Altered Dopamine Transmission as a Familial Risk Trait for Addictions

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Current Opinion in Behavioral Sciences 2017;13:130-138

Abstract

Is altered dopamine transmission a pre-existing vulnerability trait for addiction? Preliminary support for this hypothesis has been provided by recent neuroimaging studies. While most effects remain to be replicated, there is now evidence that, compared to healthy controls, people at familial risk for substance use disorders exhibit both increases and decreases in striatal dopamine function. The following review assesses the strength of this evidence, considers explanations for discrepant results, and discusses potential implications for understanding pathways to addiction.

Introduction

Is altered dopamine (DA) transmission a pre-existing vulnerability trait for addiction? There have been reasons to propose this. In animal models DA transmission increases the motivation to engage with reward related stimuli [1-3], promotes forms of motor impulsivity [4], and is altered in rodents exhibiting a greater tendency to self-administer drugs of abuse [5]. Now, recent neuroimaging studies raise the possibility that, in humans too, perturbed DA transmission occurs in those at risk for addictions before the onset of the disorder. The strength of this evidence and potential interpretations are considered below.

The Dopamine Hypothesis of Addiction

The primary DA hypothesis of addiction proposes that DA transmission becomes disproportionately tied to addiction related events [1-3,5]. This might arise as either an absolute or relative increase in DA transmission [6]. In the absolute elevation model, DA system reactivity is higher in people at high *vs.* low-risk for addictions, increasing their pursuit of rewards including the likelihood of trying drugs of abuse. In the relative elevation model, DA system reactivity is muted such that only quite potent rewards, such as drugs and drug-paired cues, can engage it. In both models, a combination of conditioning and sensitization ties DA reactivity to the drug-related events, steering behavior toward a narrowed repertoire of drug seeking [5]. In both models, the initiation of compulsive drug pursuit follows from drug- and cue-induced DA transmission that is elevated (absolute or relative) [1,5,6,7].

Defining Risk for Addictions

All but one of the studies discussed below defined risk for addictions as having a family history of substance use disorders (SUDs). Of note, familial risk is a multifaceted concept, including inherited genes and effects of growing up with people who have substance use problems. Not surprisingly, the magnitude of risk is related to the density of affected relatives. In the studies discussed here, density ranged from a minimum of one to multiply affected generations and from one to three affected relatives. Additional risk factors included age of onset of substance use (two studies), presence *vs.* absence of stimulant drug use (one study), low sedative responses to a large drink of alcohol (one study), and impulsivity related personality traits (one study) (see Tables 1 & 2). Variation in these factors might have affected the population sampled and the results obtained. Since disentangling the contributions of these factors will require more study, the focus here is on the combined influence of familial SUDs.

Dopamine Transmission in People at Familial Risk for Addictions

Dopamine DR2 availability

Six positron emission tomography (PET) [^{11}C]raclopride studies measured striatal D2 receptor availability in people selected for being at risk for addictions (Table 1). Four observed no differences between the high and low-risk subjects [8-11], while two found evidence of increased striatal D2 receptor availability in the high-risk groups [12,13]. The authors of the latter two papers proposed that elevated DRD2 densities could be a protective feature. This interpretation reflected two main observations. First, people with

a current SUD have decreased striatal D2 receptors [14]. Second, the family history positive participants with elevated DRD2 densities [12,13] exhibited little evidence that they were progressing to a SUD; *i.e.,* their drug and alcohol use was low (Table 1). Although this proposal fits with the larger literature, follow-up studies will be required to determine whether differential DRD2 densities predict who develops substance use problems.

The mechanism by which increased DRD2 densities would diminish risk for addictions is unclear [6]. One possibility is that elevated post-synaptic DA signaling increases the salience of, and interest in, diverse goals. In the absence of other risk factors (*e.g.,* adverse childhood events; impulsive personality traits; adolescent drug use) this might protect against a narrowed focus on a few goals only.

A second possibility is that increased DRD2 densities reflect higher numbers of inhibitory autoreceptors. This interpretation finds some support in recent studies conducted in laboratory rodents. Whereas upregulation of striatal post-synaptic D2 receptors had no effect on drug self-administration [15], selective upregulation of D2 autoreceptors [16] and non-specific DRD2 upregulation [17] decreased substance use. It is possible, therefore, that drug-induced DA responses in people with elevated DA autoreceptors are curtailed, reducing their susceptibility to pathologically high DA states and the development of compulsive behaviors [1,5,7]. The converse implication is that those with reduced DA autoreceptors might be at elevated risk for addictions[1]. There is some evidence supporting this proposal. Low striatal D2 receptors have been reported in laboratory animals susceptible to cocaine self-administration [18-20]. Although low striatal DRD2 densities have yet to be observed in people selected for being at risk for addictions, low midbrain D2 receptors (plausibly autoreceptors) have been seen in those exhibiting elevated striatal DA release [21,22] and impulsive personality traits [22]. Such traits might increase the likelihood of trying drugs of abuse and progressing to an SUD [5].

Insert Tables 1 and 2 near here

Dopamine release

Seven PET [^{11}C]raclopride studies have tested whether people with a family history of SUDs exhibit altered striatal DA release (Table 2). Four of these studies identified differences between high- and low-risk samples. Elevated DA responses in high-risk groups were found in three of the studies, two in response to the presentation of non-contingent reward cues [11,23] and one following ingestion of an alcoholic beverage [10]. The fourth study found evidence of reduced amphetamine-induced DA responses in

[1] The mechanisms that yield altered DRD2 densities might differ in people resilient to SUDs *vs*. those with an SUD. For example, the up-regulation seen in some people who are resilient to SUDs might be a heritable trait [52] or reflect elevated social status [20]; in comparison, the DRD2 down-regulation seen in people with SUDs might be heritable [52], an effect of early adversity [20], or produced by repeated drug-induced surges in DA release [20,53].

the high-risk participants [9]. In two of these studies the largest differences in DA release were in those with an early age of substance use onset, a behavioral marker of high risk for addictions [9,11].

Three studies did not find a difference in striatal DA release when comparing high- *vs.* low-risk samples. The first negative study was conducted in those with a family history of alcohol use disorders (AUDs) [8]. While the approach was innovative, there was some question as to whether the participants with familial alcoholism were genuinely at elevated risk since their alcohol ingestion levels were modest (*i.e.,* 4 drinks per week). Moreover, when this same group extended their sample size, they continued to see no difference in DA release yet, as noted above, did observe increased DRD2 resting state availability [13], the opposite of what has been seen in people with a current SUD [14]. This finding suggested to the authors that they had recruited family members carrying a resiliency feature rather than the expected vulnerability trait.

The second negative study compared the effects of three challenges: contingent alcohol cues, an intravenous ethanol injection, and ethanol plus cues combined [24]. While each of these conditions produced evidence of striatal DA release, and the combined ethanol plus cue condition produced an additive effect, an effect of family history was not seen. The authors attributed the lack of statistical significance to two features: (i) having a small sample size (Table 2), and (ii) differential effects of alcohol cues that are presented unexpectedly (non-contingently) *vs.* those that arrive contingent upon a behavior (Box 1).

Insert Box 1 near here

Perhaps more surprising is that one of the studies found evidence of marked decreases in DA release in the high-risk group [9]. This was not accounted for by past substance use in and of itself. The study included a control group with no family history of SUDs matched to the high-risk participants on their personal drug use histories, yet only the group with a dense, multigenerational family history of addiction problems exhibited lower DA responses than the stimulant drug-naïve healthy controls.

At least three interpretations of the opposite effects seem possible. First, high-risk individuals might have elevated DA responses to alcohol [10], a substance that activates DA transmission through actions in the cell body region, yet decreased DA responses to drugs such as amphetamine that act at the terminal region [9]. Second, it is possible that many impulsive individuals at risk for addictions are highly responsive to the presence *vs*. absence of reward-related cues [5]. Third, multiple pathways to addiction are likely: some might be associated with increased DA reactivity, others with decreased reactivity. These interpretations are addressed below.

Alcohol vs. Amphetamine

As noted, there are now reports that people at risk for addictions exhibit elevated DA responses to a drink of alcohol [10] yet a diminished response to amphetamine [9]. This could reflect the different mechanisms by which they activate DA cells. However, while plausible, there is some evidence that this is not a sufficient explanation. For example,

people with minimal histories of substance use yet histories of pathological gambling exhibit elevated striatal DA responses to an amphetamine challenge [25], suggesting that individuals with overlapping vulnerability traits can exhibit hyper-reactive responses to a stimulant drug.

Presence vs. Absence of Drug Related Cues

We recently proposed that, compared to healthy controls, at least some individuals at risk for addictions exhibit high DA cell reactivity to potent reward-related events [5]. With progressively greater drug use, these DA responses can become pathologically tied to drug-related cues. Through a combination of sensitization and conditioning, motivated behaviors are thereby steered progressively more toward drugs and drug-related stimuli and away from non-drug related goals. Replicated evidence is now available for both conditioned [26-30] and sensitized [31-33] DA responses in humans.

Studies in laboratory animals also find that the presence *vs.* absence of drug related cues can affect the magnitude of responses to other events. For example, when drug availability is explicitly paired with a particular context, behavioral activation [34,35] and DA cell reactivity [36-38] are both elevated in the drug-paired environment. When animals are tested in environments that have been paired with the absence of drug delivery, behavioral activation [34,35] and DA cell reactivity [36-38] are diminished. While the hypothesis awaits explicit testing in humans, the studies of striatal DA release reviewed here are at least not inconsistent. Young adults at familial risk for SUDs exhibited elevated striatal DA responses to alcohol cues [23], a drink of alcohol [10], and monetary rewards [11], plausibly reflecting the continued ability of money to be a high-value incentive. In comparison, high-risk youth exhibited smaller DA responses when they were tested in the absence of reward-related cues; *i.e.,* administered amphetamine tablets hidden inside a non-descript gelcap [9]. Evidence of inhibitory effects has been described in smokers also. When tobacco smokers smoke a cigarette, it increases striatal responses to reward prediction errors; in comparison, the (incorrect) belief that the smoked cigarette is denicotinized reduces the striatal response to reward prediction errors and alters choice behavior on a reward task [39].

Multiple Pathways to Addiction

Multiple pathways to addictions have been proposed based on epidemiological studies [40,41], motivational processes [42], and neuropharmacology [43]. These studies suggest that most SUDs are related to a behavioral cluster of ‘externalizing’ traits, while others are distinguished by ‘internalizing’ traits [41]. Recent functional magnetic resonance imaging (fMRI) studies have identified plausible neurobiological features of these two pathways [44,45]. For example, in a large sample of undergraduates, problem drinking was associated with two distinct patterns of brain reactivity: 1) high ventral striatal responses to positive feedback combined with low amygdala responses to threat *vs.* 2) low ventral striatal responses to positive feedback and high amygdala responses to threat. The high ventral striatal responses were mediated by impulsivity, the high amygdala responses by anxious-depressive traits [44,45]. The present review raises the possibility that differential sub-cortical DA reactivity contributes to these groups, but this has yet to be tested directly.

Origins: What Might Account for Individual Differences in Dopamine Transmission?
Familial risk for SUDs could reflect the influence of inherited genes, greater exposure to adverse early life experiences, or susceptibility to initiate drug use at an earlier age. Each of these factors can affect DA. For example, in a PET [^{18}F]DOPA twin study, high heritability scores for DA synthesis capacity were found in the bilateral sensorimotor striatum (h^2 = 0.51 to 0.64) while heritability scores in the ventral limbic striatum were low (h^2 = 0.0 to 0.21) with synthesis capacity variation more influenced by unique life experiences [46]. The relevant life experiences could include adverse events. Indeed, there is recent evidence that higher striatal DA synthesis capacity is associated with greater early life adversity [47]. Enduring effects on striatal DA function can also be produced by drug use, and there is now evidence that repeated amphetamine administration leads to greater drug- and stress-induced striatal DA release [31-33]. While these studies of sensitization and cross-sensitization tested no more than the effects of five doses of *d*-amphetamine, correlational analyses in non-dependent cocaine users raise the possibility that the augmented DA responses continue to grow for up to 200 exposures [48].

At least three neurobiological features have been identified that appear to influence individual differences in the magnitude of striatal DA responses in humans. First, striatal DA release is related to differences in the density of midbrain D2 receptors: the lower the midbrain DRD2 – plausibly autoreceptors – the higher the striatal DA response to amphetamine [22] and drug related cues [21]. Second, striatal DA release co-varies with frontal cortical thickness: the thinner the cortex, the greater the amphetamine-induced DA response [49]. Third, cocaine-induced striatal DA responses are augmented by lowered serotonergic tone [50].

Variations in DA reactivity are also related to differences in impulsive personality traits. Indeed, high novelty seeking scores and other impulsive personality traits co-vary with greater amphetamine-induced DA release within the ventral limbic striatum [22,51]. These highly heritable behavioral traits are strongly predictive of susceptibility to substance misuse [40-42].

Summary & Conclusions
The literature on individual differences in DA function and its relation to susceptibility to SUDs in humans remains in its infancy. Most core findings await replication, there is variability in the definitions of risk and the test challenges employed, and the findings might have the most relevance for stimulant drug and alcohol problems associated with early onset of use and high externalizing behavioral traits. This noted, the studies as a whole make it no longer incautious to propose that altered striatal DA reactivity might well contribute to risk for SUDs. Individual differences in these tendencies might reflect both heritable and acquired features, and be related to impulsive personality traits, early life adversity, D2 autoreceptors, serotonergic tone, cortical thickness, and enduring effects of initial drug use itself.

Acknowledgements
The author thanks Drs. Sylvia Cox and Natalia Jaworska for helpful feedback on an earlier version of this paper. Funding for cited studies by the author came from the Canadian Institutes of Health Research (# 37421, # 36429).

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Box 1. Multiple effects of reward related cues.
Cues paired with reward availability can produce multiple effects. They can elicit approach, reinforce novel actions, invigorate responding for other rewards, and increase DA transmission [54]. Cues paired with the absence of rewards can produce the converse responses [55]. Some of these effects are now well demonstrated in humans. For example, evidence of conditioned attentional biases to alcohol and methamphetamine ingestion has been reported to develop in healthy volunteers [56,57]. Drug cue-induced striatal DA release has been observed in healthy volunteers exposed to a repeated amphetamine regimen [28], in recreational cocaine users [24], and in participants with moderate to severe cocaine use disorders [25,27,29].

The exact locus of striatal responses to conditioned cues can vary depending upon the stimulus features. In rodents, the non-contingent presentation of drug-related cues leads to DA responses in the ventral striatum, and these responses become progressively larger as the number of pairings increase [7,58]. In comparison, DA responses to behaviorally contingent cues begin in the ventral striatum and then emerge in the dorsal striatum as animals transition from flexible goal-directed approach to stimulus-response habits [7,59]. Following even more extensive exposure to *ad lib* cocaine availability, these DA responses appear to decrease [66], raising the possibility that compulsive responses to freely available drug reward become independent of striatal DA bursts.

Preliminary evidence of these shifts in the locus of conditioned DA responses have also been reported in humans. In healthy volunteers exposed to a brief laboratory *d*-amphetamine regimen (3 x 0.3mg/kg, po), re-exposure to a placebo capsule and the drug-paired PET environment leads to striatal DA release with the largest effects in the ventral limbic region [28]. In comparison, in those with more extensive substance use histories, the largest effects appear in the dorsal somatosensory striatum [26,27,29], and this includes recreational cocaine users without an SUD [30]. Finally, as seen in laboratory animals [3], decreasing DA transmission does not affect the ingestion of freely available drugs in experienced users [60,61] but does lower the motivation to exert effort to obtain rewards, such as alcohol [62], tobacco [63], and money [64].

Table 1. Striatal [^{11}C]raclopride binding values (DRD2 receptor availability) in people at high *vs.* low risk for substance use disorders.

	Munro et al 2006 [7]	**Casey et al 2014** [8]	**Setiawan et al 2014** [9]	**Weiland et al 2016** [10]	**Volkow et al 2006** [11]	**Alvanzo et al 2015** [12]
Primary result	No group differences	No group differences	No group differences	No group differences	Elevated DRD2 in FHP	Elevated DRD2 in FHP
Participants	FHN: n=30 FHP: n=11	FHN1: n=17 FHN2: n=15 FHP: n=16	Low risk: n=13 High risk: n=13	FHN: n=11 FHP low-risk: n=24 FHP: high-risk: n=9	FHN: n=16 FHP: n=15	FHN: n=60 FHP: n=24
Age	FHN: 21.9±3 FHP: 21.7±3	FHN1: 20.5±2 FHN2: 22.1±2 FHP: 21.3±2	Low risk: 21.5±3 High-risk: 21.1±3	FHN: 20.6±3 FHP low-risk: 22.0±3 FHP high-risk: 24.2±3	FHN: 26±4 FHP: 24±3	FHN: 22.7±3 FHP: 23.1±3
Sex (M/F)	FHN: 20/10 FHP: 7/4	FHN1: 10/7 FHN2: 9/6 FHP: 6/10	Low-risk: 10/3 High-risk: 8/5	FHN: 11/0 FHP low-risk: 24/0 FHP: high-risk: 9/0	FHN: 14/1 FHP: 14/2	FHN: 38/22 FHP: 13/11
Family history of SUDs*	AUDs only FHN: 0.2 FHP: 1.8	FHN1: 0±0 FHN2: 0±0 FHP: 3.1±0.7	Low risk: 0.19 High risk: 1.04	AUDs only FHN: 0.04 FHP low-risk: 1.4 FHP: high-risk: 1.1	AUDs only FHN: 0.0 FHP: ≥2.0	AUDs only FHN: 0.0 FHP: 2.3
Age of onset	Not reported	First alcohol intoxication FHN1: 15.7±1 FHN2: 14.6±1.9 FHP: 15.7±3 First intoxication any drug: FHN1: 15.7±1 FHN2: 14.1±1 FHP: 13.1±2	First alcohol intoxication Low-risk: 15.5±2 High-risk: 15.2±2	First alcohol intoxication FHN: 17.8±1 FHP low-risk: 18.1±2 FHP: high-risk: 13.9±1	Not reported	Not reported
Drug and alcohol use	FHN: 1.5 drinks / week FHP: 4.3 drinks / week	Lifetime cocaine use FHN1: 0±0 FHN2: 12±24	Low risk: 8±9 drinks / week High-risk: 13±9 drinks / week	FHN: 3±4 drinks / week FHP low-risk: 1±2 drinks /	FHN: 2 current smokers FHP: 3 current	FHN: 6 drinks / week FHP: 11 drinks / week

		FHP: 30±47 Lifetime amphetamine use FHN1: 0±0 FHN2: 17±24 FHP: 11±13		week FHP: high-risk: 12±23 drinks / week	smokers	
Impulsive traits	NEO-PI Extraversion FHN: 49.7±7 FHP: 51.9±6	TPQ Novelty Seeking FHN1: 17.8±4 FHN2: 21.6±2 FHP: 22.5±5 TPQ Impulsivity FHN1: 2.8±2 FHN2: 3.6±2 FHP: 4.7±2	TPQ Novelty Seeking Low-risk: 15.7±4 High-risk: 19.0±5 TPQ Impulsivity Low-risk: 1.6±0.4 High-risk: 2.9±0.6	Zuckerman Sensation Seeking FHN: 6.1±2 FHP low-risk: 6.1±3 FHP high-risk: 8.7±2	MMPI Constraint FHN: 52.9±9 FHP: 44.0±14 MMPI Self-Control FHN: 17.7±5 FHP: 13.4±5	Not reported

* Family history of substance use disorders (SUDs): An affected 1st degree relative equals 1. An affected 2nd degree relative equals 0.5. DA: dopamine. FHN1: Stimulant drug-naïve healthy volunteers without a FH of SUDs. FHN2: Stimulant drug users without a FH of SUDs. FHP low-risk: late onset FH positive drinkers. FHP high-risk: early onset FH positive drinkers. MMPI: Minnesota Multiphasic Personality Inventory.

Table 2. Striatal [^{11}C]raclopride displacement in people at high *vs.* low risk for substance use disorders.

	Munro et al 2006 [7]	**Alvanzo et al 2015** [12]	**Oberlin et al 2015** [17]	**Casey et al 2014** [8]	**Oberlin et al 2013** [16]	**Setiawan et al 2014** [9]	**Weiland et al 2016** [10]
Primary result	No group difference in response to *d*-amphetamine (0.3 mg/kg, iv)	No group difference in response to *d*-amphetamine (0.3 mg/kg, iv) in FHP *vs.* FHN	No group difference in response to beer flavor spray, ethanol injection (0.6g/dL, iv), or spray + injection	Smaller DA response in ventral striatum to *d*-amphetamine (0.3 mg/kg, po) in FHP *vs.* FHN1 + FHN2	Greater DA response in ventral striatum to beer flavor spray in FHP *vs.* FHN	Greater DA response in ventral and dorsal striatum to a drink of alcohol (0.75g/kg, po) in FHP- *vs.* FHN	Greater DA response in ventral striatum to monetary reward in FHP *vs.* FHN
Participants	FHN: n=11 FHP: n=30	FHN: n=60 FHP: n=24 {Includes participants from Munro et al 2006}	Total sample: n=26 Sub-group data not provided	FHN1: n=17 FHN2: n=15 FHP: n=16	FHN: n= 19 FHA: n=18 FHP: n=12	Low risk: n=13 High risk: n=13	FHN: n=11 FHP low-risk: n=24 FHP: high-risk: n=9
Age	FHN: 21.9±3 FHP: 21.7±3	FHN: 22.7±3.2 FHP: 23.1±3.0	Total sample: 23.1±3.3 Sub-group data not provided	FHN1: 20.5±2 FHN2: 22.1±2 FHP: 21.3±2	FHN: 24.8±3.2 FHA: 24.7±3.9 FHP: 24.6±3.8	Low risk: 21.5±3 High-risk: 21.1±3	FHN: 20.6±2.7 FHP low-risk: 22.0±2.8 FHP high-risk: 24.2±2.9
Sex (M/F)	FHN: 20/10 FHP: 7/4	FHN: 38/22 FHP: 13/11	Total sample: 26/0 Sub-group data not provided	FHN1: 10/7 FHN2: 9/6 FHP: 6/10	FHN: 19/0 FHA: 18/0 FHP: 12/0	Low risk: 10/3 High risk: 8/5	FHN: 11/0 FHP low-risk: 24/0 FHP: high-risk: 9/0
Family history of SUDs*	AUDs only FHN: 0.2 FHP: 1.8	AUDs only FHN: 0.0 FHP: 2.3	Not provided	FHN1: 0±0 FHN2: 0±0 FHP: 3.1±0.7	AUDs only** FHN: 0.0±0.0 FHA: 1.3±0.6 FHP: 2.2±1.3	Low risk: 0.19 High risk: 1.04	AUDs only FHN: 0.04 FHP low-risk: 1.4 FHP: high-risk: 1.1
Age of onset	Not reported	Not reported	Total sample: 16.4±2.2 Sub-group data not provided	First alcohol intoxication FHN1: 15.7±1 FHN2: 14.6±1.9 FHP: 15.7±3 First intoxication any drug: FHN1: 15.7±1	Not reported	First alcohol intoxication Low-risk: 15.5±2.1 High-risk: 15.2±2.2	First alcohol intoxication FHN: 17.8±1 FHP low-risk: 18.1±2 FHP: high-risk: 13.9±1

				FHN2: 14.1±1 FHP: 13.1±2			
Drug and alcohol use	FHN: 1.5 drinks / week FHP: 4.3 drinks / week	FHN: 6 drinks / week FHP: 11 drinks / week	Total sample: 23.0±12.0 drinks per week Sub-group data not provided	Lifetime cocaine use FHN1: 0±0 FHN2: 12±24 FHP: 30±47 Lifetime amphetamine use FHN1: 0±0 FHN2: 17±24 FHP: 11±13	FHN: 13.4±12 FHA: 16.9±9.5 FHP: 20.8±12.1	Low risk: 8±9 drinks / week High-risk: 13±9 drinks / week	FHN: 3±4 drinks / week FHP low-risk: 1±2 drinks / week FHP: high-risk: 12± 22 drinks / week
Impulsive traits	NEO-PI Extraversion FHN: 49.7±7 FHP: 51.9±6	Not reported	Not reported	TPQ Novelty Seeking FHN1: 17.8±4 FHN2: 21.6±2 FHP: 22.5±5 TPQ Impulsivity FHN1: 2.8±2 FHN2: 3.6±2 FHP: 4.7±2	Not reported	TPQ Novelty Seeking Low-risk: 15.7±4 High-risk: 19.0±5 TPQ Impulsivity Low-risk: 1.6±0.4 High-risk: 2.9±0.6	Zuckerman Sensation Seeking FHN: 6.1±2 FHP low-risk: 6.1±3 FHP high-risk: 8.7±2

* Family history of substance use disorders (SUDs): An affected 1st degree relative equals 1. An affected 2nd degree relative equals 0.5. ** Did not differentiate between first and second-degree relatives. DA: dopamine. FHN1: Stimulant drug-naïve healthy volunteers without a FH of SUDs. FHN2: Stimulant drug users without a FH of SUDs. FHP low-risk: late onset FH positive drinkers. FHP high-risk: early onset FH positive drinkers. TPQ: Tridimensional Personality Questionnaire. NEO-PI: Neo-five factor Personality Inventory.