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ADOLESCENT / YOUNG ADULT ADDICTION (T CHUNG, SECTION EDITOR)

Impulsivity and Reward Processing Endophenotypes in Youth Alcohol Misuse

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Abstract
Purpose of Review We describe the contribution of impulsivity and reward processing endophenotypes to understanding youth alcohol misuse. We discuss studies that included self-report, behavioral, and neural measures of these endophenotypes.
Recent Findings Regarding impulsivity, youth who misuse alcohol tend to engage in suboptimal decision-making and have increased urgency—diminished self-control due to emotional disruption. There is some evidence that prefrontal and parietal brain regions are hypoactive during response inhibition tasks in low-to-moderate alcohol misuse, with hyperactivation of dorsolateral prefrontal cortex and cingulate cortex associated with heavier misuse. Increased self-reported reward sensitivity is a risk factor for adolescent alcohol-use. Brain responses to rewards in youth alcohol misusers have produced inconsistent findings, perhaps due to the influence of other factors, such as family history and pubertal status at first drinking episode.
Summary Understanding of the etiology and generating preventative strategies for youth alcohol misuse could be enhanced by the accurate characterization of endophenotypes related to impulsivity and reward sensitivity.

Keywords Alcohol · Adolescence · Impulsivity · Reward · Addiction · Neuroimaging · Electroencephalography

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Introduction

Adolescence and early adulthood are critical periods for neurological and psychosocial maturation. These developmental changes often correspond with increases in behaviors that confer adverse personal and social consequences [1–3], including alcohol misuse. Alcohol misuse (used here as an omnibus term for underage alcohol use, alcohol abuse, alcohol dependence, or alcohol use disorder) is operationalized according to a wide range of overt symptoms. For example, an individual can be deemed to have an alcohol use disorder (AUD) by having any two of 11 symptoms during a 12-month period [4]. This approach to phenotyping may hinder the search for biological mechanisms underlying alcohol misuse because individuals with no symptom overlap can be classified together, despite heterogeneity in symptoms. Therefore, a better approach for ultimately understanding the pathophysiology of alcohol misuse is to focus on *endophenotypes* (also known as intermediate phenotypes) [5].

Endophenotypes are neurocognitive, behavioral, or cognitive processes associated with discrete deficits in defined neural systems [6]. Two endophenotypes—impulsivity and reward processing—both have well-characterized neural substrates and are central to understanding youth alcohol misuse [7]. Accurately characterizing young alcohol misusers in terms of these endophenotypes would identify target brain

systems for future psychosocial or pharmalogical intervention. This is important because youth alcohol misuse is associated with significant impairments in health as well as social, educational, and occupational functioning [2], and early alcohol use is predictive of dependence in adulthood [8]. Here, we review the literature on endophenotypes of impulsivity and reward processing in the context of adolescent and young-adult alcohol misuse, following the criteria outlined in Table 1. All the reviewed studies are summarized in Table 2.

Impulsivity and Alcohol Use

Impulsivity is a multidimensional construct, and although definitions of impulsivity are wide-ranging, it is generally denoted as unpremeditated, disinhibited responding, and excessively risky behavior. Impulsiveness is a vulnerability factor for initiating alcohol misuse, for transitioning to habitual use, and for post-treatment relapse [9]. Impulsivity subdomains are likely derived from different neural systems that are partly independent [10–12]. Here, we distinguish between self-reported trait impulsivity, impulsive action, and impulsive choice [13]. Other classifications of impulsivity have been proposed (e.g., [14,15]) but are beyond the scope of this brief review.

Table 1 List of inclusion and exclusion criteria for the studies reviewed

	Inclusion	Exclusion
Language	English language	Non-English languages
Type of papers	Peer reviewed	Dissertations and poster abstracts
Date	Published January 2012–March 2017	
Techniques	Self-report, fMRI, and EEG	Structural MRI, genetics, PET, SPECT
Participants	Human	Animals
Age	12–25 years old[a]	
Substances	Alcohol	All other substances
Samples	Community samples, non-dependent alcohol users, and patient groups	Co-morbid clinical disorder/illnesses and high risk (genetics)
Article type	Empirical data	Reviews, systematic reviews
Familial studies	Familial studies (prenatal substance use exposure; family history of alcohol use)	Familial studies without presence of adolescent alcohol use
Keywords (Pubmed and Google Scholar)	Adolescent; adolescence; young; alcohol; neuroimaging; "magnetic resonance imaging"; fMRI; impulsivity; reward; "delay discounting"	

[a] Except for Ref. [51••] which recruited up to 30 years old but were predominately under 25

Self-Reported Impulsivity

Impulsivity as a personality trait is indexed using self-reported measurements that include the propensity to engage in risky or novelty-seeking behaviors. Widely used measures include the UPPS (urgency, lack of perseverance, lack of premeditation, and sensation seeking [16]) and UPPS-P ([17] updated to distinguish positive and negative urgency) scales, the Barratt Impulsiveness Scale (BIS-11 [18]), and substance use risk profile scale (SURPS [19]). Figure 1 includes details and subscales of these self-report impulsivity measures. An extensive literature of cross-sectional and prospective research links this self-reported trait impulsivity to alcohol misuse [20].

The SURPS examines impulsive traits related to substance misuse risk and has cross-cultural utility. A multi-site examination of the SURPS in over 2000 14-year-olds found that measures of impulsivity and sensation-seeking predicted alcohol use 2 years later [21•]. Both traits also showed significant associations with the drinking motives "coping with anxiety" or "coping with depression" on the Drinking Motives Questionnaire, regardless of alcohol consumption levels. It is possible that these personality vulnerabilities are causal risk factors for alcohol misuse; adolescents high in sensation-seeking could be especially sensitive to rewarding outcomes of alcohol-use to alleviate negative emotions associated with depression and anxiety, resulting in the heightened reinforcement of alcohol-related behaviors.

The UPPS includes an "Urgency" scale, which captures the extent to which positive and negative emotions disrupt the ability to exercise self-control (i.e., the inability to modify or inhibit prepotent reward-driven behaviors, despite potential negative consequences) and increase rash behaviors. As we outline here, a number of studies have shown that increased urgency is related to higher levels of alcohol use. For example, the four-factor UPPS was administered to 190 18–25-year-olds and examined in relation to frequency of alcohol-use over 12 months, alcohol-related problems (the Rutgers Alcohol Problem Index; RAPI), and binge-drinking scores (≥ 5 drinks for males and ≥ 4 drinks for females, ≥2 days per month in the past year) based on the AUD section of the Composite International Diagnostic Interview [22]. Results indicated that urgency and sensation-seeking traits were associated with increased frequency of alcohol use and alcohol-related problems, but lack of premeditation related only to alcohol use, and lack of perseverance was not associated with any alcohol-use measure, after controlling for peer and parental alcohol use, psychological distress and developmental correlates. In a similar study of 268 18–25-year-olds using the four-factor UPPS [23], urgency mediated an association between childhood emotional abuse and increased binge-drinking, alcohol-

Table 2 Summary of reviewed studies on impulsivity and reward endophenotypes in youth alcohol misuse

Author (year) [reference no.]	Age (years) mean (SD)/range (where available)	*N*	Sample characteristics	Substance-use measure	Endophenotype measure	Main results
Trait impulsivity						
Shin et al. (2012) [22]	21.9 (2.1)/18–25	190	Range of alcohol-users	Alcohol-use, binge-drinking, alcohol-related problems, AUDs	UPPS	↑ Urgency and sensation-seeking related to all of alcohol-use constructs
Stojek and Fischer (2013) [25]	Mode = 18 (first year students)	319	235 drinkers and 84 non-drinkers	TLFB, DMQ, S-MAST	UPPS-P	Negative urgency, coping motives, lack of deliberation and enhancement motives predicted ↑ dependency symptoms 3 months later
Kaiser et al. (2016) [24]	18.95 (0.77) (first year students)	525	Range of alcohol-users	Life history calendar	UPPS-P	Bidirectional relationship between positive urgency and AU
Shin et al. (2015) [23]	21.9 (2.1)/18–25	268	Range of alcohol-users	RAPI	UPPS	Urgency mediated association between emotional abuse and alcohol-related items
Wardell et al. (2016) [27•]	19.75 (1.02)/18–25	300	Range of alcohol-users	TLFB, RAPI	UPPS-P BIS-11	Response and reflection impulsivity predicted variance in impaired control over alcohol and heavy drinking frequency
Impulsive action						
Whelan et al. (2012) [34]	14.5 (.45)		1–4 lifetime uses of alcohol vs. non-drinkers	ESPAD	SST	↓ lateral OFC activity during successful response inhibition
Ahmadi et al. (2013) [35]	18.9 (0.7)/18–20	92	36 light drinkers and 56 heavy drinkers	DSM-IV, SCID	GNG	Heavy drinkers had ↑ RTs and ↓ motor, prefrontal, BOLD responses
Ames et al. (2014) [36]	20.5 (1.2)/18–22	41	21 heavy drinkers vs. 20 light drinkers	AUDIT	GNG with alcohol cues	Heavy drinkers had ↑ prefrontal, insula and cingulate activation, and poorer behavioral response inhibition
Wetherill et al. (2013) [37]	14.4 (1.2)/11.7–16.7	40	20 heavy drinker vs. 20 non-drinkers	DSM-IV, CDDR, TLFB	GNG	Heavy drinkers had ↓ baseline frontoparietal, putamen, and cerebellar activation
Worhunsky et al. (2016) [38]	18.4 (0.5)/18–19	36	18 escalating drinkers vs. 18 constant drinker	SCID, SSAGA, MINI	GNG	Escalating drinkers had ↑ impulsivity and frontoparietal activation
Beltz et al. (2013) [39]	18–19 (first year students)	11	Range of alcohol-related behaviors	YAAPST	GNG	Consequences of alcohol-use related to ↑ DLPFC and ACC connectivity
López-Caneda et al. (2012) [40]	18.7 (0.5)/18–19	48	23 binge drinkers and 23 Controls	AUDIT	GNG	Bingers had ↑ NoGo-P3 amplitude at follow-up
Wetherill et al. (2013) [41]	13.4 (0.7)/12–14	60	40 heavy drinkers (20 blackout + and 20 blackout −)	The customary drinking and drug use record	GNG	Blackout + had ↑ frontal and cerebellar brain activation during response inhibition. MFG activation predicted future blackouts experience 5 years later
	23.2 (9.3)	97		QFV	GNG	

Table 2 (continued)

Author (year) [reference no.]	Age (years) mean (SD)/range (where available)	*N*	Sample characteristics	Substance-use measure	Endophenotype measure	Main results
Franken et al. (2017) [42]			48 heavy drinkers vs. 49 light drinkers			No behavioral or response inhibition ERP differences, with the exception of ↓ ERN/Pe amplitude in heavy drinkers
Impulsive choice						
Schneider et al. (2014) [44•]	14.3 (0.8)/13–15	48	Healthy adolescents	ESPAD alcohol use questions (30 days, past year, lifetime)	DD	Steeper DD associated with ↑ alcohol-use and ↓ reward-related activation in the nucleus accumbens and vmPFC
Xiao et al. (2013) [46]	17.2 (0.6)/16–18	24	14 binge drinkers vs. 14 never-drinkers	RAPI; 2 questions on last month use and age of onset	IGT	BD had poorer decision-making and ↑ emotion-related brain activation in amygdala and insula
Multiple impulsivity measures						
Moreno et al. (2012) [48]	20 (1.8) 18–24	66	22 binge drinkers, 20 cannabis users, 26 non-drug users	CAGE	BIS-11, SSS-V, GNG, SST, IGT, 2-choice task	Bingers had ↑ trait impulsivity and sensation-seeking and impulsive decision-making, but no SST difference
Sánchez-Roige et al. (2014) [50••]	21.18 (1.89)/18–25	44	22 binge drinkers vs. 22 non-binge drinkers	AUQ	BIS-11, Sx-5CSRTT, SST, TCIP	BIS-11 5x-5CSRTT ↑ associated with binging; no differences in SST and DD between groups
Mckillop et al. (2016) [51••]	21.5/18–30	1252	Young adults with l ow levels of addictive behavior	AUDIT	DD, MCQ, CCPT, GNG, SST, BIS-11, UPPS-P	↑ AUDIT scores associated with trait impulsivity and choice impulsivity, but not action impulsivity
Henges et al. (2012) [53]	19.6 (1.1)/18–21	109	Range of alcohol-users	TLFB, PDHQ	BIS-11, GNG	↑ Trait impulsivity significant for number of drunk days; ↑ action impulsivity was significant for highest number of drinks consumed on one occasion in a month
Fernie et al. (2013) [54]	13.3 (0.3)/12–13	287	Range of alcohol-users	AUQ, API	DD, BART, SST	All impulsivity tasks predicted alcohol involvement 6 months later, but not vice versa
Self-reported reward sensitivity						
van Hemel-Ruiter, et al. (2015) [66]	14.8 (1.3)/12–18	86	Drinkers vs. non-drinkers	TRAILS	SPSRQ	↑ Reward sensitivity was related to heavier adolescent alcohol-use
Lyvers et al. (2012) [68]	20 (1.7)/18–26	124	40 low-risk, 58 hazardous, 26 harmful drinkers	AUDIT, age of onset of weekly drinking	SPSRQ, FrSBe	Harmful drinkers had ↑ trait impulsivity, reward sensitivity, and disinhibition and executive dysfunction
Reward anticipation and outcome						
Nees et al. (2012) [73]	14	324	Range of alcohol-users	AUDIT	MID	

Table 2 (continued)

Author (year) [reference no.]	Age (years) mean (SD)/range (where available)	*N*	Sample characteristics	Substance-use measure	Endophenotype measure	Main results
						Behavior, personality and reward-associated brain responses related and contribute to early alcohol intake
Weiland et al. (2013) [75]	20.1 (1.3)/18–22.3	70	Young adults with and without FH + and a typical range of SU	DSM-IV, DDHx	MID	FH + group had ↑ striatal coupling with precuneus and paracentral lobule during reward anticipation
Boecker-Schlier et al. (2016) [78•]	24.6 (0.5)/15–25	168	Pubertal and postpubertal drinker beginners	AUDIT	MID	↓ Frontal cortical activation in reward anticipation and ↑ alcohol problems in pubertal vs. postpubertal alcohol onset
Whelan et al. (2014) [80•]	14.5 (0.4)	692 (in total)	Non-drinkers vs. current binge drinkers and vs. future binge drinkers	ESPAD	SST, MID, CANTAB, WISC-IV, Kirby discounting, SURPS, TCI-R	Current BD ↓ limbic and striatal activity for reward anticipation and outcome. Future BD ↓ activation during reward anticipation in occipito-temporal and posterior cingulate regions; for reward outcome ↓ activity in left temporal pole but ↑ activity in bilateral SFG

AU alcohol use, *API* Alcohol Problems Index, *AUD* alcohol use disorder, *UPPS* Impulsive Behavior Scale, *TLFB* Alcohol Timeline Followback, *DMQ* Drinking Motives Questionnaire, *S-MAST* The Short-Form Michigan Alcoholism Screening Test, *BIS-11* Barratt impulsiveness scale, *AUDIT* Alcohol Use Disorders Identification Test, *FrSBE* Frontal System Behavior Scale, *OFC* orbitofrontal cortex, *VmPFC* ventromedial prefrontal cortex, *SPSRQ* sensitivity of punishment and sensitivity of reward questionnaire, *YAAPST* Young Adult Alcohol Problems Screening Test, *GNG* Go/No Go task, *DLPFC* dorsolateral prefrontal cortex, *ACC* anterior cingulate cortex, *MFG* middle frontal gyrus, *DSM-IV* diagnostic and statistical manual of mental disorders, *SCID* structured clinical interview for DSM-IV, *RT* reaction time, *SSAGA* semi-structured assessment for the genetics of alcoholism, *MINI* mini international neuropsychiatric interview, *CDDR* Customary Drinking and Drug Use Record, *BART* Balloon Analogue Risk Task, *QFV* Quantity Frequency-Variability Index, *ERP* event-related potentials, *Pe* evoked potentials, *RAPI* Rutgers Alcohol Problem Index, *BD* binge drinkers, *TRAILS* Tracking Adolescents' Individual Lives Survey, *MID* monetary incentive delay task, *DDHx* Drinking and Drug History Questionnaire, *FH* family history of alcoholism, *fMRI* functional magnetic resonance imaging, *M* mean, *SST* Stop Signal Task, *CAGE* CAGE Questionnaire, *SU* substance-use, *PDHQ* Personal Drinking Habits Questionnaire, *SSS-V* sensation-seeking scale form V, *ESPAD* European school survey project on alcohol and other drugs, *Sx-5CRTT* five-choice serial reaction time task, *TCIP* two-choice impulsivity paradigm, *IGT* Iowa gambling task, *AUQ* alcohol use questionnaire, *MCQ* monetary choice questionnaire, *CCPT* Conners' Continuous Performance Test, *SURPS* substance use risk profile scale, *CANTAB* Cambridge Neuropsychological Test Automated Battery, *WISC-IV* Wechsler intelligence scale for children, *SFG* superior frontal gyrus, *DD* delay discounting task, *TCI-R* temperament and character inventory-revised, *ERN* error-related negativity (*Pe* amplitude reflects the perception of the error), ↑ = increase, ↓ = decrease, + = symptom present, − = symptom absent

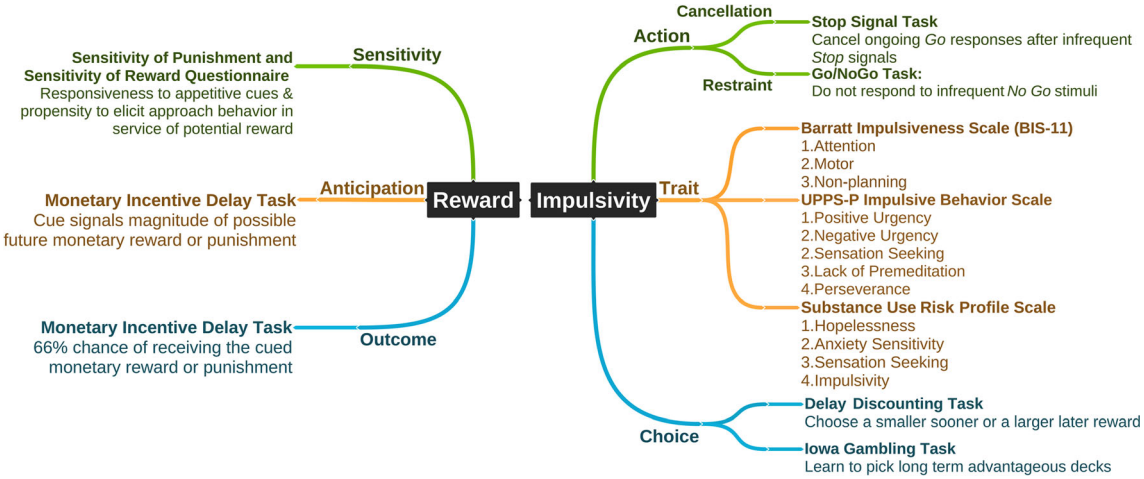

Fig. 1 Impulsivity and reward processing endophenotypes and common subdomains, associated with youth alcohol misuse

related problems, and AUDs, using identical alcohol-related measures to [22]. These results suggest an important dynamic between urgency, adverse life events, and alcohol use.

Prospective research studies have further explored the links between alcohol misuse and the UPPS urgency construct, distinguishing between positive and negative urgency. In one longitudinal study, the relationship between impulsivity using the UPPS-P and average weekly alcohol-use was examined in 525 college students (52% females) during a year-long period [24]. A bidirectional association was observed, with baseline positive urgency predicting future alcohol-use, and the rate of baseline alcohol consumption also predicting future increases in positive urgency. Baseline average weekly alcohol-use also predicted future negative and positive urgency. However, neither sensation-seeking nor lack of premeditation predicted alcohol use 1 year later, but lack of perseverance predicted less alcohol use at follow-up. The authors suggested that surges in positive emotions underlying impulsive behavior might relate to peer acceptance of heavy-drinking in young people, which in turn contributed to further alcohol-use [24]. However, in a separate study [25] involving 235 female college students, negative urgency and lack of premeditation on the UPPS-P, but not positive urgency, significantly predicted increased alcohol consumption 3 months later. The discordance between [24, 25] may be partially attributable to the different timescales (1 year vs. 3 months) or to sex differences underlying urgency as it relates to alcohol misuse (although sex differences in urgency have been previously found to be weak [26]). More research is required to disentangle the role of positive and negative urgency and possible sex differences, in youth drinking. Nevertheless, urgency appears to be an important dimension of impulsive traits associated with alcohol-use.

Some researchers have combined self-report impulsivity measures to generate higher-order factors that may better explain alcohol-use behavior. For example, Wardell and colleagues [27•] combined UPPS-P and BIS-11 scores in order to assess self-reported control over alcohol (Impaired Control Scale) in 300 18–25-year-old heavy drinkers, using a Timeline Follow-back [28] for alcohol frequency and RAPI for alcohol-related problems. The first higher-order factor—*response impulsivity*—describes difficulties inhibiting thoughts and behaviors, especially in the context of reinforcement. The second—*reflection impulsivity*—is the tendency to make quick decisions without sufficiently gathering or evaluating relevant information. Response impulsivity accounted for unique variance in impaired control over alcohol and in alcohol problems, whereas reflection impulsivity accounted for unique variance in heavy drinking frequency only. Further, indirect associations were observed from response and reflection impulsivity to alcohol problems, mediated via impaired control and heavy drinking frequency, respectively. The results suggest that impaired control may play a specific role in the pathway to alcohol problems from response impulsivity, but not from reflection impulsivity.

Impulsive Action

Impulsive action is often measured using the Stop Signal Task (SST) [29] or the Go/NoGo (GNG) task [see 30]. The SST measures *action cancelation*, where fast responses to "go" stimuli are required and an intermittent "stop" stimulus signals the need to cancel a prepotent motor response. Impaired action impulsivity is reflected by increased stop signal reaction times (SSRTs). The GNG measures *action restraint*, whereby participants quickly respond in the context of frequent "go" stimuli and restrain in the context of infrequent "no-go" stimuli. Several studies have shown that both action cancelation and restraint are impaired in substance misusers, including alcohol misusers [31, 32].

Tasks assaying impulsive action, combined with neuroimaging, have the potential to detect subtle neurobehavioral vulnerability and predictive factors of alcohol-use [33]. For example,

1896 healthy 14-year-olds [34], with only 1–4 lifetime uses of alcohol, versus non-drinkers, had reduced lateral orbitofrontal cortex activity during response inhibition on an SST. This suggests that the lateral orbitofrontal cortex may underlie impulsivity associated with alcohol initiation in young adolescents. Importantly, given the low-volume alcohol intake, these neural makers are less likely to be a consequence of alcohol use. Hypoactivation in frontoparietal, temporal, and subcortical brain regions was also observed in college drinkers who binged in over 50% weeks in the past 6 months, when compared to light drinkers who binged fewer than 50% weeks in the past 6 months on a GNG task [35], with longer reaction times (RTs) for heavy drinkers. Another study [36], however, has found increased activity in the right dorsolateral prefrontal cortex and cingulate cortex, as well as significantly longer RTs, during a GNG task in 18–22-year-olds classified as very heavy drinkers (≥ 15 drinks/week for males and ≥ 8 drinks/week for females when compared to light drinkers (< 3 drinks/week and ≤ 2 drinks during any drinking episode). It is possible that in the latter study the amount of alcohol consumed regularly was sufficient to impair brain function, leading the drinking group to recruit additional brain resources in response to cognitive demands. This is speculative because disentangling cause and effect is difficult in cross-sectional designs. Therefore, we turn next to prospective studies of action impulsivity in youth alcohol misuse.

Two studies have shown that frontoparietal hypoactivation during response inhibition on GNG tasks predicted subsequent heavy drinking in 11–16-year-old drinkers (1–2 drinks daily or > 4 drinks/month) versus continuous non-drinkers 3 years later [37] and 18-year-old college student heavy drinkers (number of drinks > 4 on an occasion; mean drinks = 10.3), versus lighter drinkers (maximum of 3 drinks per occasion) 1 year later [38], respectively. In both studies, behavioral differences between groups were absent at baseline. Supporting evidence for hyperactivation as a compensatory mechanism comes from an fMRI GNG task with alcoholic and non-alcoholic drinks as response cues [39], in which 18–19-year-olds whose alcohol exposure increased during college had greater connectivity between prefrontal and anterior cingulate regions 1 year later. Behaviorally, participants' performance improved over time, showing faster reaction times and improved response accuracy from baseline for the alcohol condition 1 year later.

A similar result to [39] was found by examining the N2 and P3 event-related potentials (ERPs; time-locked electroencephalograms). In a longitudinal study [40] of 48 18–19-year-old light (n = 25) and heavy (n = 23) drinking students, no P3 amplitude differences were observed at baseline during a GNG task. However, those who binged (at least 6 drinks per occasion once per month) for 2 years exhibited larger P3 amplitudes during a GNG task at follow-up. This study also estimated the ERP cerebral origin using tomography analysis, finding that bingers had significantly greater inferior frontal cortex activation, in the absence of behavioral performance differences, at follow-up.

A pattern of hypoactivation prior to very heavy use, however, is not uniform across studies. For example, an fMRI showed that future problematic drinkers had frontal hyperactivation during inhibitory processing at baseline, which predicted alcohol-related blackouts 5 years later [41]. An ERP analysis [42] reported no differences in behavioral or neural indices of response inhibition (N2 and P3 components) when comparing 48 23-year-old heavy drinkers (mean of 3.9 drinks per occasion) to 49 lighter drinkers (mean 1.9 drinks per occasion) during a GNG task. The mixed findings regarding a pattern of hypoactivation in certain brain regions during response inhibition tasks prior to heavy alcohol use may be due, for example, to differences in sample characteristics (e.g., age range, how drinking groups are defined) and relatively small differences in brain activation between groups.

Impulsive Choice

Impulsive choice encompasses decision-making based on evaluations of delayed consequences of behavior. That is, an impulsive choice can be characterized by the tendency to choose a smaller immediate reward rather than waiting for a larger, but delayed, reward. The following paragraphs review research using delay discounting tasks and the Iowa gambling task as measures of impulsive choice.

The delay discounting (DD) task is an established behavioral measure of impulsive choice, quantifying the decline in the subjective value of a reward as the delay to its receipt increases (e.g., "Would you prefer €5 now or €10 in one month?"). Steeper discounting is robustly associated with addictive behaviors in general, including severity and quantity-frequency of substance misuse [43]. However, there is relatively less literature on non-dependent youth in relation to alcohol misuse. This may be because discounting in adolescents and young adults is more malleable by environmental factors. For example, 13–15-year-olds who reported uncertainty about receiving promised delayed rewards from their parents exhibited steeper DD [44•]. This steeper DD gradient in Ref. [44•] was also associated with increased alcohol-use, as well as reduced reward-related activation in the nucleus accumbens and ventromedial prefrontal cortex (key regions in reward processing). The finding sheds new insights into how parenting can shape choice impulsivity; adolescents may learn to develop a preference for immediately rewarding experiences, fueled by experiences of unpredictable and undependable reward schedules, leading to alcohol misuse.

The Iowa gambling task (IGT [45]) is often used to assess decision-based impulsive choices in the context of reward and punishment. During the IGT, individuals select a card from a predefined sequence of rewards and punishments across four

different decks. Two decks are deemed disadvantageous because they yield greater immediate gains but greater long-term losses, whereas the other two decks are deemed advantageous because they yield lower gains but lower long-term losses. During an IGT, 16–18-year-old binge-drinkers displayed poorer decision-making (a tendency to consistently select disadvantageous decks) and increased emotion-related brain activation in the amygdala and insula, compared to matched never-drinkers [46]. Furthermore, higher alcohol-related problems (RAPI) and urgency (UPPS) were negatively associated with task-related activation in the orbitofrontal cortex, a brain region associated with goal-directed behavior, in the binge-drinkers. These cross-sectional findings suggest links between behavioral and brain-based endophenotypes of decision-making that may be related to binge drinking, but cannot disentangle pre-existing risk from possible effects of alcohol use on brain functioning.

Multiple Impulsivity Measures

Given that impulsivity is multifaceted [47], the within-subject recording of multiple behavioral and self-report measures can potentially disentangle the overlap between alcohol-use and various impulsivity subdomains. Generally, parallel measures have shown that increased trait and choice impulsivity tend to be consistently associated with alcohol misuse, whereas the relationship between action impulsivity and alcohol misuse is mixed. For example, 19-year-old binge-drinkers (mean of 6.18 drinks on the last drinking episode) made poorer decisions on an IGT and had higher trait impulsivity (BIS-11), compared to both cannabis-using and non-drug-using groups, but the binge drinkers did not show behavioral differences on an SST relative to controls [48]. A broadly similar result was reported in 44 18–25-year-old bingers (a binge score calculated using the Alcohol Use Questionnaire (AUQ [49]) based on average of drinks consumed per hour, number of times being drunk in 6 months, and percentage of times getting drunk while drinking) when compared to non-binge drinkers [50••]. Trait impulsivity (BIS-11) and waiting impulsivity (5-choice serial reaction time task) were associated with binging, whereas neither action impulsivity (SST) nor choice impulsivity (DD) differences were observed between groups.

As an alternative to comparing drinking and non-drinking groups on individual measures of impulsivity, factor analysis of multiple impulsivity measures in 1252 18–30-year-olds with low levels of addiction [51••] revealed three factors of impulsivity: trait (UPPS-P, BIS-11), choice (Monetary Choice Questionnaire, DD task), and action (GNG, SST, Conner's Continuous Performance Test) impulsivity. Impulsive traits were not strongly related to choice (r = 0.10) or to action (r = 0.16), with choice and action unrelated (r = 0.01). Alcohol Use Disorder Identification Test (AUDIT [52]) scores were significantly associated with trait and choice impulsivity, but not with action impulsivity. However, contrary findings have also been reported with respect to action impulsivity. In 109 18–21-year-old social drinkers, trait (BIS-11) and action (GNG) impulsivity predicted various aspects of drinking [53]. Both trait and action impulsivity were significantly associated with total number of drinks consumed and number of heavy drinking days. However, trait impulsivity was only significant for number of drunk days whereas action impulsivity was significant only for the highest number of drinks consumed on one occasion in a month. In a prospective design [54], action impulsivity (SST) and choice impulsivity (DD and Balloon Analogue Risk Task; BART) each predicted frequency and severity of alcohol problems 6 months later in 287 12–13-year-olds. The mixed findings across studies may reflect differences in the age range of the samples. Alcohol misuse in early adolescence often focuses on the initiation of alcohol consumption and perhaps the willingness to experiment, whereas research on college-age alcohol misuse tends to orient towards episodic heavy use. It is likely that different impulsivity endophenotypes underlie different patterns of alcohol misuse.

In general, increased trait impulsivity is consistently associated with alcohol-use, particularly in studies using the BIS-11 [50••, 51••, 53] and the UPPS [24, 25]. With respect to impulsive choice, steeper delay discounting is associated with higher alcohol use and reduced reward-related activation in the nucleus accumbens and ventromedial prefrontal cortex. During assays of impulsive action, bilateral hypoactivity of lateral orbitofrontal [34], middle frontal gyrus and parietal regions [35], was associated with low-to-moderate youth alcohol misuse, while frontoparietal regions may shift from hypoactivation to hyperactivation in adolescents who subsequently transition to heavier alcohol-use. Due to continuing development of prefrontal structures into emerging adulthood [55, 56], youth drinkers in particular are exposed to alcohol's neurotoxic effects on vulnerable brain regions [57]. Thus, increasing external cognitive demands may require heightened brain activity to produce a similar level of behavioral performance in those with a history of adolescent alcohol misuse. However, it is difficult to reach firm conclusions on this conjecture, perhaps partly due to variations in measures used across studies and definitions of groups based on alcohol intake. We return to this issue in the discussion.

Reward

An important component of increased risk-taking, including youth alcohol misuse, involves processing of rewards [9]. Rewards are stimuli that are consequences of a behavior and increase the probability of that behavior recurring in the future. Individual differences in reward learning can be studied using a variety of protocols. Reward sensitivity is a personality trait that quantifies the ability to get pleasure or reward

from natural rewards/reinforcers, such as food, and also from pharmacologic rewards. Measures of brain activity during reward anticipation (prediction of potential reward by a signal) and reward outcome (delivery of reward) have revealed distinct neural processes [58]. The ventral striatum (VS), part of the mesolimbic dopamine system, is a key brain region involved in adolescent reward processing [59, 60], including substance misuse [61].

Self-Reported Reward Sensitivity

Reward sensitivity is characterized by heightened emotional, cognitive, and physiological reactivity to appetitive outcomes (e.g., money or food) [62, 63]. Self-report measurements are often used to indirectly measure reward sensitivity. This includes the Sensitivity of Punishment and Sensitivity of Reward Questionnaire (SPSRQ [64]; Fig. 1.), which gauges responsiveness to appetitive cues and the propensity to elicit approach behavior in the service of potential reward. Adolescents with heightened reward sensitivity may, for instance, experience stronger reinforcement from alcohol use and develop stronger associations with continued use [65].

The SPSRQ was administered to 86 adolescents (12–18 years old) [66], who were then presented with a visual probe task [67] to measure attention deployment towards pictures of alcohol, tobacco, or cannabis (relative to a neutral within-subject control picture). Higher reward sensitivity, higher alcohol-related attentional bias, and weaker executive control (measured in a separate task) were all related to heavier adolescent alcohol use and development of alcohol abuse problems. Reward sensitivity has also been shown to interact with self-reported aspects of impulsivity, such as disinhibition. For example, after controlling for duration of alcohol exposure, a study of 124 18–26-year-old students [68] found that harmful drinkers as defined by the AUDIT (mean score of 10.75) reported earlier alcohol initiation compared to a lower risk group. Furthermore, harmful drinkers had higher trait impulsivity (BIS-11), reward sensitivity (SPSRQ), and disinhibition and executive dysfunction as measured by the Frontal Systems Behavior Scale [69]. Trait impulsivity and reward sensitivity were the strongest unique contributors (14 and 7% of variance, respectively) in explaining AUDIT scores.

Reward Anticipation and Reward Outcome

Reward processing involves activation to anticipatory cues that predict rewards and to the delivery of rewards themselves. Both processes can be individually studied, with neuroimaging, through the monetary incentive delay (MID; see Fig. 1) task. The MID separates reward anticipation from reward outcome by providing participants information about the potential outcome of an upcoming trial, typically either a reward, punishment, or neutral outcome that follows a speeded choice response. Several studies have reported that adult alcohol misusers have reduced activation in the VS and anterior cingulate during the anticipation of monetary reward (e.g., [70]). The hypoactivation of reward-related brain regions is commonly reported in studies of adults with addiction [71]. In addition, adolescent smokers showed reduced VS activity during reward anticipation [72] but there is relatively less research on youth alcohol misuse.

A large study ($n = 324$; [73]) of 14-year-olds with a range of alcohol use who completed the MID found that VS activity during reward anticipation in MID only accounted for a small, non-significant portion of drinking behavior, in contrast to personality measures. However, one explanation is that the relationship between reward processing and alcohol misuse in adolescents and young adults may be dependent on other factors such as parental alcohol misuse [74]. Weiland and colleagues [75] classified 70 18–22-year-olds as either positive or negative for a family history of alcoholism (49 FH +/21 FH −). During reward anticipation in a MID task during fMRI, FH + participants had increased VS connectivity with a wide range of brain regions, including sensorimotor areas, precuneus, and paracentral lobule, relative to FH − participants. Differences in the VS connectivity of the FH + adolescents mediated the effect of sensation-seeking effect on drinking. These results suggest inherited differences in a VS reward-related functional connectivity vulnerability factor for alcohol misuse.

Adolescence is a time of physical changes, including the onset of puberty and the consequent increase in hormonal activity [76]. The pubertal stage at first drink has been proposed as a predictor of progression to later alcohol abuse [77], possibly via its interaction with reward processing. A study [78•] of 168 healthy young adults (mean age at fMRI assessment of 24.5 years old) collected simultaneous EEG-fMRI during a MID task and investigated the association of self-reported pubertal stage at first drink with subsequent alcohol-related problems in early adulthood. Results indicated that individuals whose first alcohol intake was during, rather than after, puberty, had decreased frontal cortex activity and increased preparatory EEG activity during reward anticipation. Alcohol-related problems during early adulthood were also increased in those who consumed alcohol earlier in puberty. The authors suggested that pubertal stage at first drink is a potential modulator of psychopathology that is linked to altered reward anticipation processing.

Multi-modal Assessment of Both Impulsivity and Reward

Although some research has examined relationships between youth alcohol misuse and impulsivity or reward processing separately, the combination of both impulsivity and reward endophenotypes and their subdomains, in a single study, is rare. Recently, however, large collaborative efforts, such as IMAGEN [79] and ABCD [https://abcdstudy.org], have

begun to collect self-report, behavioral, and brain data. For example, in the IMAGEN study, an analysis of alcohol misuse in 14-year-olds [80•] included trait, action, and choice impulsivity measures, in addition to reward anticipation and outcome. Cross-sectional analyses showed that current binge-drinkers (n = 115; ≥ 3 binge-drinking episodes by age 14 years) had reduced limbic and striatal activation during reward anticipation and outcome, and greater motor-related and precuneus activation during response inhibition, compared to controls (n = 150; ≤ 2 lifetime alcohol uses). Higher trait and choice impulsivity characterized current binge drinkers.

A longitudinal IMAGEN analysis [80•] compared 121 future binge-drinkers (≤ 2 lifetime alcohol uses drink occasions by age 14 and ≥ 3 lifetime binge drinking episodes by age 16) to the 150 controls. The strongest brain predictors (measured at age 14) of binge-drinking at age 16 included decreased occipito-temporal and posterior cingulate activation during reward anticipation on the MID, greater prefrontal activation during reward outcome, and greater motor-related activation during failed response inhibition on the SST. Neither trait nor choice impulsivity were predictors of future alcohol misuse. Notably, each of the impulsivity and reward endophenotypes individually had only modest utility in predicting future bingeing. Furthermore, the endophenotypes predicting future alcohol misuse (longitudinal analysis) differed from those classifying baseline binge-drinkers and non-binge drinkers (cross-sectional analysis). Emerging results from the IMAGEN study highlight the importance of examining a range of impulsivity and reward measures, each of which contributes uniquely to explaining alcohol misuse in cross-sectional and longitudinal analyses. A feasible method of collecting data on a variety of endophenotypes could be accomplished using web-based designs [81], in which large numbers of participants can complete both questionnaires and tasks.

Implications of Impulsivity and Reward Endophenotypes for Prevention

A focus on endophenotypes may help to inform prevention strategies. Early adolescent alcohol use including binge drinking remains a health issue (see [3]), despite endeavors to curb adolescent alcohol misuse in health sectors [82]. Moving away from generic prevention approaches and towards the targeting of particular endophenotypes (e.g., specific impulsive personality traits) may be more effective. Such personality-targeted approaches have a moderate effect size in reducing various substance-use outcomes [83]. The application of "Big Data" methods may further aid implementation of tailored treatment interventions [84]. Another approach could involve mindfulness-based interventions; trait mindfulness is associated with decreased alcohol use [85], as well as decreased trait impulsivity (BIS-11) [86]. Mindfulness-based interventions are widely used in clinical practice, and there is some evidence that these interventions improve executive functioning [87], yet this approach remains relatively underexplored for youth alcohol misuse prevention.

Challenges in Quantifying Alcohol Consumption and Defining Alcohol-Use Phenotypes

One challenge in studying alcohol misuse is that there are many different methods of quantifying alcohol consumption (e.g., definitions of heavy vs. light alcohol use) and alcohol-related consequences. For example, the definition of "standard drink" (i.e., ethanol grams in a standard drink) is variable across different countries (see [88]), as well as in binge drinking cutoff scores [see 89]. Single consumption-based measures of alcohol use are particularly problematic and are argued to lack predictive validity, ecological bias, and appropriate group dichotomization [90, 91]. With regard to the consequences of alcohol use, drunkenness in young adolescents, not drinking per se, is a stronger risk factor for later problems [92]. Sanchez-Roige and colleagues [50••] suggest that a "binge score" focusing on patterns of drinking (including drunkenness) rather than a typical quantity measurement "drinks in a row" may provide better predictors of potential dependency on alcohol. Furthermore, specific contextual factors promote, hinder, or intensify individual risk factors for adolescent alcohol-use (e.g., peers, family, and cultural norms for drinking) [24, 44]. Therefore, we suggest that the use of multiple alcohol measurements (including aspects mentioned above) may better capture the relationship between alcohol involvement and endophenotypic diversity.

Conclusion

Increased trait impulsivity is consistently related to alcohol use, although the precise relationship of positive and negative urgency with alcohol-use patterns requires further investigation. In tests of impulsive action, behavioral differences were not always observed in alcohol misusers, but measures of brain activity tended to show hypoactivation in frontoparietal, temporal, and orbitofrontal brain regions in low-moderate alcohol misusers. Youth alcohol misusers tend to make suboptimal choices, such as choosing smaller sooner rewards over larger later rewards. Increased reward sensitivity may contribute to alcohol misuse, as does decreased ventral striatum brain activity during reward anticipation, although the latter is subject to the influence of other variables such as family history of alcohol misuse.

Future research should strive to combine multi-modal (e.g., self-report, behavioral tasks, neuroimaging) measures of impulsivity and reward processing. In addition, the design of future studies needs to consider that a measure's association with alcohol use may differ across adolescent and young adult

development and may depend on whether cross-sectional or prospective analyses are conducted. Classifying individuals according to impulsivity and reward processing endophenotypes, rather than grouping together individuals with disparate symptoms of alcohol misuse (e.g., DSM-based diagnostic categories), may ultimately prove more fruitful in understanding the etiology of youth alcohol misuse.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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