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Title: Computational risk profiles of impulsive decision-making for substance use disorders: similarities and differences between stimulants and opioids

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Abstract

Objective: Impulsive decision-making is strongly associated with substance use disorders (SUD). We used a battery of decision-making tasks to investigate similarities and differences in decision-making patterns between stimulant (amphetamine) and opioid (heroin) users. Additionally, we explored whether impulsive decision-making could serve as a potential endophenotype for addiction using a sibling comparison design.

Methods: Participants included individuals with "pure" SUD (opioids: N=157, stimulants: N=140), healthy controls (N=240), and unaffected siblings of opioid (N=67) and stimulant (N=52) users. We used the Iowa Gambling Task (IGT), Cambridge Gambling Task (CGT), Balloon Analogue Risk Task (BART), and Delayed Reward Discounting Task (DRDT) to measure decision-making. Task behaviors were analyzed using hierarchical Bayesian modeling and we compared the group-level decision-making computational parameters.

Results: Both drug groups had higher temporal discounting of rewards on the DRDT and CGT; tended to prioritize their past choices over past rewards on the IGT, indicated by high perseverance weight and low outcome frequency weight; and weighed more recent choices over distant ones on the IGT. These patterns were also observed in their unaffected siblings, indicating potential endophenotypes. Opioid users and their siblings displayed reduced loss sensitivity on the IGT and CGT, indicating that this might be an endophenotype specific to opioid addiction.

Conclusions: This study provides insights into common and specific decision-making vulnerabilities of different types of drug addictions, some of which were observed in unaffected siblings, suggesting potential endophenotypes. Such computational decision-making profiles could increase the precision of neurocognitive assessment and aid in developing targeted intervention strategies.

Introduction

Substance use disorders (SUDs) are characterized by an uncontrollable urge to seek and use drugs despite their adverse impacts on psychological and physical health. Prioritizing drug use over personal well-being is typically accompanied by decision-making impairments (1–3), making it crucial to identify the distinctive dysfunctions associated with SUD. However, it remains unclear which specific decision-making patterns are common across addictions and which are unique to specific classes of drugs.

Although all addictive drugs engage the dopaminergic reward system, their mechanisms of action and neuropsychological profiles differ, as shown in many preclinical studies (e.g., stimulants vs. opioids) (4–6). In humans, Fernández-Serrano et al. (2011) reviewed studies revealing distinct decision-making patterns in users of different drugs (7). Specifically, stimulants were linked to impairments in inhibition and shifting, while opioids were associated with impairments in reasoning (8). Both types of drugs, however, were associated with higher delay discounting (9). This finding aligns with previous research (10–13) using a Bulgarian sample, which provided a rare opportunity to study relatively "pure" drug effects on human subjects. With opioids and stimulants introduced sequentially in the country, there was a predominance of mono-dependent participants. Studies using this sample also found higher delay discounting in both the stimulant and opioid groups (12, 13). Additionally, reduced loss sensitivity was observed only in opioid users (10, 11).

Of particular interest is whether these decision-making impairments are endophenotypes of addiction. Endophenotypes are quantitative neurobiological correlates of clinical disorders, thought to be genetically determined and stable over time (14). One of the criteria outlined by Gottesman and Gould (14) suggests that they should be observable both in individuals with the disorder and their first-degree relatives. In previous research, Ersche and colleagues found that not only chronic stimulant users but also their unaffected siblings exhibit increased levels of impulsivity and anxiety (15, 16), and deficits in executive function and response control (15, 17). These deficits correlated with white matter loss in frontal regions and greater volume in the amygdala and putamen in both groups. Another recent study reported similar findings of impaired response inhibition and an impulsivity-anxiety profile in

stimulant users and their siblings (18). Additionally, they observed that opioid users and their siblings showed increased risk-taking, delay aversion, sensation seeking, and hopelessness.

However, there are several limitations in previous research. First, most studies have primarily focused on a single type of drug or polydrug use, rather than examining different types of drugs. This approach precludes identifying common and unique vulnerabilities among users of different types of drugs, each with distinct neurobiological mechanisms. Additionally, there has been a lack of comprehensive exploration of decision-making across multiple tasks using computational modeling. Computational modeling quantifies the underlying decision-making processes and offers sophisticated means to capture latent decision-making parameters. However, none of the previous endophenotype studies using sibling comparisons have utilized computational measures or an array of tasks.

Our study aimed to address these research gaps by exploring similarities and differences in decision-making styles between users of two different types of drugs (stimulants and opioids), using multiple decision-making tasks and computational modeling. We used the aforementioned Bulgarian sample of mono-dependent participants, which allowed us to observe relatively "pure" drug effects. Also, we compared decision-making profiles between drug users and their unaffected siblings to investigate potential endophenotypes. Based on previous studies (10–13), we hypothesized that increased delay discounting would be a common endophenotype of stimulant and opioid use disorders, while decreased loss sensitivity would be a unique endophenotype of opioid use disorder.

Methods

Participants

The study included 656 participants, enrolled in a larger study on impulsivity in opioid and stimulant users in Sofia, Bulgaria. Participants were recruited through collaborations with NGOs, treatment facilities, and outreach via flyers at clinics, nightclubs, bars, and cafés in Sofia, as well as through the study website. Initial screenings were conducted by phone and in person, covering self-reported demographic data, medical and substance use histories. The study received approval from the

Institutional Review Boards of Virginia Commonwealth University and the Medical University-Sofia, and written informed consent was obtained from all subjects. For further details on the study and participant recruitment, refer to our previous works (19). Inclusion criteria included: (1) age between 18 and 50 years; (2) estimated IQ greater than 75, (3) at least an 8th-grade education, (4) no history of neurological illness, traumatic brain injury or loss of consciousness for more than 30 minutes, (5) HIV seronegative status, (6) no history of serious psychiatric illness (e.g., psychotic or mood disorders), (7) not in active treatment with opioid agonists, (8) no current use of medications that affect impulsivity (e.g., neuroleptics, sedatives, antidepressants) and (9) negative breathalyzer test for alcohol and negative urine toxicology screen for amphetamines, methamphetamine, cocaine, opioids, methadone, cannabis, benzodiazepines, barbiturates, and MDMA. To assess for potential endophenotypes, the study included participants with SUD (opioids: N=157; stimulants: N=140), their biological siblings with no history of substance dependence (opioids: N=67; stimulants: N=52), and controls (N=240). Participants with SUD met DSM-IV criteria for opioid or stimulant dependence. They were mono-dependent on opioids or stimulants with no history of dependence on other substances, except for caffeine and nicotine. Most SUD participants had maintained protracted abstinence for over 12 months at the time of testing.

Demographic and psychological information

Demographic measures included self-reported biological sex, age, ethnicity, years of education, General Equivalency Diploma (GED), and work status. IQ was assessed with the Raven's Progressive Matrices (Table 1). We assessed the psychological characteristics of impulsivity, sensation seeking, depression, anxiety, aggression, ADHD symptoms, psychopathy, and nicotine dependence (see section 1.2 in the online supplement for detailed information).

TABLE 1. Demographic and Substance Use Information.

		Control (N=240)	Heroin (N=157)	Amph (N=140)	Sibling heroin (N=67)	Sibling amph (N=52)	P-value
Length of abstinence	0-12 months	-	26 (20.2%)	48 (43.6%)	-	-	< 0.001
	12 + months	-	103 (79.8%)	62 (56.4%)	-	-	
Age[a]		27.39 (7.10)	33.84 (6.03)	25.72 (5.47)	34.15 (7.49)	28.65 (8.27)	< 0.001
Biological sex	Male	147 (61.2%)	120 (76.4%)	96 (68.6%)	31 (46.3%)	21 (40.4%)	< 0.001
	Female	93 (38.8%)	37 (23.6%)	44 (31.4%)	36 (53.7%)	31 (59.6%)	
Ethnicity	Bulgarian	221 (92.1%)	155 (98.7%)	138 (98.6%)	67 (100.0%)	51 (98.1%)	0.001
	Roma/Gypsy	19 (7.9%)	2 (1.3%)	1 (0.7%)	0 (0.0%)	1 (1.9%)	
	Other	0 (0.0%)	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	
Education[b]		14.30 (2.87)	13.05 (2.56)	13.14 (2.22)	15.00 (2.67)	14.98 (2.56)	< 0.001
IQ[c]		109.74 (14.14)	104.47 (13.05)	108.57 (12.18)	110.00 (12.43)	109.17 (13.90)	0.002
GED	No diploma	25 (10.4%)	19 (12.2%)	14 (10.0%)	1 (1.5%)	2 (3.8%)	0.071
	Has diploma	215 (89.6%)	137 (87.8%)	126 (90.0%)	66 (98.5%)	50 (96.2%)	
Work	Doesn't work	106 (44.2%)	74 (47.1%)	81 (57.9%)	15 (22.4%)	23 (44.2%)	< 0.001
	Works	134 (55.8%)	83 (52.9%)	59 (42.1%)	52 (77.6%)	29 (55.8%)	

[a] Heroin > Control, Amph, Sibling Amph; Sibling Heroin> Control, Amph, Sibling Amph
[b] Heroin < Control, Sibling Heroin, Sibling Amph; Amph < Control, Sibling Heroin, Sibling Amph
[c] Heroin < Control, Sibling Heroin

Decision-making tasks and computational modeling

We used four well-established decision-making tasks: the Delayed Reward Discounting Task (DRDT), the Iowa Gambling Task (IGT), the Balloon Analogue Risk Task (BART), and the Cambridge Gambling Task (CGT). We fitted several computational models to each task to assess the latent decision-making parameters and identify the best model. We also fitted the models separately to each group (10).

See sections 1.1 and 1.3 in the online supplement for detailed descriptions of the tasks and their behavioral indices.

We used hierarchical Bayesian analysis (HBA) for model-fitting and parameter estimation, which offers advantages over the conventional Maximum Likelihood Estimation (MLE) method. HBA provides parameters as posterior distributions (unlike point estimates of MLE), providing additional information on the uncertainty of the values. The hierarchical structure of HBA allows for stable estimation of individual parameters even with limited data, addressing the noise and unreliability often associated with individual-level MLE estimates (20, 21). HBA was conducted using hBayesDM (version 1.1.1) (22), based on R Stan (version 2.21.0) (23), which utilizes Markov chain Monte Carlo (MCMC) algorithms, including the Hamiltonian Monte Carlo method. To minimize the influence of priors, weakly informative priors were chosen (22) and a non-centered parameterization was employed for sampling efficiency (24).

We used four independent chains with a sample size of 2000 including 1000 burn-in samples per chain, and employed variational Bayes methods for setting initial values. In cases where this default setting did not achieve chain mixing, we used four chains of 4000 samples, with 2000 burn-in samples, with or without manually setting initial values. To ensure the accuracy of parameter estimation, we conducted a thorough examination of well-mixed trace plots and monitored the Rhat values (Rhat < 1.1). The few individuals who did not converge and exhibited Rhat values larger than 1.1 were excluded from the analysis (e.g. 2 individuals in the control group when fitting the best-fitting model for the IGT, Outcome-Representation Learning model).

To compare and identify the best-fitting model for each task, we conducted the Leave-One-Out Information Criterion (LOOIC) (25) using the R package “loo”. LOOIC assesses out-of-sample prediction accuracy by calculating log-likelihood from posterior simulations of estimated parameters. We selected the best-fitting model for each task by identifying the model with the lowest LOOIC value (25) and also considered the reliability of model performance based on previous literature (11, 12, 26, 27).

Group comparisons of model parameters

We conducted group-level analyses by comparing the posterior distribution of the control group with that of other groups. We first identified the differences between the control group and SUD groups to uncover common and unique decision-making patterns among substance users. Subsequently, for parameters that exhibited differences in the initial analysis, further comparisons were made between the controls and unaffected siblings to identify potential endophenotypes (15). Credible group differences were considered when the 95% highest density interval (HDI) of posterior difference distributions did not include the value 0 (21).

Results

Group characteristics

We analyzed data from 656 participants, including demographic information (Table 1) and psychological characteristics (Table S2). There were significant group-level differences in age, biological sex, ethnicity, education, IQ, and working status ($p < 0.05$; Table 1). From the psychological characteristics, psychopathy, depression, impulsivity, ADHD symptoms, and aggression were significantly different between groups ($p < 0.05$ for all).

Computational modeling (best-fitting models)

In each task, multiple computational models were assessed (section 1.3 in the online supplement), and the best-fitting model was chosen based on LOOIC (25) (Table S3). Table S4 provides an overview of the parameters from the best-fitting models and their interpretations.

The best-fitting model for the IGT was the Outcome-Representation Learning model (11) with five parameters: A+ and A- for reward and punishment learning rates, β_P and β_F for perseverance weight and outcome frequency weight, and K for perseverance decay. Higher values for A+ and A- suggest a

greater reliance on past reward or punishment outcomes. Increased β_P and β_F values indicate a stronger influence of past choice frequency or reward outcome frequency on choices, respectively. Lastly, K governs the extent to which choice perseverance diminishes over time.

In the CGT, we assessed the Cumulative model (12) with five parameters: α, c, ρ, β, and γ. The α reflects subjective probabilities for color choices, indicating the perceived likelihood of a token being under a red or blue box. Higher α values suggest a preference for the color with a higher probability of containing a token. The color bias parameter, c, accounts for potential color preferences, with values closer to 1 indicating a bias for the color red. The utility parameter ρ governs sensitivity to losses relative to gains, where values less than 1 indicate risk-seeking and values greater than 1 indicate risk aversion. β represents the delay discounting rate, reflecting a preference for small immediate over large delayed rewards. Lastly, γ captures the degree of randomness in choices based on expected values, with higher values indicating more deterministic choices and lower values indicating greater randomness.

In the DRDT, we used a hyperbolic model with two key parameters: k and β. The k parameter represents the delay discounting rate. The β is the inverse temperature, capturing the degree of randomness in choices.

In the BART, the best model was the Exponential-Weighted Mean-Variance model (28), consisting of five parameters: φ, η, ρ, τ, and γ. The φ parameter quantifies initial beliefs about the likelihood of a balloon exploding. The η serves as an updating coefficient that adjusts beliefs based on observed data, with higher values indicating rapid alignment with observed data. The ρ characterizes risk preference. The τ represents choice randomness, and γ reflects loss aversion.

Group Comparisons of Model Parameters

We computed the posterior distributions of all group-level parameters for the best-fitting model in each task and conducted comparisons among the healthy control group, the stimulant group, the opioid group, as well as the unaffected siblings. We also computed the standard neurobehavioral task differences between groups (Table S1).

Common Characteristics of Opioid and Stimulant Users

We found common decision-making patterns of increased delay discounting on the DRDT and CGT (Figure 1). Both the opioid and stimulant groups demonstrated high delay discounting rate (k) on the DRDT, indicating greater devaluation of rewards with increasing time delays (opioid: 95% HDI=[0.006, 0.035]; stimulant: 95% HDI=[0.003, 0.036]). The delay discounting parameter (β) on the CGT showed an increasing trend consistently for both groups. The trend was marginally credible, where opioid users showed a 95% HDI from -0.0002 to 0.033 and the stimulant group showed a 95% HDI ranging from -0.0002 to 0.026.

On the IGT (Figure 2), both opioid and stimulant users exhibited a decrease in outcome frequency weight (β_F) when compared to controls (opioid: 95% HDI=[-1.24, -0.168]; stimulant: 95% HDI=[-1.319, -0.297]). Opioid and stimulant users also had increased perseverance weight (β_P) compared to controls (opioid: 95% HDI=[0.145, 2.825]), marginally different between stimulant and control groups (95% HDI=[-0.264, 2.422]). Additionally, both stimulant and opioid groups exhibited an increase in perseverance decay (K), indicating a tendency to consider shorter past histories of their deck selections on each trial (opioid: 95% HDI=[0.549, 1.263]; stimulant: 95% HDI=[0.165, 1.022]).

In terms of choice randomness, both opioid and stimulant groups showed increased randomness in their choice behavior (lower choice sensitivity; γ) on the CGT (opioid: 95% HDI=[-1.25, -0.916]; stimulant: 95% HDI=[-1.178, -0.836]), but the stimulant group also displayed decreased randomness (low inverse temperature; β) on the DRDT (95% HDI=[-0.089, -0.001]).

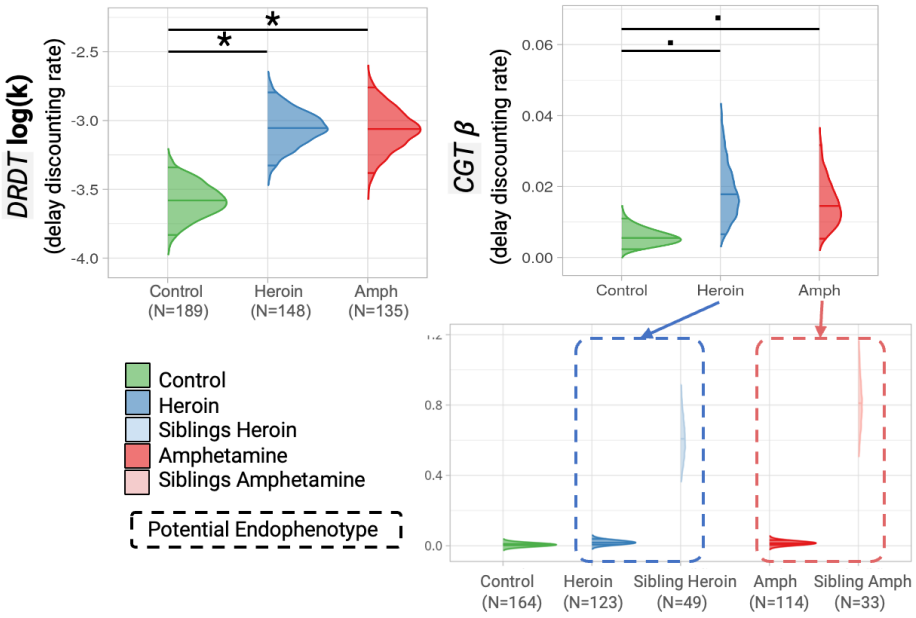

FIGURE 1. Common Characteristics of Temporal Discounting in the Opioids (Heroin) and Stimulants (Amphetamine) Groups.

* Credible difference: HDI does not include 0. · Trend: HDI does include 0 but 90% of samples are located under 0.

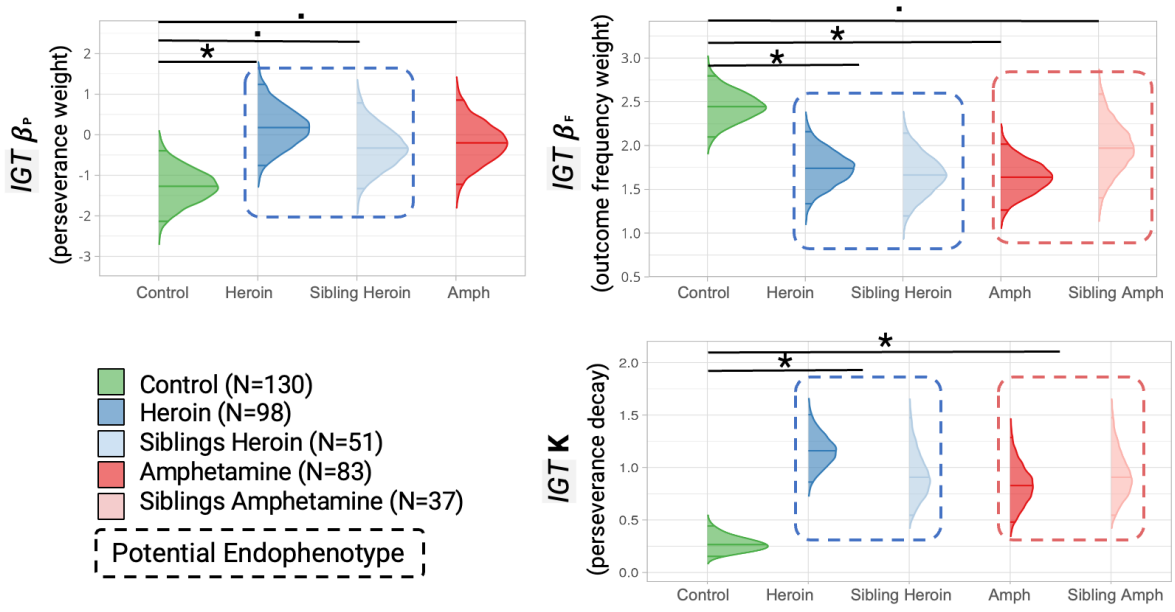

FIGURE 2. Common Characteristics of IGT in the Opioids (Heroin) and Stimulants (Amphetamine) Groups.

* Credible difference: HDI does not include 0. · Trend: HDI does include 0 but 90% of samples are located under 0.

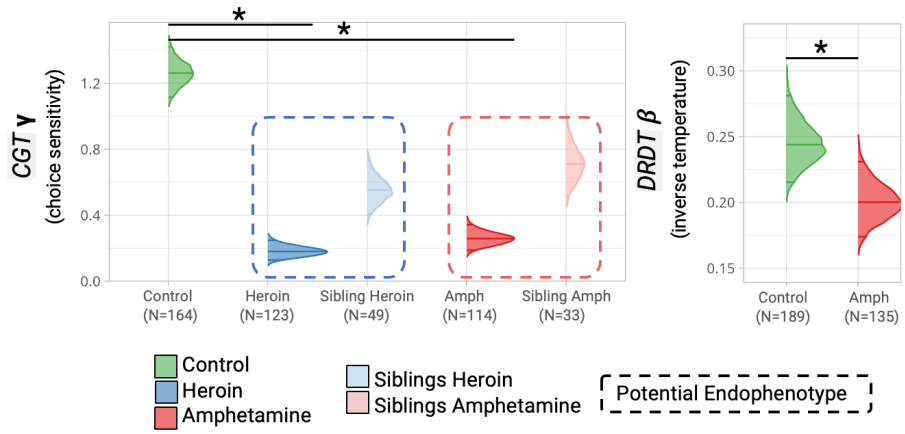

FIGURE 3. Common Characteristics of CGT Choice Randomness in the Opioids (Heroin) and Stimulants (Amphetamine) Groups.

* Credible difference: HDI does not include 0. · Trend: HDI does include 0 but 90% of samples are located under 0.

Unique Characteristics of Opioid and Stimulant Users

The opioid group showed reduced sensitivity to loss on both the IGT and the CGT (Figure 4). On the IGT, opioid users displayed diminished punishment learning rate (A-) (95% HDI=[-0.032, -0.001]). This reduction showed a decreased propensity to update expectations following a loss, indicating lower sensitivity to loss. Similarly, on the CGT, they demonstrated reduced relative loss sensitivity (ρ) (95% HDI=[-2298.793, 138.752]; 95.17% MCMC samples < 0) with marginal credibility. Stimulant users were not characterized by any unique decision-making characteristics.

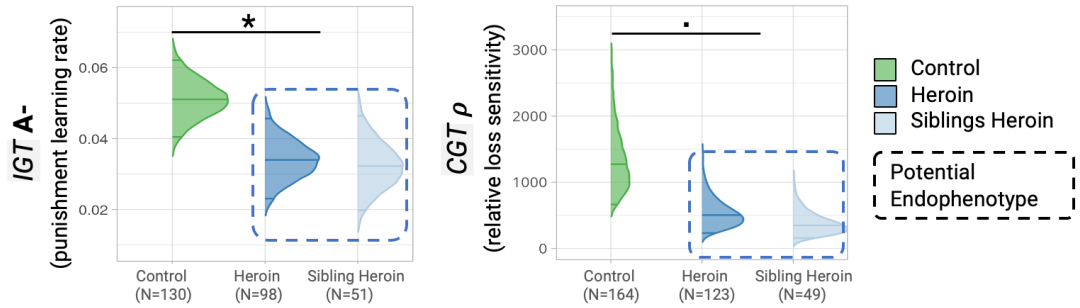

FIGURE 4. Unique Characteristics of Loss Sensitivity in the Opioids (Heroin) Groups.

* Credible difference: HDI does not include 0. · Trend: HDI does include 0 but 90% of samples are located under 0.

Potential Endophenotypes

Focusing on the decision-making parameters displaying credible differences between SUD groups and the control group, we evaluated their patterns in unaffected siblings. Arguably, if the aberrant decision-making serves as an endophenotype of addiction, it should be observed not only in the groups with SUD but also in their unaffected siblings. The pattern of high delay discounting rate observed in opioid and stimulant users was not found in their unaffected siblings on the DRDT (k) but was observed on the CGT (β) (opioid sibling: 95% HDI=[-0.911, -0.38]; stimulant sibling: 95% HDI=[-1.195, -0.52]) (Figure 1). For both opioid and stimulant groups, the stronger preference toward perseverating on their past choices (β_P) and its decay rate (K) (compared to the control group) on the IGT, were found in their unaffected siblings as well (Figure 2). The siblings of opioid users showed both low outcome frequency weight (β_F) (95% HDI=[0.196, 1.363]), marginally high perseverance weight (β_P) (95% HDI=[-2.325, 0.401]), and high perseverance decay (K) (95% HDI=[-1.213, -0.241]). The siblings of stimulant users showed marginally high outcome frequency weight (β_F) (95% HDI=[-0.23, 1.14]) and high perseverance decay (K) (95% HDI=[-1.23, -0.282]). Further, the increased choice randomness (γ) on the CGT was also found in the unaffected siblings of both opioid and stimulant groups (opioid sibling: 95% HDI=[0.752, 1.192]; stimulant sibling: 95% HDI=[0.285, 0.806]). Lastly, the unique pattern of low loss sensitivity found in the opioid group was also present in their unaffected siblings with a 95% HDI from 0.001 to 0.035 for the IGT (A-) and a 95% HDI from 358.703 to 2554.725 for the CGT (ρ) (Figure 4).

Discussion

In this study, we examined decision-making patterns in stimulant (amphetamine) and opioid (heroin) mono-dependent users, investigating their potential as endophenotypes using a sibling comparison design. The “pure” addiction phenotypes of our participants allowed us to address the question of whether these putative endophenotypes are specific to opioid or stimulant addiction, or

whether they are shared across addictions.

We hypothesized that higher delay discounting rate would serve as a potential endophenotype common to both stimulant and opioid addictions. We found partial support for this hypothesis. Specifically, we observed higher delay discounting in stimulant and opioid users compared to controls on both the DRDT and CGT. This pattern was also seen in their unaffected siblings on the CGT, but not on the DRDT. This aligns with previous research, which has consistently linked delay discounting to various SUDs in both animals and humans (1, 3, 29, 30). Notably, a meta-analysis (30) reported a robust connection between delay discounting and addiction severity across various SUDs. MacKillop (2013) suggested that delay discounting might be an endophenotype of addictive behaviors due to its stability, heritability, and presence among unaffected family members (31). However, Levitt and colleagues (2020) proposed that delay discounting might be both a cause and a consequence of drug use, challenging its role as an endophenotype (32). This highlights the need for further investigation.

We further hypothesized that reduced sensitivity to loss would be a potential endophenotype specific to opioids. Our findings reveal that opioid users and their siblings consistently show reduced loss sensitivity across multiple tasks, supporting the hypothesis. This finding is in line with previous research (1, 3, 10, 11, 29), which reports risky decision-making and lower sensitivity to potential losses in opioid users compared to healthy controls. Meta-analyses focusing on opioid users demonstrate a similar pattern on various decision-making tasks, including the IGT and CGT (3). Further supporting these findings, two studies using the same Bulgarian sample reported reduced loss aversion in opioid users. Ahn et al. (2014) applied multiple computational models to IGT data, consistently finding reduced loss aversion among opioid users across these models (10). Similarly, Haines et al. (2018) introduced a novel reinforcement learning model for the IGT, observing a lower punishment learning rate in opioid users compared to controls, indicating reduced loss aversion (11).

The reduced loss aversion, observed in both opioid users and their unaffected siblings, might be a vulnerability factor specific for opioid addiction, potentially linked to genetic predispositions. We can speculate that vulnerable individuals might be under chronic pain or stress in their daily lives, leading to a minimal response to virtual money in laboratory tasks. This is supported by evidence of reduced amygdala volume and functional connectivity in opioid-dependent individuals (33), which

mirrors findings in those with post-traumatic stress disorder who showed reduced amygdala volume (34). In this context, the reduced loss aversion observed on decision-making tasks among vulnerable individuals could be related to chronic pain or emotional distress such as depression in everyday life (Figure S5). Indeed, it has been suggested that the decision-making style of opioid users is mediated primarily by negative reinforcement mechanisms related to negative affective states (35). In other words, this heightened daily pain might result in desensitization to virtual monetary losses, reflecting a ceiling effect of pain. Also, chronic exposure and vulnerability to pain could potentially enhance susceptibility to heroin use, known for its analgesic properties. However, these hypotheses remain speculative, as the current study did not include neuroimaging data. Future research incorporating such data is necessary to further explore the underlying mechanism.

Besides our main hypotheses, we found that both opioid and stimulant user groups and their siblings showed increased perseverance on more recent choices and decreased consideration of reward frequency on the IGT, suggesting potential endophenotypes. This aligns with research indicating that SUD involves a shift from goal-directed to habitual drug-seeking behavior despite a lack of positive outcomes (36). Additionally, heightened choice randomness on the CGT was observed in both SUD and sibling groups (potential endophenotype), consistent with findings in rats and humans (37, 38). Zhukovsky et al. linked increased cocaine self-administration in rats to higher choice randomness (37), while similar trends were seen in humans after nicotine abstinence (38).

There were no unique decision-making patterns specifically associated with stimulant use among both users and their siblings. This aligns with our previous machine-learning study, which found that few neurocognitive indices uniquely predicted stimulant dependence, unlike the many unique predictors of opioid dependence (19). This might be explained by the common effect that both opioids and stimulants exert on the dopamine system. Prior research indicates that both drugs influence dopaminergic pathways, albeit through different mechanisms: stimulants increase dopamine release by activating dopamine transporters in the mesocorticolimbic pathway (39), while opioids enhance dopamine release by inhibiting the GABAergic or glutamate system, particularly in the nucleus accumbens or ventral tegmental area (40). Given this shared mechanism of dopamine modulation by both stimulants and opioids, it is plausible that this overlap is the reason behind the absence of a unique

decision-making pattern in the stimulant group.

The current study has several limitations. First, the sibling comparison design used in this study fulfills only one of the endophenotype criteria (14). Also, the sibling comparison design itself assumed that unaffected siblings, sharing approximately half of their genetic makeup, might inherit genetic vulnerabilities contributing to the disorder. However, shared environmental influences, like family dynamics, could also play a role, highlighting the need for a longitudinal design to examine pre- and post-drug use. Second, the lack of neuroimaging data limits the exploration of underlying neural mechanisms. We are currently collecting neuroimaging data on our participants, which may help delineate the neurobiological pathway from genetic predisposition to brain function and decision-making. Third, results may be specific to the protracted abstinence stage of addiction and should be interpreted with caution for other stages of the addiction cycle. However, to the best of our knowledge, this study is the first to compare latent decision-making parameters through computational modeling in a sibling comparison design to identify potential endophenotypes. The insights gained could contribute to clinical practice by increasing the precision of neurocognitive assessment and facilitate the development of targeted prevention and intervention strategies based on computational decision-making endophenotypes.

References

1. Baldacchino A, Balfour DJK, Passetti F, et al.: Neuropsychological consequences of chronic opioid use: a quantitative review and meta-analysis. Neurosci Biobehav Rev 2012; 36:2056–2068

2. Verdejo-Garcia A, Chong TT-J, Stout JC, et al.: Stages of dysfunctional decision-making in addiction. Pharmacol Biochem Behav 2018; 164:99–105

3. Biernacki K, McLennan SN, Terrett G, et al.: Decision-making ability in current and past users of opiates: A meta-analysis. Neurosci Biobehav Rev 2016; 71:342–351

4. Badiani A, Caprioli D, De Pirro S: Opposite environmental gating of the experienced utility ('liking') and decision utility ('wanting') of heroin versus cocaine in animals and humans: implications for computational neuroscience. Psychopharmacology 2019; 236:2451–2471

5. Badiani A, Belin D, Epstein D, et al.: Opiate versus psychostimulant addiction: the differences do matter. Nat Rev Neurosci 2011; 12:685–700

6. Verdejo-García AJ, Perales JC, Pérez-García M: Cognitive impulsivity in cocaine and heroin polysubstance abusers. Addict Behav 2007; 32:950–966

7. Fernández-Serrano MJ, Pérez-García M, Verdejo-García A: What are the specific vs. generalized effects of drugs of abuse on neuropsychological performance? Neurosci Biobehav Rev 2011; 35:377–406

8. Verdejo-Garcia A, Garcia-Fernandez G, Dom G: Cognition and addiction. Dialogues Clin Neurosci 2019; 21:281–290

9. Kirby KN, Petry NM: Heroin and cocaine abusers have higher discount rates for delayed rewards than alcoholics or non-drug-using controls. Addiction 2004; 99:461–471

10. Ahn W-Y, Vasileva G, Lee S-H, et al.: Decision-making in stimulant and opiate addicts in protracted abstinence: evidence from computational modeling with pure users. Front Psychol 2014; 5:849

11. Haines N, Vassileva J, Ahn W-Y: The Outcome-Representation Learning model: A novel reinforcement learning model of the Iowa Gambling Task. Cogn Sci 2018; 42:2534–2561

12. Romeu RJ, Haines N, Ahn W-Y, et al.: A computational model of the Cambridge gambling task

with applications to substance use disorders. Drug Alcohol Depend 2020; 206:107711

13. Kvam PD, Romeu RJ, Turner BM, et al.: Testing the factor structure underlying behavior using joint cognitive models: Impulsivity in delay discounting and Cambridge gambling tasks. Psychol Methods 2021; 26:18–37

14. Gottesman II, Gould TD: The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry 2003; 160:636–645

15. Ersche KD, Turton AJ, Chamberlain SR, et al.: Cognitive dysfunction and anxious-impulsive personality traits are endophenotypes for drug dependence. Am J Psychiatry 2012; 169:926–936

16. Ersche KD, Bullmore ET, Craig KJ, et al.: Influence of compulsivity of drug abuse on dopaminergic modulation of attentional bias in stimulant dependence. Arch Gen Psychiatry 2010; 67:632–644

17. Ersche KD, Jones PS, Williams GB, et al.: Abnormal brain structure implicated in stimulant drug addiction. Science 2012; 335:601–604

18. Long EC, Kaneva R, Vasilev G, et al.: Neurocognitive and Psychiatric Markers for Addiction: Common vs. Specific Endophenotypes for Heroin and Amphetamine Dependence. Curr Top Med Chem 2020; 20:585–597

19. Ahn W-Y, Vassileva J: Machine-learning identifies substance-specific behavioral markers for opiate and stimulant dependence. Drug Alcohol Depend 2016; 161:247–257

20. Ahn W-Y, Krawitz A, Kim W, et al.: A model-based fMRI analysis with hierarchical Bayesian parameter estimation. J Neurosci Psychol Econ 2011; 4:95–110

21. Kruschke J: Doing Bayesian Data Analysis: A Tutorial with R, JAGS, and Stan. Academic Press, 2014

22. Ahn W-Y, Haines N, Zhang L: Revealing Neurocomputational Mechanisms of Reinforcement Learning and Decision-Making With the hBayesDM Package. Comput Psychiatr 2017; 1:24–57

23. Stan Development Team: RStan: the R interface to Stan [Internet]. R package version 2326 2024; Available from: https://mc-stan.org/

24. Papaspiliopoulos O, Roberts GO, Sköld M: A General Framework for the Parametrization of Hierarchical Models. Stat Sci 2007; 22:59–73

25. Vehtari A, Gelman A, Gabry J: Practical Bayesian model evaluation using leave-one-out cross-validation and WAIC. Stat Comput 2017; 27:1413–1432

26. Green L, Myerson J: Exponential Versus Hyperbolic Discounting of Delayed Outcomes: Risk and Waiting Time. Integr Comp Biol 1996; 36:496–505[cited 2024 Aug 2]

27. McKerchar TL, Green L, Myerson J, et al.: A comparison of four models of delay discounting in humans. Behav Processes 2009; 81:256–259

28. Park H, Yang J, Vassileva J, et al.: Development of a novel computational model for the Balloon Analogue Risk Task: The exponential-weight mean–variance model. J Math Psychol 2021; 102:102532

29. Chen S, Yang P, Chen T, et al.: Risky decision-making in individuals with substance use disorder: A meta-analysis and meta-regression review. Psychopharmacology 2020; 237:1893–1908

30. Amlung M, Vedelago L, Acker J, et al.: Steep delay discounting and addictive behavior: a meta-analysis of continuous associations. Addiction 2017; 112:51–62

31. MacKillop J: Integrating behavioral economics and behavioral genetics: delayed reward discounting as an endophenotype for addictive disorders. J Exp Anal Behav 2013; 99:14–31

32. Levitt E, Sanchez-Roige S, Palmer AA, et al.: Steep Discounting of Future Rewards as an Impulsivity Phenotype: A Concise Review. Curr Top Behav Neurosci 2020; 47:113–138

33. Upadhyay J, Maleki N, Potter J, et al.: Alterations in brain structure and functional connectivity in prescription opioid-dependent patients. Brain 2010; 133:2098–2114

34. Morey RA, Gold AL, LaBar KS, et al.: Amygdala volume changes in posttraumatic stress disorder in a large case-controlled veterans group. Arch Gen Psychiatry 2012; 69:1169–1178

35. Vassileva J, Psederska E, Bjork JM: Negative affectivity drivers of impulsivity in opioid use disorder. Nat Rev Psychol 2025; 4:170–192[cited 2025 Apr 6]

36. Everitt BJ, Robbins TW: Drug Addiction: Updating Actions to Habits to Compulsions Ten Years On. Annu Rev Psychol 2016; 67:23–50

37. Zhukovsky P, Puaud M, Jupp B, et al.: Withdrawal from escalated cocaine self-administration impairs reversal learning by disrupting the effects of negative feedback on reward exploitation: a behavioral and computational analysis. Neuropsychopharmacology 2019; 44:2163–2173

38. Roewer I, Wiehler A, Peters J: Nicotine deprivation, temporal discounting and choice consistency

in heavy smokers. J Exp Anal Behav 2015; 103:62–76

39. Koob GF: Drugs of abuse: anatomy, pharmacology and function of reward pathways. Trends Pharmacol Sci 1992; 13:177–184

40. Le Merrer J, Becker JAJ, Befort K, et al.: Reward processing by the opioid system in the brain. Physiol Rev 2009; 89:1379–1412