations

This study recruited healthy adolescents, and this analysis is based on a small sample. Our sample was predominantly Caucasian, with middle-class socio-economic backgrounds, and not of sufficient size to fully examine contributions from sex and ethnicity. In addition, the clinical implications of these findings are not yet clear. Further longitudinal study is needed to confirm whether increases in behavioral aspects of

reward sensitivity, as well as Nacc structural differences, prior to use initiation predict substance use disorders and how this cascade, if present, might be modulated by other sources of neural influence, such as prefrontal integrity. Our approach within this study was theoretically guided and did not involve a whole-brain assessment. Given the a priori ROI-based hypotheses and the preliminary nature of the work, no corrections for multiple comparisons were applied in the brain ROI analyses. Accordingly, replications of the present findings in larger samples with diverse backgrounds and with correction for multiple-comparisons are needed.

Summary

This study is unique in its ability to longitudinally identify prospective risk factors, at both the neural and behavioral levels, associated with substance use vulnerability. Findings imply that adolescents with the greatest developmental increases in aspects of reward sensitivity that are tightly linked with the BAS and with potential neurobiological predispositions, i.e. structural differences in regions involved in reward pursuit (Nacc) are at greater risk for substance use initiation and greater alcohol consumption. Additional studies are needed to fully examine functional implications of individual differences in regional brain volumes of interest and their behavioral correlates. Overall, this study suggests novel neurobehavioral methods for prospectively identifying individuals who may be at risk for later substance-related difficulties.

FINANCIAL DISCLOSURES

The authors have no biomedical financial interests or potential conflicts of interest to report.

SUPPLEMENTARY DATA

Supplementary data are available at SCAN online.

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