Neuroscience and Biobehavioral Reviews 108 (2020) 295–307

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

# Substance related disorders are associated with impaired valuation of delayed gratification and feedback processing: A multilevel meta-analysis and meta-regression

B. Kluwe-Schiavon[a,b,*], T.W. Viola[b], B. Sanvicente-Vieira[b], F.S. Lumertz[b], G.A. Salum[c], R. Grassi-Oliveira[b], B.B. Quednow[a,d]

[a] Experimental and Clinical Pharmacopsychology, Department of Psychiatry, Psychotherapy, and Psychosomatics, Psychiatric Hospital, University of Zurich, Lenggstrasse 31, CH-8032, Zurich, Switzerland
[b] Developmental Cognitive Neuroscience Laboratory, Brain Institute, Pontifical Catholic University of Rio Grande do Sul, Pontifical Catholic University of Rio Grande do Sul, Ipiranga Avenue, 6681, 11, 936. Partenon, 90619-900, Porto Alegre, RS, Brazil
[c] Hospital de Clínicas de Porto Alegre, Federal University of Rio Grande do Sul, Hospital de Clínicas de Porto Alegre, Ramiro Barcelos Street, 2350 - Santa Cecilia, Porto Alegre, RS 90035-007, Brazil
[d] Neuroscience Center Zurich, University of Zurich and Swiss Federal Institute of Technology Zurich, Rämistrasse 101, CH-8092 Zürich, Switzerland

ARTICLE INFO

*Keywords:*
Addiction
Decision-making
Substance use related disorders
Cognition
Impulsivity
Temporal discounting
Risk-taking
Impulse control
Reward impulsivity

ABSTRACT

Across numerous studies, individuals with substance use disorders (SUDs) differed from non-using controls regarding valuation of delayed gratification and feedback processing. However, it remains unclear whether the magnitude of the effect sizes is different across these two cognitive processes and how specific SUDs as well as demographic and clinical moderators influence these effects. In this study we thus performed multilevel linear mixed-effects meta-analyses and meta-regressions to examine the effects of SUDs on the Delay Discounting Task (DD) and on the Iowa Gambling Task (IGT). We found a moderate to large effect for SUD on both, the IGT and DD. While the effect on the DD was generalized to all substance classes, a smaller effect for cannabis-related disorder when compared to other SUDs was found with regard to the IGT. Early onset of substance use and psychiatric comorbidities were associated with stronger effects on the DD. Our findings suggest that feedback processing is more vulnerable to specific substance effects, while valuation of delayed gratification depends more on developmental and clinical factors.

## 1. Introduction

Substance use disorders (SUDs) are chronic psychiatric conditions that comprise a cluster of cognitive, behavioural and physiological symptoms indicating that the individual continues using a substance despite significant substance-related problems (APA., 2013). The diagnosis of a substance use disorder is based on a pathological pattern of behaviours, which often involve shifting from an impulsive initial drug use to a compulsive drug-seeking behaviour and loss of control over limited drug intake (Volkow and Morales, 2015). An increasing amount of research has associated decision-making impairments with addiction, leading to proposals that impairments in this function could play a role in the aetiology – but also occur as consequence – of SUDs, thereby contributing to both the initiation and maintenance of addictive behaviour (Bickel et al., 2018; Koffarnus and Kaplan, 2018). Decision-making reflects the ability to choose the most advantageous option from a range of alternatives, considering both their short-term and long-term consequences (Bechara, 2005). It involves a series of different processes that has been summarized e.g., in the three-stage framework proposed by Verdejo-Garcia et al. (2018) and the neurobiological framework of value-based decision-making proposed by Rangel et al. (2008). Despite some conceptual differences, it is well-accepted that two key processes involved in decision-making are the choice implementation or action selection, and the feedback processing or outcome evaluation (Rangel et al., 2008; Verdejo-Garcia et al., 2018). Remarkably, it has been shown that substance-dependent individuals differ from drug-naive controls regarding their valuation of delayed rewards during choice implementation and their learning from

* Corresponding author.
*E-mail addresses:* brunokluwe@gmail.com (B. Kluwe-Schiavon), thiago.viola@acad.pucrs.br (T.W. Viola), brenosanvicente@gmail.com (B. Sanvicente-Vieira), fsindermannlumertz@gmail.com (F.S. Lumertz), gsalumjr@gmail.com (G.A. Salum), rodrigo.grassi@pucrs.br (R. Grassi-Oliveira), quednow@bli.uzh.ch (B.B. Quednow).

https://doi.org/10.1016/j.neubiorev.2019.11.016
Received 29 January 2019; Received in revised form 13 November 2019; Accepted 23 November 2019
Available online 25 November 2019
0149-7634/ 

feedback processing (Verdejo-Garcia et al., 2018).

With regard to choice implementation, people with SUDs tend to evaluate delayed rewards as less worth than immediate rewards, showing a clear preference for smaller immediate rewards over a larger delayed reward – known as the temporal discounting effect (Amlung et al., 2017; Biernacki et al., 2016; MacKillop et al., 2011). Concerning feedback processing, SUDs are associated with difficulties in terms of learning from punishment or the history of reinforcement, resulting in worse performance on tasks where they are required to incorporate prediction errors to optimally guide future behaviour (Biernacki et al., 2016; Kovacs et al., 2017).

Such impairments display correspondence with clinical outcomes, given that people with SUDs often forgo occupational or recreational activities in order to use drugs. Such self-defeating behaviours might indicate that, as the immediate rewards associated with drugs increase in subjective value, the delayed rewards associated with ordinary life events decrease in subjective value (Bickel and Marsch, 2001) – however, based on a means-end analysis it was recently suggested that self-defeating behaviours can also demonstrate the "hallmarks of goal pursuit" (Kopetz and Orehek, 2015). Additionally, people with SUDs habitually keep using drugs despite the short- and long-term negative consequences associated with this behaviour, such as financial costs (Vonmoos et al., 2018), increases in psychiatric symptoms (Cunha et al., 2011), cognitive impairments (Hulka et al., 2014; Vonmoos et al., 2014), and social dysfunction (Preller et al., 2014a, b). Importantly, although the Delay Discounting paradigms (DD) and the Iowa Gambling Task (IGT) are not representative for the entire field of decision-making, they are two of the most established behavioural tasks for assessing different facets of decision-making in the addiction field, being used to mainly investigate, but not exclusively, valuation of delayed rewards during choice implementation and feedback processing (Verdejo-Garcia et al., 2018), respectively. The wealth of recent literature produced with these two tasks raises an opportunity to generate estimates across several SUD samples and to analyse such data through advanced meta-analytic approaches.

### 1.1. The delay discounting

DD paradigms were initially introduced in the behavioural economics field following the observation that the value of a delayed reward is discounted when compared to the value of an immediate reward (for a review see Bickel and Marsch, 2001). In this paradigm, participants are usually requested to choose between a small immediate monetary reward and a large delayed reward, designed such that researchers can identify at which amount of immediate reward the probability of choosing the immediate or delayed reward becomes 50 %, known as the indifference point. Based on the hyperbolic function developed by Mazur (1987), the indifference point to calculate an empirically derived constant that is proportional to the degree of delay discounting for each participant – the k parameter or its log ("Ln(k)") – one of the most commonly interpreted outcomes of DD paradigms. Additionally, is also possible to obtain the area under the curve (AUC) as a DD outcome (Yoon et al., 2017), which usually shows a parametric distribution of the data and carries no assumptions regarding the mathematical form of the temporal discounting function, and is therefore not related to any specific economic framework (Myerson et al., 2001).

DD can be assessed using a variety of techniques, the most commonly implemented being the 27-item questionnaire developed by Kirby and Marakovic (1996) (also known as the Monetary Choice Questionnaire - MCQ). However, DD can also be assessed via multi-item choice tasks (MICT), wherein the amount of immediately available money and delay durations are systematically modified (MacKillop et al., 2011). As highlighted by two previous meta-analyses (Amlung et al., 2017; MacKillop et al., 2011), several studies have shown that substance users differ from non-using controls regarding temporal discounting, and that the paradigm can also predict clinically-relevant addictive behaviours such as poor treatment response (Washio et al., 2011). In addition, some studies have suggested DD behaviour as an addiction endophenotype, due to associations with conduct disorder, attention deficit/hyperactivity disorder, high novelty-seeking and poor self-regulation (Anokhin et al., 2011, 2014). Together, these findings highlight the crucial role of this paradigm in tracking individual differences and psychobiological processes that may underlie important outcomes across the lifespan (Mischel et al., 2011).

### 1.2. The Iowa gambling task

The IGT is a computerized behavioural task in which participants are asked to choose 100 times between four virtual decks (usually labelled A, B, C, and D). After each choice, participants can either win, or win and lose money, depending on the ratio of wins and losses of each deck. In the beginning of the task participants are informed that some decks are more profitable than others. Most often, decks C and D can be categorized as advantageous, because they deliver small to moderate rewards with or without small losses, providing a positive profit to the participants in the long run. On the other hand, decks A and B are disadvantageous, since they deliver moderate to large rewards, but usually large losses as well, providing a negative profit to the participants in the long run. The main outcome of the IGT is usually the net score, which can be obtained by subtracting the total number of selections from disadvantageous decks from the total number of selections from advantageous decks.

The IGT was first introduced to examine the somatic marker hypothesis, which states that stronger physiological responses (i.e., somatic markers) occur during anticipation of high-risk decisions when compared to low-risk decisions (Bechara et al., 1994). Specifically, the authors observed that people with orbitofrontal cortex (OFC) injuries have a decreased capacity to produce distinct anticipatory somatic markers, which might explain their worse decision-making performance when compared to controls. Intriguingly, similar results have also been observed in SUDs samples (Bechara, 2005; Bechara and Damasio, 2002; Bechara et al., 2002), contributing to the development of neuroscientific models of addiction that emphasise the role of the OFC and the ventromedial prefrontal cortex in the loss of control and compulsive drug use (Verdejo-García and Bechara, 2009). Accordingly, some studies have already reported that better IGT net score predicts fewer drinking problems and fewer average drinks per year in adolescents, as well as lower relapse rates in polysubstance-dependent alcohol patients within 3 months after treatment (De Wilde et al., 2013; Xiao et al., 2009). Likewise, it was shown that subjective weight to gains vs. losses predicted current smokers and current smoking levels 1 year later in adolescents (Xiao et al., 2013). In conclusion, it has been proposed that SUDs are associated to failures in the induction of appropriate somatic markers, contributing to disruptions in self-regulation and the capacity to learn from the consequences of actions (Olsen et al., 2015).

### 1.3. Previous meta-analyses

Previous meta-analyses have revealed a number of addiction-related effects on decision-making processes. MacKillop et al. (2011) meta-analysed data from 46 studies that used a DD task comparing a control group with a substance user group (including tobacco, alcohol, stimulant, opiate, and polysubstance drug use), as well as samples composed of individuals with gambling disorder. Similarly, Amlung et al. (2017) performed a meta-analysis on 64 studies to investigate the associations between addiction severity and DD performance, focusing on SUDs of tobacco, alcohol, cannabis, stimulants, and opiates, and gambling disorder. Both meta-analyses indicated that addictive behaviours are indeed associated with a reduced capacity to delay gratification, and that this effect was associated with continuous measures of addiction severity.

Regarding the IGT, Kovacs et al. (2017) investigated the effects of gambling and alcohol use disorders in this task, meta-analysing data from 17 studies. The authors found that both alcohol use disorder and gambling disorder impair IGT performance, with higher effects for the latter category. Finally, Biernacki et al. (2016) specifically examined the effects of current and past opioid use on decision-making, including not only the IGT and the DD, but also the Game of Dice Task, the Balloon Analogue Risk Task, the Cambridge Gambling Task, and the Information Sampling Task in one single analysis (see Biernacki et al., 2016, for task descriptions). The authors found that opioid users perform worse than controls, with evidence suggesting that decision-making deficits may persist at least 1.5 years after cessation of use (Biernacki et al., 2016).

Although these previous meta-analyses all provided important insights into the associations of addiction behaviours and decision-making, the evidence gleaned from them is limited in three important ways:

(1) Previous analyses have failed to identify differences concerning the effects of specific types of SUDs on DD assessment. Given the high heterogeneity of effect sizes in the studies comprised in the meta-analyses of MacKillop et al. (2011) and Amlung et al. (2017) meta-analyses, it is possible that the inclusion of samples composed of individuals with gambling disorder, nicotine use disorder, and non-clinical samples (e.g., recreational users) might have prevented the identification of specific substances associated with a greater impact on delayed gratification in relation to other drugs. For instance, larger effects sizes were associated with studies performed with clinical rather than nonclinical samples (MacKillop et al., 2011). Moreover, nicotine addicts retain autonomous control over their actions, even though they lose control over their motivation to smoke (Baumeister, 2017). Therefore, even though nicotine addiction leads to clinically significant psychological distress and physical long-term consequences, this disorder is unlikely to be associated with problems at work (e.g., repeated work absences, poor performance) or incapacity of dealing with family obligations (e.g., neglect of children, failure to meet household responsibilities), which are important characteristics of alcohol, cocaine, and heroin addiction, among others. This indicates that nicotine addiction may have a much slower escalation to such impairments.
(2) Some meta-analyses included multiple decision-making tasks with different conceptual frameworks within the same analysis (Biernacki et al., 2016). While the IGT is clearly a feedback processing decision paradigm where participants should implicitly (re) learn by trial and error, the Game of Dice Task can be categorized as decision under risk where the risks and the profits are explicit and can be estimated by the agents (Rzezak et al., 2012). On the other hand, the DD could be understood as decision under certainty, because the probability associated with the profit is always 100 % and the task aims to depict choice preference as a function of the delayed reward. Although from a psychological perspective all tasks investigated by Biernacki et al. (2016) can be categorized as accessing a broad range of decision-making, from a neurobiological value-based decision-making framework (Rangel et al., 2008; Verdejo-Garcia et al., 2018), each task manipulates information in a different way and, therefore, they cannot be assumed to galvanise the same decision processes or to depict the same concepts. For instance, the Balloon Analogue Risk Task requires decisions under dynamic risk, in which at each single choice – to pump or not to pump a balloon – within a trial, participants may consider a trade-off between maximizing their profit in detriment of an increasing risk (Lejuez et al., 2002). Moreover, the frequently used Cambridge Gambling Task was designed to assess risk-taking behaviour outside a learning context (Rogers et al., 1999).
(3) Previous analyses suffer from methodological issues arising from the incorporation of multiple effect sizes from a single study. Given that some contributing studies could provide more than one clinical sample (e.g., Ahn, WY. 2014; Bickel, WK., 2017; Mejía-Cruz, D. 2016), in this case the assumption of independence between outcomes is violated when performing a meta-analysis. Kovacs et al. (2017) stressed the violation of independency as one of their limitations, while MacKillop et al. (2011) included all reported comparisons for maximum representativeness and Amlung et al. (2017) opted to repeat the main analysis by merging studies with multiple associations into a single effect size. However, ignoring such dependencies in the meta-analytical model can lead to biases or lack of efficiency in statistical inference (Gleser and Olkin, 2009). Together, such limitations are crucial when trying to clarify specific decision-making behaviours over a general set of disorders, such as addiction.

### 1.4. Aims of the study

To overcome the limitations of previous studies, we, therefore, aimed to specifically investigate how SUDs affects delayed gratification (DD) and feedback processing (IGT) by performing two independent multilevel mixed-effects meta-analyses and univariate and multivariate mixed-effects meta-regressions considering demographic and clinical moderators. Our main research questions and hypotheses were:

(1) Is there any difference between the DD and the IGT concerning the magnitude of the effect size of SUDs on decision-making behaviour? We therefore performed a meta-analysis to initially compare both tasks regarding the magnitude of the effect sizes of SUDs in comparison to controls. Based on previous meta-analyses, we expect no significant differences in the magnitude of the effect sizes of SUDs between both tasks.
(2) Do specific SUDs differ regarding the magnitude of the effect size on the DD and IGT relative to others? Here, we carried out univariate and multivariate meta-regressions, separately for each task, to explore both the magnitude of the effect size of different SUDs to the controls and the magnitude of the effect size of additional demographic (e.g., years of education, percentage of men, age), clinical (e.g., abstinence duration, presence or the absence of psychiatric comorbidities), and methodological (e.g., recruitment bias) moderators. We expect to find smaller effect sizes for substances with an addictive potential in the lower range (Nutt et al., 2007), such as cannabis. By explorative analyses of the other moderators, we intend to identify important factors that might attenuate or exacerbate decision-making impairments in this population, such as being in remission or have been using substances for a long period.
(3) Which demographic, clinical or methodological moderators might have a differential effect on the DD relative to the IGT or vice versa? We expect that demographic and clinical moderators, such as age and psychopathologies, might have an effect on the DD estimates given that the performance in this task has been shown to be influenced by individual differences (Steward et al., 2017; Urosevic et al., 2016). Conversely, we expect to find an effect for substance use moderators specifically on the IGT, as it was already shown that the performance in the IGT can covary with changing cocaine use (Hulka et al., 2015).

Our findings will provide a basis for a better understanding of how specific SUDs and their demographic and clinical contexts relate to decision-making deficits, which have been proposed to play such an important role in the development, maintenance and outcome of SUD.

## 2. Method

### 2.1. Literature search and study selection

The search was performed in MEDLINE Complete, Web of Science

Core Collection, and EMBASE online databases, from May until October 2018, following the recommendation checklist of the Cochrane Guidelines (Higgins and Green, 2011) and the PRISMA guidelines for systematic review (McInnes et al., 2018). No restrictions were applied regarding publication language or publication date. We searched for studies that specifically reported to have measured decision-making using any Delay Discounting task/questionnaire or the Iowa Gambling Task and that compared a SUDs group (except for nicotine) to a control group. Search terms related to SUDs and the name of the two tasks of interest were used, "('Drug dependence') OR (Addiction) OR ('Substance-related disorders') AND ('Iowa Gambling Task') OR ('Delay Discounting') OR ('Intertemporal choice') OR ('Delay of gratification') OR ('Temporal discounting')". The search terms were required to be presented in the title/abstract or topic and a filter to select only studies with humans was used.

### 2.2. Inclusion criteria

A two-step screening of the literature was done. Initially, at the identification phase, the results from all databases were merged and the duplicates excluded (based on titles and abstracts) using EndNote X7 reference management software (Bramer et al., 2016; Thomson Reuters, 2017). Subsequently, references were imported to Rayyan (https://rayyan.qcri.org), a free web application for management of systematic reviews. At the second step, full texts were screened for inclusion by two authors (BKS and TWV) based on six criteria. (1) Peer-reviewed published research reporting a comparison between a SUD group and a healthy control group. Because we were mainly interested in investigating the effect of SUDs on decision-making, articles reporting compulsive disorders, or addictive behavioural disorders not related to substance use (e.g., gambling disorders, binge eating), or studies that did not specified any SUD, were not included. (2) Reported on participants aged between 18 and 65 years. Thus, studies with adolescents and high-risk populations that had not thus far developed any SUDs (e.g., history of parental drug abuse or dependency) were not included. (3) Studies available in full text format. (4) Provided group means and standard deviations from which an effect size could be calculated – if research articles did not provide statistics for effect size calculation (i.e., the DD overall estimators or IGT overall net score) the corresponding authors were contacted (see also Acknowledgement section). The GetData Graph Digitizer (version 2.26.0.20) was used to extract data from figures when corresponding authors did not answer.

Cohen's kappa coefficient (k) was calculated as a measure of inter-rater reliability (IRR), providing a "chance-corrected" percentage of agreement between all the coders. After coding, all disagreements concerning the exclusion of a research article were discussed until consensus was reached. For more detailed information about the identification, screening, reference search, eligibility and inclusion, the flowchart is shown in Fig. 1.

### 2.3. Decision-making measures

This review included studies that reported DD or IGT measures only, performing independent analyses for each task (please, see Section 2.5 Meta-analytic and meta-regression approach). This is an important distinction because our rationale was based on a neurobiological value-based framework (Rangel et al., 2008; Verdejo-Garcia et al., 2018) that distinguish valuation and choice implementation (DD) from feedback processing (IGT).

### 2.4. Data extraction

The following data were extracted for each study: (a) number of participants in each group and (b) group means and standard deviations of the DD and/or IGT. Additionally, for each study, we extracted the averaged demographic, clinical/methodological moderators (i.e., years of education, percentage of men, age, abstinence duration before the testing session in weeks and recruitment bias) for the SUD samples. As some studies reported more than one clinical group, one with people with SUDs and the other one composed with people with SUDs plus an additional psychiatric disorder, a dichotomous predictor was included to identify the presence or the absence of psychiatric comorbidities. Based on the mean abstinence duration before the testing session a dichotomous predictor was build: SUD in early remission according to DSM 5 (> 12 weeks of abstinence) or not (< 12 weeks of abstinence) (APA, 2013). SUDs were coded as alcohol, cannabis, stimulants (cocaine, amphetamine and its derivatives, respectively), opioids (heroin and opiate substitutes such as methadone or buprenorphine, respectively), and polysubstance SUD. Polysubstance SUD was coded if this diagnosis was directly reported but also when participants with more than one diagnosed SUD were included in the same sample in a study. The data were independently extracted by three authors (BKS, BSV, and TWV). During this process, any doubt was immediately discussed between the three authors. Finally, the methodological quality of each included study was rated independently by two reviewers (BKS and BSV) using the Newcastle-Ottawa scale (Stang, 2010). A Cohen's kappa coefficient (k) was calculated between the two authors.

### 2.5. Meta-analytic and meta-regression approach

The statistical analyses were performed in three main steps. First, we performed a meta-analysis to investigate whether the magnitude of effect of SUDs differed regarding DD and IGT. This step was taken even though we clearly distinguished delayed gratification processes from feedback processing at a theoretical level. In a second step, two independent meta-analyses were performed to investigate the magnitude of effect of SUDs for each task (DD and IGT).

In a third step, univariate meta-regression models were used to explore the moderating effects of each demographic and clinical/methodological variables on both the DD and the IGT standardized mean differences, separately, using Q-statistics. Subsequently, as a complementary meta-regression procedure, multivariate meta-regression models including the most influential demographic and clinical/methodological variables were performed for both the DD and the IGT standardized mean differences, separately. All the moderators that contributed to heterogeneity in mean estimates at $p < 0.2$ in the univariate meta-regression models were included in the multivariate meta-regression models (Polanczyk et al., 2015; Viola et al., 2016). The estimated proportional reduction in the total variance for both the univariate and multivariate meta-regression models were computed using the variance accounted for (VAF), a pseudo R-squared value.

In order to overcome previous methodological constraints regarding the heterogeneity of the studies, the violation of the independency assumption within studies, the overweighting of the effect sizes, and the correction for multiple comparisons, appropriate analytical strategies were adopted in all data analyses. Initially, concerning the effect size heterogeneity, both Cochran's Q (sum of squared differences between individual weighted study effects and the overall mean) and I-squared (percentage of variation within study effect sizes that can be explained by heterogeneity) indices were calculated.

Because significant results for the Q tests and moderate I-squared values were considered as indicators of heterogeneity, we performed multilevel linear mixed-effects meta-analytical models based on the standardized mean differences with the maximum likelihood estimator (Huedo-Medina et al., 2006; Kelley and Kelley, 2012) in all steps described above. This strategy allowed us to account for the heterogeneity of the studies and the fact that some studies brought data from independent SUDs subgroups contributing with multiple different effect sizes – given that some studies with more than one independent SUDs subgroups compared these groups with the same control group. In this regard, in our models the subsamples of a given study received the same identification and thus, the same random effects, while effects from

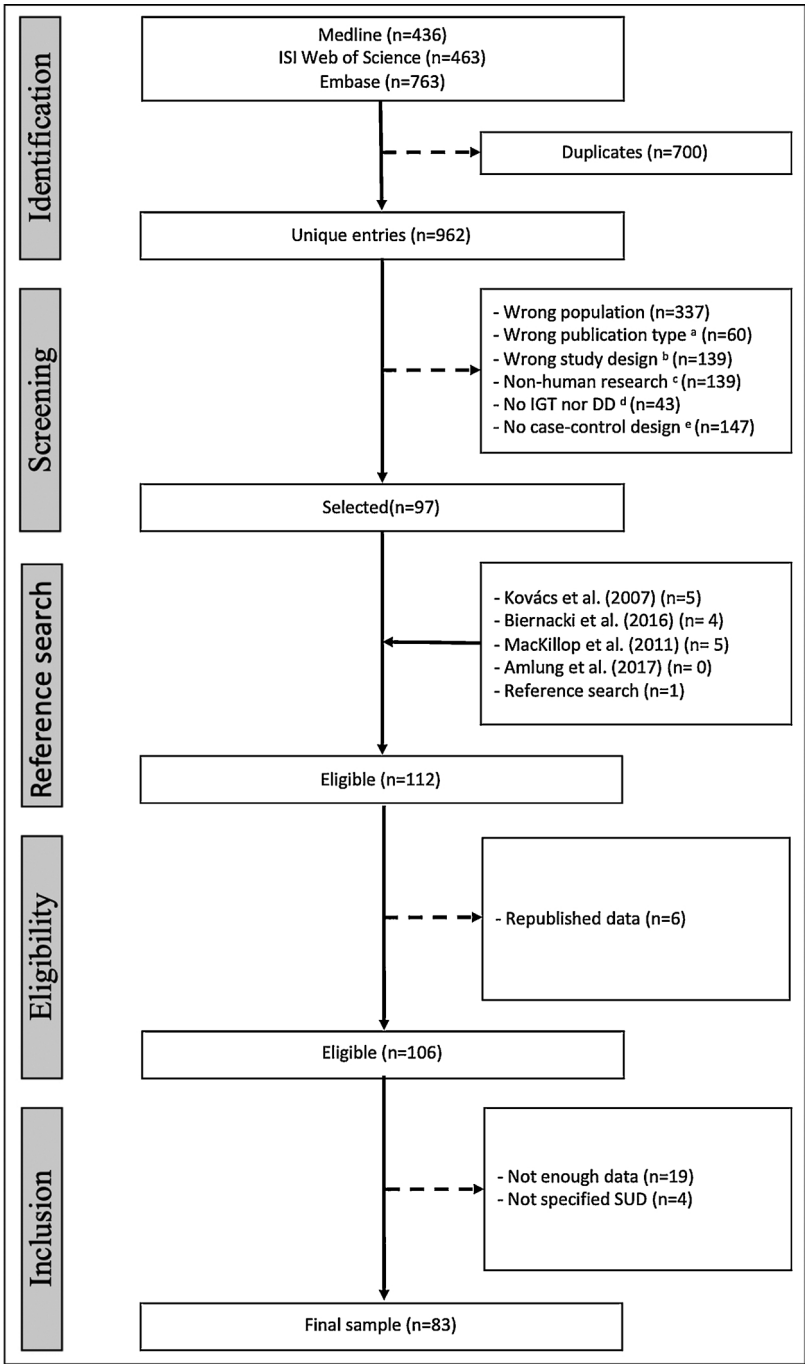


**Fig. 1.** Flowchart.
Note: [a] Studies investigating any other than targeted SUD (e.g., nicotine use disorder), behavioural addictions (e.g., gambling disorder, eating disorder, sex addiction disorder), or that did not include adults. [b] Conference abstracts, book chapters. [c] No empirical studies, such as mini-reviews, theoretical reviews, systematic reviews, meta-analyses. [d] Pre-clinical research studies. [d] Studies that have used a modified version of the tasks or any other decision-making task than the Iowa Gambling Task and Delay Discounting. [e] Studies that did not include a control group sample.

different studies were assumed to be independent. Additionally, we also included the methodological quality as random effects in both main meta-analyses (DD and IGT) and all disagreements concerning the exclusion of a research article were discussed until consensus was reached.

Furthermore, because DD studies used either the MICT or the MCQ and reported either the k, Ln(k), or AUC index, we therefore included these variables in our main DD meta-analytical model. The type of the index variable was included as a fixed effect, given that we were interested in investigating whether the indices (k, Ln(k), AUC) differ from each other regarding the magnitude of their effect size. In contrast, the DD task type (i.e., MCQ or MICT) was included as a random effect, as it was already shown that the different task types revealed comparable effect sizes in SUD (Amlung et al., 2017), and we therefore were interested in the variation reflected by the different levels of task type in the overall magnitude of the effect size, but not in the effect of each different level of the variable. Using the same strategy as Amlung et al. (2017), the signs for associations using k and Ln(k) were reversed prior to inclusion in the analysis, since they are inversely related to AUC and IGT score.

**Table 1**
Sample characteristics and descriptive data from moderators per substances.

| | Alcohol | Cannabis | Stimulants | Opioids | Polysubstance SUD |
|---|---|---|---|---|---|
| **Delay Discounting Task** | | | | | |
| Number of participants SUD | 867 | 135 | 508 | 329 | 671 |
| Number of participants HC | 627 | 143 | 547 | 318 | 507 |
| *SUD characteristics* | | | | | |
| Age | 35.2 (11.3) | 30.0 (3.3) | 35.1 (6) | 37.1 (6.6) | 40.7 (5.8) |
| % of men in the SUD sample | 73.6 (15.6) | 64.2 (31) | 76.4 (17.1) | 68.2 (19.7) | 79.0 (11.5) |
| Abstinence duration (weeks) | 10.0 (22.8) | 0.79 (-) | 12.9 (26.3) | 57.9 (42.7) | 21.0 (27.6) |
| SUD recruitment | | | | | |
| Flyers/newspapers/internet | 7 | 1 | 6 | 4 | 9 |
| Prevention/treatment centres | 2 | 1 | 9 | 2 | 1 |
| Inpatient care facility | 2 | 0 | 2 | 1 | 0 |
| **Iowa Gambling Task** | | | | | |
| Number of participants SUD | N = 654 | N = 213 | N = 421 | N = 683 | N = 573 |
| Number of participants HC | N = 752 | N = 194 | N = 443 | N = 630 | N = 483 |
| *SUD characteristics* | | | | | |
| Age | 42.1 (8.7) | 23.0 (2.4) | 34.6 (10.1) | 34.4 (4.6) | 34.6 (7.6) |
| % of men in the SUD sample | 76.6 (20.5) | 80.3 (18) | 80.0 (13.4) | 86.9 (16.7) | 62.8 (27.3) |
| Abstinence duration (weeks) | 19.8 (32.5) | 0.42 (.35) | 20.3 (38.6) | 44.7 (48.6) | 31.3 (18.2) |
| SUD recruitment | | | | | |
| Flyers/newspapers/internet | 4 | 5 | 7 | 3 | 6 |
| Prevention/treatment centres | 6 | 0 | 4 | 9 | 6 |
| Inpatient care facility | 10 | 0 | 3 | 1 | 1 |

**Note.** HC, healthy controls; SUD, substance use disorder. Sample size numbers and means and standard deviations are shown in parenthesis.

However, because performing multilevel linear mixed-effects meta-analytical models are not sufficient to completely deal with the violation of the independency assumption within studies, a variance-covariance matrix of the effect size estimates was calculated based on Gleser and Olkin (2009) and then incorporated into the models. Additionally, following the Cochrane guidelines, an overweighting of the effect sizes was counteracted by dividing the sample size of the shared control group by the number of comparisons with independent clinical groups from the same study.

Finally, although few outliers were expected due to the large number of studies and samples retrieved (Voyer and Voyer, 2014), small study bias and influential cases were investigated by examining the standardized residual for each study and checking for outliers (Biernacki et al., 2016; Viechtbauer and Cheung, 2010). The influence of studies that had a z-scores of greater than ± 1.96 was examined using the "leave one out" method. Hence, the results of our meta-analysis were recalculated n-1 times, each time leaving out one possible influential study (Viechtbauer, 2010). If the studies did not substantially change the overall effect size, we opted to retain them in the overall analyses. Publication bias was assessed by visually inspecting funnel plots and by calculating Rosenthal's fail-safe N, which calculates the number of studies averaging null results that would have to be added to the given set of observed outcomes in order to reduce the combined significance level (p-value) to a target alpha level (e.g., 0.05) (Rosenberg, 2005; Rosenthal, 1979), wherein a larger N indicates more confidence in the findings.

Estimate effect sizes of each individual study are shown in forest plots, in which negative estimated effect sizes represents the deleterious effect of the SUD on the DD or IGT. All analyses were performed using the package "metafor" (version 2.0-0) (Viechtbauer, 2010) from the open source statistical software R (version 3.4.3) (R Development Core Team, 2010; Viechtbauer, 2010).

## 3. Results

### 3.1. Included articles

As shown in Fig. 1, 1662 articles were initially found. After excluding duplicated entries 962 articles were screened to check against the exclusion criteria, resulting in 97 articles being retained (IRR, k = 0.848). In addition to the main literature search, references of four previous meta-analysis were screened and 15 new studies were found. From a total of 112 research articles we identified that 6 of them had republished data or a significant overlap between reported samples and, therefore, they were excluded, resulting in 106 research articles that were elected to be individually fully reviewed. The means and standard deviations from 5 of the articles, for which we received no answer from the authors, were estimated by using the open source software for data extraction GetData Graph Digitizer (version 2.26.0.20). We were not able to include data from 19 studies, because for 6 of these studies the authors stated that they had no longer access to the data and regarding 13 further studies the authors did not respond to our requests. As these 19 studies did not include figures representing the main DD and IGT variables, the GetData Graph Digitizer could not be used. Additionally, 4 studies were excluded because SUDs were not specified. In the end, 83 research articles (31 using DD, 44 using IGT, and 8 using both the DD and the IGT) and 115 comparisons (49 for the DD and 66 for the IGT) were considered viable for data analysis. For clinical trials and longitudinal study designs, only one sample was included; either the condition without treatment or the baseline measurement, respectively. The IRR of the methodological quality total score was 0.720, for detailed information, please see Table S1. The reference list of all included studies can be found in the supplementary material.

### 3.2. Sample characteristics

Table 1 displays the mean and SD for the chosen moderators per substance and for each task. Studies investigating alcohol-related disorders provided the highest number of participants in both tasks, while studies investigating cannabis-related disorders generated the lowest number of participants. As expected, the percentage of men among all studies was, on average, two-thirds of the total sample. Cannabis also showed the shortest abstinence period when compared to the other substances.

### 3.3. Meta-analyses and meta-regressions

Initially, when investigating whether SUDs might have a different impact on DD and IGT, we found a significant effect on the standardized mean differences of DD when compared to IGT (β = −0.30, CI 95 % [−0.41, −0.19], Q[1] = 30.06, $p < .001$). This result was sustained even when removing outliers (β = −0.27, CI 95 % [−0.38, −0.17], Q

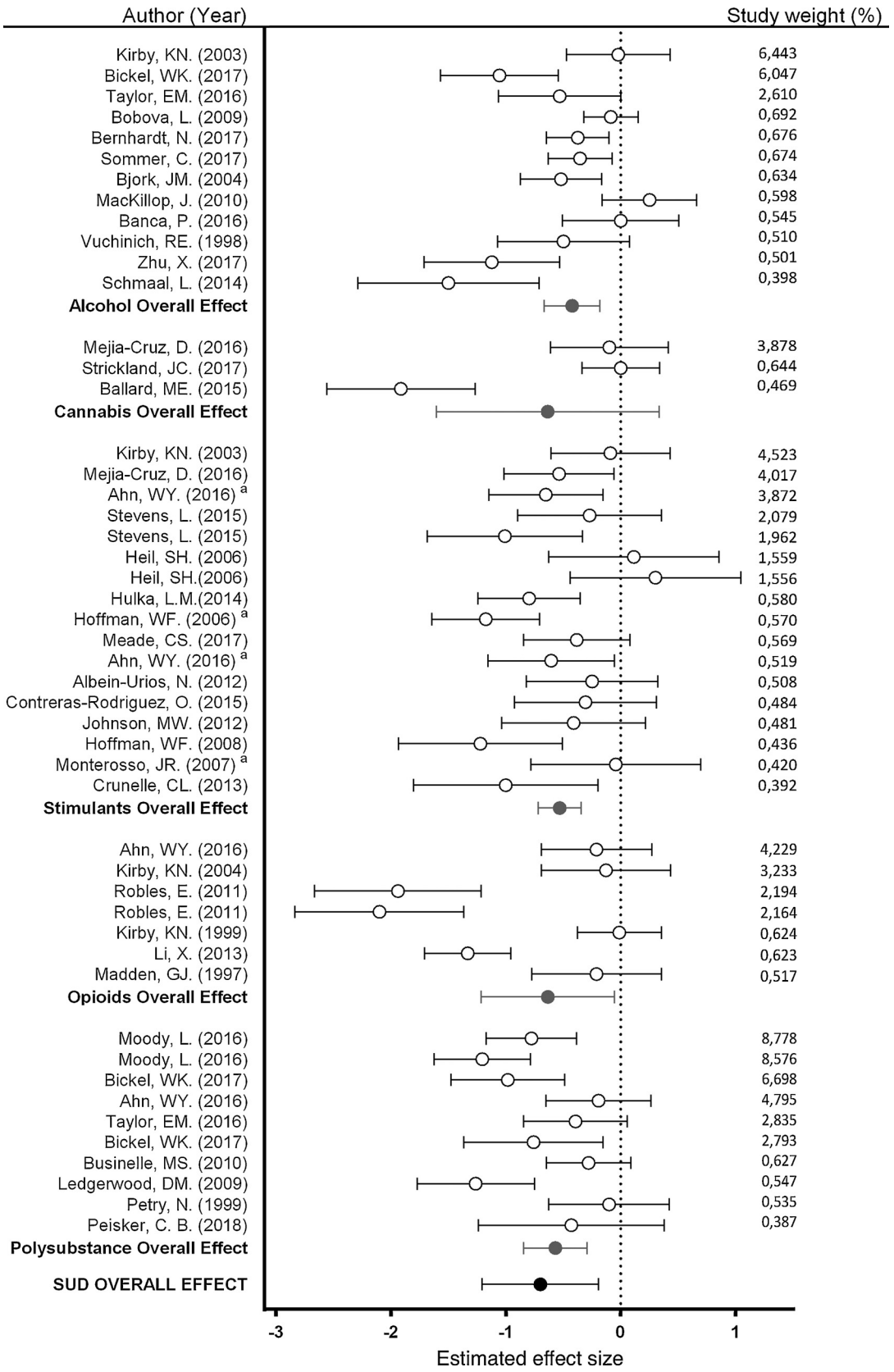


**Fig. 2.** Delay-Discounting meta-analysis.
Note: [a] Amphetamine sample.

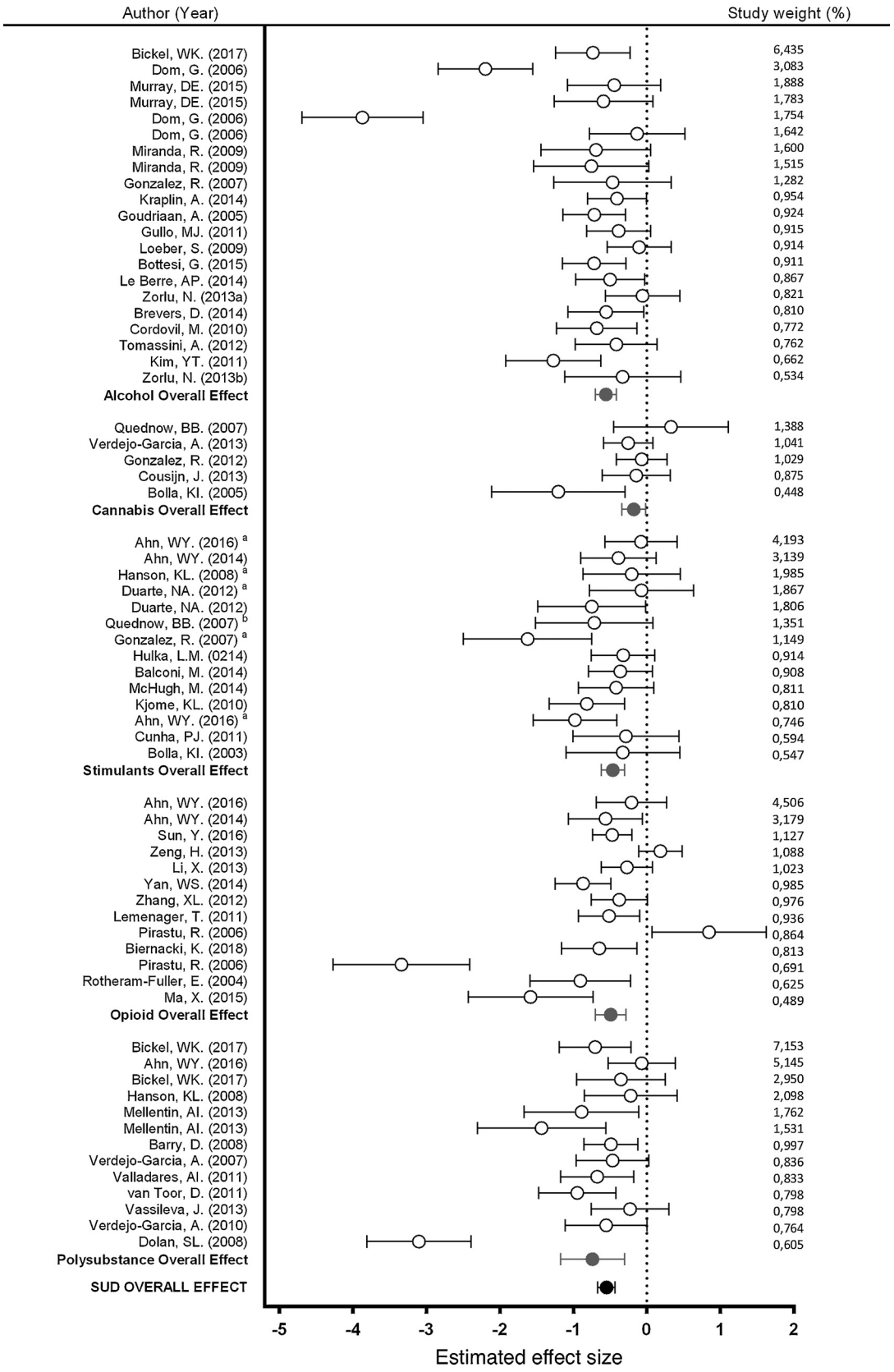


**Fig. 3.** Iowa Gambling Task meta-analysis.
Note: [a] Amphetamine sample. [b] 3,4-Methylenedioxymethamphetamine (MDMA) sample.

[1] = 27.43, $p < .001$). Based on our theoretical background – that IGT and DD probe different decision-making processes – and supported by our finding that a significant smaller effect with a larger dispersion was found for DD when compared to IGT, our next analytical steps were independently performed for each task (Figs. 2 and 3).

At the second step and concerning the DD, our results revealed a significant effect of SUDs (β = −0.70, CI 95 % [−1.22, −0.19], Q[46] = 189.11, $p < .001$), even when removing outliers (β = −0.68, CI 95 % [−1.15, −0.21], Q[43] = 147.40, $p < .001$). No significant differences were found concerning the DD indices (i.e., AUC, k or Ln(k); Q[2] = 0.95, $p = .621$). Similarly, regarding IGT an effect for SUDs was also found (β = −0.55, CI 95 % [−0.66, −0.43], Q[66] = 327.34, $p < .001$), remaining significant after removing outliers (5 % of the included sample of studies) (β = −0.47, CI 95 % [−0.56, −0.38], Q [60] = 109.28, $p < .001$). Rosenthal's classic fail-safe N indicated that there would need to be 3969 unpublished studies to raise the p-value to above the threshold for statistical significance for the DD primary analysis and 7167 to raise the p-value to above the threshold for statistical significance for the IGT primary analysis (funnel plots can be found in the supplementary material; S1–S3). As depicted in Figs. 2 and 3, independent meta-analyses for each substance revealed no significant effect for cannabis use disorders on the IGT and DD.

As a third step, we performed multilevel univariate meta-regressions for each task independently. With regards to the DD, multilevel univariate meta-regression models revealed a positive effect for years of substance consumption, a negative effect for early onset of substance consumption (i.e., the ratio between years of substance consumption and age), and a negative effect for psychiatric comorbidities (Table 2). Additional pairwise comparisons showed a significant positive effect for stimulants when compared to polysubstance dependence, only (Table 3), suggesting that the effect of polysubstance related disorder is not as deleterious as the effect of stimulant related disorders. In contrast, concerning the IGT, the models showed a significant positive effect for cannabis related disorders when compared to alcohol (Table 2), and additional pairwise comparisons also suggested a similar significant positive effect for cannabis when compared to stimulants, opioids, and polysubstance dependence (Table 3). These findings suggest the effect of cannabis related disorders are not as deleterious as the effect found for other SUDs.

As a complementary meta-regression procedure, we performed two multilevel multivariate meta-regression models, one for each task. Although the effect of cannabis over alcohol was not observed anymore for the IGT, the effect of remission remained as a trend ($p = .053$) (Table 2). Similarly, additional pairwise comparisons showed an effect of cannabis when compared with stimulants, opioids, and polysubstance SUDs (Table 3). For the DD, the multilevel multivariate meta-regression model revealed an effect for early onset of substance consumption and for psychiatric comorbidities (Table 2). Because no robust effect was found for any substance in the DD, no additional pairwise comparisons were performed for this task. Finally, because our stimulant group included cocaine and amphetamine type users as well, we explored whether the later (i.e. amphetamines derivate) have differential effects on IGT and DD. No effect was found for the IGT (β = 0.09, CI 95 % [−0.23, 0.42], $p = .570$), but a significant effect was observed for the DD (β = −.36, CI 95 % [−0.70, −0.02], $p = .038$), suggesting that other stimulants have a smaller effect when compared to cocaine. However, it must be highlighted that this effect is driven by only 4 studies on stimulants other than cocaine, in comparison with 11 studies on cocaine use.

## 4. Discussion

The primary aim of this study was to explore the influence of SUDs and demographic, clinical features, and methodological moderators on two main facets of decision-making: valuation processing (assessed through the DD) and feedback processing (assessed through the IGT). In total, 88 studies were taken into account and different subsets were generated depending on the respective research questions. Our main results suggest that: (1) the magnitude of the difference between the effect sizes among samples with and without SUDs is moderate, and SUDs are generally associated with impaired valuation of delayed gratification (b = −0.305) and impaired feedback processing (b = −0.423); (2) the effect of cannabis use disorder on feedback processing is not as deleterious as the effect of other SUDs; (3) there are no robust differences between the effect of diverse SUDs on valuation of delayed gratification; and (4) early onset of substance consumption and presence of psychiatric comorbidities is associated with stronger effect of SUDs specifically on valuation of delayed gratification.

With regards to the main effect of SUDs on decision-making processes, our results are in accordance with previous meta-analyses. With respect specifically to valuation processing, some studies already showed that people with SUDs and gambling disorders performed worse than non-user controls on the DD, while no differences were found between the MICT and the MCQ (Amlung et al., 2017; MacKillop et al., 2011). Regarding feedback processing, our results support the finding that the observed impairments on the IGT seem to vary according the addictive disorder (Kovacs et al., 2017), with no significant difference in the magnitude of the effect on those people with and without psychiatric and neurological co-morbidities (Biernacki et al., 2016). However, our empirical results contrast with a recent systematic review that proposed that there is no current evidence supporting the view that chronic cocaine use is associated with broader decision-making impairments (Frazer et al., 2018). By performing meta-analyses and multilevel meta-regressions on feedback processing, our results reveal a robust effect of stimulants, opioids and polysubstance SUDs over cannabis, even when using a multivariate model.

The idea that stimulant users might perform worse on cognitive tasks compared with cannabis users was recently shown by Kaag et al. (2018). Neuroimaging data support these findings, given that a negative correlation between lifetime cocaine use and grey matter volume of the prefrontal cortex has been observed, while there were no positive or negative associations between grey matter volume and lifetime cannabis use (Kaag et al., 2018). Likewise, we here did not observe that cannabis abusers presented decision-making deficits when compared to non-substance abusers. However, this finding must be interpreted with caution considering the small number of included studies, pinpointing the necessity for more research into the adverse effects of cannabinoid use and decision-making processes (Curran et al., 2016).

Moreover, and together with our previous findings (Kluwe-Schiavon et al., 2016), the effect of SUDs on learning from feedback proffers some important hypotheses on how these processes interact. We have shown in this prior study that women with crack-cocaine use disorder were able to adjust their risk-taking behaviour when facing immediate feedback on a decision-making task. It must be noted that, however, that we used the Columbia Card Task, a decision-making task under explicit risk where the feedback occurs immediately after the participant's choice, while the IGT is a decision-making task under uncertainty and implicit learning where participants must 'relearn' that what they initially thought was a good deck to choose from was, indeed, a bad deck in the long term. With this difference in mind, future studies could specifically investigate how SUDs may affect learning from feedback in both explicit risk and uncertainty-dependent decision-making scenarios.

Furthermore, our moderators' analyses also seem to be in accordance with earlier findings. Concerning valuation of delayed gratification processing, Amlung et al. (2017) found an association between continuous measures of addiction severity and worse performance on the DD, while MacKillop et al. (2011) found larger effect sizes for studies using clinical samples when compared with studies using non-clinical samples. Of note, both Amlung et al. (2017) and MacKillop et al. (2011) included also non-SUDs samples, while we included SUDs samples only. Such a difference might explain the stronger association

**Table 2**
Multilevel univariate and multivariate meta-regression models for the Iowa Gambling Task and Delay Discounting.

| | | Univariate models | | | | | | Multivariate models | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n (k) | Coefficient | SE | 95 % CI | *p*-value | VAF (%) | n (k) | Coefficient | SE | 95 % CI | *p*-value | VAF (%) |
| **Delay Discounting** | | | | | | | | | | | | |
| *DD Index* | | | | | | | | | | | | |
| AUC | 5 (6) | Reference | | | | 0.02 | | | | | | |
| k | 10 (11) | 0.27 | 0.28 | [-0.28, 0.83] | 0.332 | | | | | | | |
| Ln(k) | 22 (32) | 0.17 | 0.25 | [-0.33, 0.67] | 0.503 | | | | | | | |
| *Substance Use Disorder* | | | | | | | | | | | | |
| Alcohol | 12 (12) | Reference | | | | 0.08 | | | | | | |
| Cannabis | 3 (3) | 0.12 | 0.19 | [-0.25, 0.51] | 0.515 | | | | | | | |
| Stimulants | 15 (17) | −0.20 | 0.11 | [-0.42, 0.02] | 0.086 | | | | | | | |
| Opioids | 6 (7) | −0.05 | 0.13 | [-0.32, 0.20] | 0.672 | | | | | | | |
| Polysubstance | 8 (10) | 0.06 | 0.10 | [-0.13, 0.26] | 0.522 | | | | | | | |
| *Demographics* | | | | | | | | | | | | |
| Age | 37 (49) | −0.01 | 0.00 | [-0.03, 0.00] | 0.143 | 0.08 | | | | | | |
| Years of education | 23 (33) | 0.12 | 0.06 | [-0.00, 0.26] | 0.058 | 0.03 | 10 (13) | −0.05 | 0.10 | −0.26 to 0.15 | 0.596 | 0.16 |
| % of men in the SUD sample | 34 (42) | −0.00 | 0.00 | [-0.01, 0.00] | 0.704 | 0.03 | | | | | | |
| *Clinical / Methodological* | | | | | | | | | | | | |
| Years of consumption | 19 (22) | 0.03 | 0.01 | [0.00, 0.06] | **0.013** | 0.33 | | | | | | |
| Years of consumption/Age | 19 (22) | −0.08 | 0.03 | [-0.14, -0.02] | **0.009** | 0.37 | 10 (13) | −0.08 | 0.03 | −0.15 to -0.00 | **0.027** | |
| Remission (< 12 weeks) | 23 (30) | −0.12 | 0.18 | [-0.48, 0.22] | 0.481 | 0.04 | | | | | | |
| Psychiatric Comorbidities | 24 (31) | −0.24 | 0.08 | [-0.40, -0.07] | **0.005** | 0.29 | 10 (13) | −0.48 | 0.22 | −0.91 to 0.04 | **0.030** | |
| Recruitment | | | | | | | | | | | | |
| Flyers/newspapers/internet | 18 (27) | Reference | | | | 0.13 | | | | | | |
| Prevention/treatment centres | 13 (15) | 0.02 | 0.17 | [-0.31, 0.37] | 0.877 | | | | | | | |
| Inpatient care facility | 4 (5) | −0.22 | 0.26 | [-0.74, 0.29] | 0.395 | | | | | | | |
| **Iowa Gambling Task** | | | | | | | | | | | | |
| *Substance Use Disorder* | | | | | | | 22 (32) | | | | | .29 |
| Alcohol | 17 (21) | Reference | | | | 0.05 | 8 (12) | Reference | | | | |
| Cannabis | 5 (5) | 0.45 | 0.19 | [0.07, 0.83] | **0.018** | | 3 (3) | 0.30 | 0.37 | −0.43 to 1.04 | 0.417 | |
| Stimulants | 13 (14) | −0.06 | 0.12 | [-0.30, 0.18] | 0.622 | | 11 (12) | −0.36 | 0.24 | −0.84 to 0.11 | 0.147 | |
| Opioids | 12 (13) | −0.06 | 0.12 | [-0.31, 0.18] | 0.613 | | 6 (6) | −0.42 | 0.27 | −0.96 to 0.11 | 0.122 | |
| Polysubstance | 11 (13) | −0.05 | 0.10 | [-0.26, 0.15] | 0.625 | | 4 (4) | −0.42 | 0.27 | −0.95 to 0.11 | 0.124 | |
| *Demographics* | | | | | | | | | | | | |
| Age | 51 (66) | −0.00 | 0.00 | [-0.02, 0.00] | 0.196 | 0.08 | 22 (32) | −0.00 | 0.01 | −0.03 to 0.02 | 0.594 | |
| Years of education | 36 (50) | 0.06 | 0.04 | [-0.02, 0.15] | 0.130 | 0.79 | 22 (32) | 0.15 | 0.08 | −0.01 to 0.32 | 0.069 | |
| % of men in the SUD sample | 49 (52) | 0.00 | 0.00 | [-0.00, 0.00] | 0.981 | 0.04 | | | | | | |
| *Clinical / Methodological* | | | | | | | | | | | | |
| Years of consumption | 34 (45) | −0.01 | 0.01 | [-0.03, -0.00] | 0.218 | 0.46 | | | | | | |
| Years of consumption/Age | 34 (45) | 0.03 | 0.03 | [-0.03, 0.10] | 0.373 | 0.42 | | | | | | |
| Remission (< 12 weeks) | 37 (48) | 0.19 | 0.14 | [-0.08, 0.47] | 0.170 | 0.41 | 22 (32) | 0.42 | 0.21 | −0.00 to 0.85 | 0.053 | |
| Psychiatric Comorbidities | 38 (52) | −0.05 | 0.08 | [-0.22, 0.10] | 0.497 | 0.71 | | | | | | |
| Recruitment | | | | | | | | | | | | |
| Flyers/newspapers/internet | 17 (25) | Reference | | | | 0.03 | 8 (11) | Reference | | | | |
| Prevention/treatment centres | 21 (25) | −0.24 | 0.16 | [-0.56, 0.06] | 0.126 | | 9 (15) | −0.18 | 0.42 | −1.01 to 0.64 | 0.660 | |
| Inpatient care facility | 12 (15) | −0.09 | 0.13 | [-0.36, 0.17] | 0.478 | | 9 (11) | 0.68 | 0.42 | −0.14 to 1.52 | 0.107 | |

**Note.** CI, confidence interval; k, number of comparisons; n, number of studies included in the respective analysis; SE, standard error; SUD, substance use disorder; VAF, variance accounted for. The multivariate meta-regression models included the most influential demographic and clinical/methodological variables, only. Significant p-values are in bold.

**Table 3**
Pairwise comparisons of substance classes using univariate and multivariate multilevel meta-regressions.

| | | Univariate models | | | | Multivariate model | | | |
|---|---|---|---|---|---|---|---|---|---|
| Reference category | Comparative category | Coefficient | SE | 95 % CI | p-value | Coefficient | SE | 95 % CI | p-value |
| **Delay-Discounting** | | | | | | | | | |
| Cannabis | Stimulants | −0.32 | 0.16 | [-0.65, 0.00] | 0.052 | | | | |
| Cannabis | Opioids | −0.18 | 0.21 | [-0.59, 0.23] | 0.383 | | | | |
| Cannabis | Polysubstance | −0.06 | 0.20 | [-0.45, 0.33] | 0.759 | | | | |
| Stimulants | Opioids | 0.14 | 0.14 | [-0.13, 0.41] | 0.308 | | | | |
| Stimulants | Polysubstance | 0.26 | 0.12 | [0.02, 0.51] | **0.034** | | | | |
| Opioids | Polysubstance | 0.12 | 0.13 | [-0.15, 0.39] | 0.377 | | | | |
| **Iowa Gambling Task** | | | | | | | | | |
| Cannabis | Stimulants | −0.51 | 0.18 | [-0.88, -0.14] | **0.005** | −0.66 | 0.29 | −1.25 to -0.08 | **0.024** |
| Cannabis | Opioids | −0.52 | 0.19 | [-0.90, -0.13] | **0.007** | −0.73 | 0.34 | −1.39 to -0.06 | **0.031** |
| Cannabis | Polysubstance | −0.50 | 0.19 | [-0.89, -0.12] | **0.008** | −0.72 | 0.32 | −1.37 to -0.08 | **0.027** |
| Stimulants | Opioids | −0.00 | 0.11 | [-0.23, 0.22] | 0.973 | −0.06 | 0.15 | −.37 to 0.25 | 0.702 |
| Stimulants | Polysubstance | 0.00 | 0.11 | [-0.21, 0.23] | 0.937 | −0.05 | 0.14 | −.34 to 0.23 | 0.703 |
| Opioids | Polysubstance | 0.01 | 0.12 | [-0.22, 0.24] | −0.914 | 0.00 | 0.17 | −.34 to 0.35 | 0.981 |

**Note**. Significant p-values are in bold.

between the variability on DD performance and substance use severity that previous studies found. Despite this, in our study we observed a significant effect on DD concerning the ratio between years of substance consumption and age – which one could infer to be an index of the years of consumption adjusted to individual age at the time of the measurement – in which small ratios represent a shorter period of consumption in relation to the individual age. This finding also suggests that alterations in valuation of delayed gratification are associated with earlier onset of substance consumption, which corroborates the literature regarding substance consumption and decision-making and impulsive behaviour during adolescence (Audrain-McGovern et al., 2009).

Remarkably, our results may suggest that remission can have an effect on feedback processing, by suggesting that people that were not using substances over 12 weeks prior to the measurement performed better than those that were not remitted. Although this result is not significant, this trend is in line with previous studies from our lab that revealed that cocaine users who substantially decreased the amount of cocaine consumption over one year showed improved performance regarding attention, working memory, declarative memory, and executive functions (Vonmoos et al., 2014), key cognitive functions involved in learning and decision-making. In the present analysis, the average of weeks in remission over all SUDs samples that performed the IGT was 23, suggesting that after this period it is possible to nevertheless observe some improvement trends on IGT performance. This does not mean that people with SUDs will perform as well as people without SUDs, or that this improvement might be directly observed in daily life situations. However, this was a trend only, and it may be interpreted as a potential marker of interest for future studies.

Taken together, our findings suggest that valuation processing is not specially affected by different substances of abuse and other SUDs related moderators, while feedback processing might be more vulnerable for SUDs specific effects. Therefore, it is reasonable to hypothesize that individual differences in valuation processing of delayed gratification, such as psychiatric disorders (e.g. ADHD) and developmental stages, can trigger risk-taking behaviours and might lead to the beginning of substance use. Once a recurrent substance use pattern is established, it can lead to alterations in feedback processing, resulting in the maintenance of the consumption despite the negative consequences of it (Bolla and Cadet, 2007). In accordance with this, opponent process theories of addiction have postulated that SUDs are triggered by a dysregulated brain reward function and the recruitment of antireward systems that drive the compulsive substance-related behavior by diminishing the aversive states in spite of the associated risks (Bickel et al., 2018). Moreover, the idea that delay discounting may reflect a temporally stable individual trait is not new (Odum, 2011), and it was already shown that delay discounting might have predictive effects on regular smoking during adolescence (Audrain-McGovern et al., 2009) and treatment response for heavy drinkers (MacKillop and Kahler, 2009). Longitudinal future studies may focus on this issue by, for instance, investigating whether delay discounting performance can predict the onset of, or changes in, substance consumption patterns of people with SUDs. Meanwhile, our results can be interpreted in line with the idea that DD could be deeper investigated as an addiction endophenotype, as it is less specifically associated with SUDs moderators, but rather with individual differences, such as psychiatric comorbidities and the ratio of years of consumption/age.

### 4.1. Limitations

Although we overcame several methodological constraints of previous meta-analyses (e.g., violation of the independency assumption within studies, the overweighting of effect sizes, and the correction for multiple comparisons), our results might be interpreted in light of some limitations. First, we only included peer-reviewed articles listed in established research databases, neglecting other materials or/and researches produced by organizations outside of the academic publishing channels, which may have influenced effect sizes and publication biases of our analyses. However, the benefits and challenges of including so called “grey” literature are still a matter of debate (Paez, 2017). Second, case groups were considered as “polysubstance SUD” if they were directly reported as polysubstance SUD but also when participants with more than one SUD were included in a study. Therefore, the surprising finding that the effect on DD was smaller in polysubstance than in the stimulants class might reflect poorly defined consumption patterns of the polysubstance category. Accordingly, it should be noted that we did not specifically account for severity of substance use given that there was not a standard measure of severity across the included studies. However, we included clinical moderators such as years of consumption, remission, recruitment bias that could be understood as indirect indicators of substance-related disorders severity.

Third, here we investigated DD and IGT as key tasks used to access temporal discounting and feedback processing, respectively. However, the outcomes measured in both tasks also engage other decision-making stages and, therefore, impairments on both DD and IGT cannot be understood, exclusively, as deficits in choice implementation and feedback processing. For example, choice implementation comprises different processes such as response initiation, self-regulation, cognitive inhibition; while it is known that the IGT requires the valuation of decision options with ambiguous outcomes, a component of preference formation representing an earlier decision-making stage (Verdejo-Garcia et al., 2018). Moreover, it is also possible that several other cognitive functions involved in both choice implementation and feedback processing, that have been reported to be susceptible to SUD, such as working memory and executive functioning (Vonmoos et al., 2018, 2014), played an important role in the decision-making outcomes that we showed. Finally, we could not assess and, therefore, include in our analysis the co-use of other substances (even of tobacco and alcohol) beyond the main SUD, as this information was not systematically assessed in most of the included studies. The lack of this information should be acknowledged as a potential limitation of the present analysis and argues for a standardized assessment and reporting of co-used substances in our field in the future. Nevertheless, our meta-analysis considered the two most established tasks that access decision-making in SUDs and intended to investigate these two key processes involved in decision-making.

### 4.2. Conclusion

Our results extend the current literature in three main ways. Firstly, we showed that SUDs are associated with impairments in the implicit learning from feedback processing and valuation of delayed gratification. Secondly, we replicated previous findings showing no differences between distinct SUDs on the valuation of delayed gratification impairments. However, our data indicates that cannabis related disorders have a smaller negative effect on implicit learning from feedback processing when compared to other substances, suggesting that either cannabis related disorders are not as deleterious as other SUDs or that cannabis dependent users do not have stronger decision-making impairments as other SUDs. Thirdly, we demonstrated that remission might have a positive effect on IGT performance, and that early onset of substance consumption and psychiatric comorbidities are associated with worse DD performance, advocating for the hypothesis that deficits in valuation of delayed gratification can precede deficits in feedback processing in SUDs. Lastly, in this study multilevel linear mixed-effects meta-analytic and meta-regression models were used, for the first time, to investigate the effect of SUDs on two different decision-making processes, adding an important contribution to the field and underlining several questions for future investigations.

## Contributors

Bruno Kluwe-Schiavon contributed with the design of the study,

data extraction, data analyses, write of the first draft and final version of the manuscript. Thiago Wendt Viola contributed with the design of the study, data extraction, data analyses, write of the first draft. Breno Sanvicente-Vieira contributed with the design of the study, data extraction and preparation of the manuscript. Francisco S. Lumertz contributed to data extraction. Prof. Giovanni Salum extensively contributed with data analyses and methodological improvements. Prof. Rodrigo Grassi-Oliveira contributed with the theoretical and methodological suggestions regarding the design of the study. Prof. Boris B. Quednow contributed with the design of the study, theoretical and methodological suggestions over the writing process. All authors have read, contributed and approved the final article.

## Role of funding source

This study was supported by the Coordination for the Improvement of Higher Education Personnel, CAPES, Brazil (grant number: 99999.001968/2015-07) and the Swiss National Science Foundation, SNSF, Switzerland (grant number: 105319_162639).

## Declaration of Competing Interest

All authors report no financial interests or potential conflicts of interest.

## Acknowledgements

We thank all corresponding authors who kindly dedicated part of their time to look for the requested data and send this information to us. Specially, we would like to thank Dr. Antonio Verdejo-Garcia, Dr. Anna E.Goudriaan, Dr. Brandon G. Oberlin, Dr. Craig G.A. Jones, Dr. Canan B. Peisker, Dr. Damien Brevers, Dr. Diana Mejía-Cruz, Dr. John Robert Monterosso, Dr. Lara Moody, Dr. Nancy M. Petry, Dr. Neomi van Duijvenbode, Dr. Nichole A.Duarte, Dr. Raul Gonzalez, Dr. Sarah H.Heil, Dr. Warren K. Bickel, and their respective team members.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neubiorev.2019.11.016.

## References

Amlung, M., Vedelago, L., Acker, J., Balodis, I., MacKillop, J., 2017. Steep delay discounting and addictive behavior: a meta-analysis of continuous associations. Addiction 112, 51–62.
Anokhin, A.P., Golosheykin, S., Grant, J.D., Heath, A.C., 2011. Heritability of delay discounting in adolescence: a longitudinal twin study. Behav. Genet. 41, 175–183.
Anokhin, A.P., Golosheykin, S., Mulligan, R.C., 2014. Long-term test-retest reliability of delayed reward discounting in adolescents. Behav. Processes 111C, 55–59.
APA, 2013. Diagnostic and Statistical Manual of Mental Disorders, 5 ed. American Psychiatric Publishing, Arlington, VA.
Audrain-McGovern, J., Rodriguez, D., Epstein, L.H., Cuevas, J., Rodgers, K., Wileyto, E.P., 2009. Does delay discounting play an etiological role in smoking or is it a consequence of smoking? Drug Alcohol Depend. 103, 99–106.
Baumeister, R.F., 2017. Addiction, cigarette smoking, and voluntary control of action: Do cigarette smokers lose their free will? Addict. Behav. Rep. 5, 67–84.
Bechara, A., 2005. Decision making, impulse control and loss of willpower to resist drugs: a neurocognitive perspective. Nat. Neurosci. 8, 1458–1463.
Bechara, A., Damasio, A.R., Damasio, H., Anderson, S.W., 1994. Insensitivity to future consequences following damage to human prefrontal cortex. Cognition 50, 7–15.
Bechara, A., Damasio, H., 2002. Decision-making and addiction (part I): impaired activation of somatic states in substance dependent individuals when pondering decisions with negative future consequences. Neuropsychologia 40, 1675–1689.
Bechara, A., Dolan, S., Hindes, A., 2002. Decision-making and addiction (part II): myopia for the future or hypersensitivity to reward? Neuropsychologia 40, 1690–1705.
Bickel, W.K., Marsch, L.A., 2001. Toward a behavioral economic understanding of drug dependence: delay discounting processes. Addiction 96, 73–86.
Bickel, W.K., Mellis, A.M., Snider, S.E., Athamneh, L.N., Stein, J.S., Pope, D.A., 2018. 21st century neurobehavioral theories of decision making in addiction: review and evaluation. Pharmacol. Biochem. Behav. 164, 4–21.
Biernacki, K., McLennan, S.N., Terrett, G., Labuschagne, I., Rendell, P.G., 2016. Decision-making ability in current and past users of opiates: a meta-analysis. Neurosci. Biobehav. Rev. 71, 342–351.
Bolla, K., Cadet, J., 2007. Cocaine. In: Kalechstein, A., van Gorp, W. (Eds.), Neuropsychology and Substance Use: State-of-the-Art and Future Directions. Psychology Press.
Bramer, W.M., Giustini, D., de Jonge, G.B., Holland, L., Bekhuis, T., 2016. De-duplication of database search results for systematic reviews in EndNote. J. Med. Libr. Assoc. 104, 240–243.
Cunha, P.J., Bechara, A., de Andrade, A.G., Nicastri, S., 2011. Decision-making deficits linked to real-life social dysfunction in crack cocaine-dependent individuals. Am. J. Addict. 20, 78–86.
Curran, H.V., Freeman, T.P., Mokrysz, C., Lewis, D.A., Morgan, C.J.A., Parsons, L.H., 2016. Keep off the grass? Cannabis, cognition and addiction. Nat. Rev. Neurosci. 17, 293–306.
De Wilde, B., Verdejo-Garcia, A., Sabbe, B., Hulstijn, W., Dom, G., 2013. Affective decision-making is predictive of three-month relapse in polysubstance-dependent alcoholics. Eur. Addict. Res. 19, 21–28.
Frazer, K.M., Richards, Q., Keith, D.R., 2018. The long-term effects of cocaine use on cognitive functioning: a systematic critical review. Behav. Brain Res. 348, 241–262.
Gleser, L., Olkin, I., 2009. Stochastically dependent effect sizes. In: Cooper, H., Hedges, L., Valentine, J. (Eds.), The Handbook of Research Synthesis and Meta-Analysis, 2nd ed. Russell Sage Foundation, New York, pp. 357–376.
Higgins, S.T., Green, S., 2011. Cochrane Handbook for Systematic Reviews of Interventions Version. The Cochrane Collaboration.
Huedo-Medina, T.B., Sanchez-Meca, J., Marin-Martinez, F., Botella, J., 2006. Assessing heterogeneity in meta-analysis: Q statistic or I2 index? Psychol. Methods 11, 193–206.
Hulka, L.M., Eisenegger, C., Preller, K.H., Vonmoos, M., Jenni, D., Bendrick, K., Baumgartner, M.R., Seifritz, E., Quednow, B.B., 2014. Altered social and non-social decision-making in recreational and dependent cocaine users. Psychol. Med. 44, 1015–1028.
Hulka, L.M., Vonmoos, M., Preller, K.H., Baumgartner, M.R., Seifritz, E., Gamma, A., Quednow, B.B., 2015. Changes in cocaine consumption are associated with fluctuations in self-reported impulsivity and gambling decision-making. Psychol. Med. 45, 3097–3110.
Kaag, A.M., Schulte, M.H.J., Jansen, J.M., van Wingen, G., Homberg, J., van den Brink, W., Wiers, R.W., Schmaal, L., Goudriaan, A.E., Reneman, L., 2018. The relation between gray matter volume and the use of alcohol, tobacco, cocaine and cannabis in male polysubstance users. Drug Alcohol Depend. 187, 186–194.
Kelley, G.A., Kelley, K.S., 2012. Statistical models for meta-analysis: a brief tutorial. World J. Methodol. 2, 27–32.
Kirby, K.N., Marakovic, N.N., 1996. Delay-discounting probabilistic rewards: rates decrease as amounts increase. Psychon. Bull. Rev. 3, 100–104.
Kluwe-Schiavon, B., Viola, T.W., Sanvicente-Vieira, B., Pezzi, J.C., Grassi-Oliveira, R., 2016. Similarities between adult female crack cocaine users and adolescents in risky decision-making scenarios. J. Clin. Exp. Neuropsychol. 38, 795–810.
Koffarnus, M.N., Kaplan, B.A., 2018. Clinical models of decision making in addiction. Pharmacol. Biochem. Behav. 164, 71–83.
Kopetz, C., Orehek, E., 2015. When the end justifies the means: self-defeating behaviors as “Rational” and “Successful” self-regulation. Curr. Dir. Psychol. Sci. 24, 5.
Kovacs, I., Richman, M.J., Janka, Z., Maraz, A., Ando, B., 2017. Decision making measured by the Iowa Gambling Task in alcohol use disorder and gambling disorder: a systematic review and meta-analysis. Drug Alcohol Depend. 181, 152–161.
Lejuez, C.W., Read, J.P., Kahler, C.W., Richards, J.B., Ramsey, S.E., Stuart, G.L., Strong, D.R., Brown, R.A., 2002. Evaluation of a behavioral measure of risk taking: the Balloon Analogue Risk Task (BART). J. Exp. Psychol. Appl. 8, 75–84.
MacKillop, J., Amlung, M.T., Few, L.R., Ray, L.A., Sweet, L.H., Munafo, M.R., 2011. Delayed reward discounting and addictive behavior: a meta-analysis. Psychopharmacology (Berl.) 216, 305–321.
MacKillop, J., Kahler, C.W., 2009. Delayed reward discounting predicts treatment response for heavy drinkers receiving smoking cessation treatment. Drug Alcohol Depend. 104, 197–203.
Mazur, J., 1987. An Adjusting Procedure for Delayed Reinforcement. Erlbaum, New Jersey.
McInnes, M.D.F., Moher, D., Thombs, B.D., McGrath, T.A., Bossuyt, P.M., the, P.-D.T.A.G., et al., 2018. Preferred reporting items for a systematic review and meta-analysis of diagnostic test accuracy studies: the PRISMA-DTA statement. JAMA 319, 388–396.
Mischel, W., Ayduk, O., Berman, M.G., Casey, B.J., Gotlib, I.H., Jonides, J., Kross, E., Teslovich, T., Wilson, N.L., Zayas, V., Shoda, Y., 2011. ’Willpower’ over the life span: decomposing self-regulation. Soc. Cogn. Affect. Neurosci. 6, 252–256.
Myerson, J., Green, L., Warusawitharana, M., 2001. Area under the curve as a measure of discounting. J. Exp. Anal. Behav. 76, 235–243.
Nutt, D., King, L.A., Saulsbury, W., Blakemore, C., 2007. Development of a rational scale to assess the harm of drugs of potential misuse. Lancet 369, 1047–1053.
Odum, A.L., 2011. Delay discounting: Trait variable? Behav. Processes 87, 1–9.
Olsen, V.V., Lugo, R.G., Sutterlin, S., 2015. The somatic marker theory in the context of addiction: contributions to understanding development and maintenance. Psychol. Res. Behav. Manag. 8, 187–200.
Paez, A., 2017. Grey literature: an important resource in systematic reviews. J. Evid. Med.
Polanczyk, G.V., Salum, G.A., Sugaya, L.S., Caye, A., Rohde, L.A., 2015. Annual Research Review: a meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. J. Child Psychol. Psychiatry 56, 345–365.
Preller, K., Herdener, M., Schilbach, L., Staempfli, P., Hulka, L., Vonmoos, M., Ingold, N., Vogeley, K., Tobler, P., Seifritz, E., Quednow, B., 2014a. Functional changes of the reward system underlie blunted response to social gaze in cocaine users. Proc. Natl.

Acad. Sci. U. S. A. 111, 2842–2847.
Preller, K., Hulka, L., Vonmoos, M., Jenni, D., Baumgartner, M., Seifritz, E., Dziobek, I., Quednow, B., 2014b. Impaired emotional empathy and related social network deficits in cocaine users. Addict. Biol. 19, 452–466.
R Development Core Team, 2010. R: a Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria.
Rangel, A., Camerer, C., Montague, P.R., 2008. A framework for studying the neurobiology of value-based decision making. Nat. Rev. Neurosci. 9, 545–556.
Rogers, R.D., Everitt, B.J., Baldacchino, A., Blackshaw, A.J., Swainson, R., Wynne, K., Baker, N.B., Hunter, J., Carthy, T., Booker, E., London, M., Deakin, J.F., Sahakian, B.J., Robbins, T.W., 1999. Dissociable deficits in the decision-making cognition of chronic amphetamine abusers, opiate abusers, patients with focal damage to prefrontal cortex, and tryptophan-depleted normal volunteers: evidence for monoaminergic mechanisms. Neuropsychopharmacology 20, 322–339.
Rosenberg, M., 2005. The file-drawer problem revisited: a general weighted method for calculationg fail-safe numbers in meta-analysis. Evolution 59, 4.
Rosenthal, R., 1979. The file drawer problem and tolerance for null results. Psychol. Bull. 86, 638–641.
Rzezak, P., Antunes, H.K., Tufik, S., dMello, M.T., 2012. Translation and cultural adaptation of the Game Dice Task to Brazilian population. Arq. Neuropsiquiatr. 70, 929–933.
Stang, A., 2010. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur. J. Epidemiol. 25, 603–605.
Steward, T., Mestre-Bach, G., Vintro-Alcaraz, C., Aguera, Z., Jimenez-Murcia, S., Granero, R., Fernandez-Aranda, F., 2017. Delay discounting of reward and impulsivity in eating disorders: from anorexia nervosa to binge eating disorder. Eur. Eat. Disord. Rev. 25, 601–606.
Thomson Reuters, 2017. EndNote, x7 ed. Clarivate Analytics.
Urosevic, S., Youngstrom, E.A., Collins, P., Jensen, J.B., Luciana, M., 2016. Associations of age with reward delay discounting and response inhibition in adolescents with bipolar disorders. J. Affect. Disord. 190, 649–656.
Verdejo-García, A., Bechara, A., 2009. A somatic marker theory of addiction. Neuropharmacology 56 (Suppl. 1), 48–62.
Verdejo-Garcia, A., Chong, T.T., Stout, J.C., Yucel, M., London, E.D., 2018. Stages of dysfunctional decision-making in addiction. Pharmacol. Biochem. Behav. 164, 99–105.
Viechtbauer, W., 2010. Conducting meta-analyses in R with the metafor package. J. Stat. Softw. 36, 47.
Viechtbauer, W., Cheung, M.W., 2010. Outlier and influence diagnostics for meta-analysis. Res. Synth. Methods 1, 112–125.
Viola, T.W., Salum, G.A., Kluwe-Schiavon, B., Sanvicente-Vieira, B., Levandowski, M.L., Grassi-Oliveira, R., 2016. The influence of geographical and economic factors in estimates of childhood abuse and neglect using the Childhood Trauma Questionnaire: a worldwide meta-regression analysis. Child Abuse Negl. 51, 1–11.
Volkow, N.D., Morales, M., 2015. The brain on drugs: from reward to addiction. Cell 162, 712–725.
Vonmoos, M., Hirsiger, S., Preller, K.H., Hulka, L.M., Allemann, D., Herdener, M., Baumgartner, M.R., Quednow, B.B., 2018. Cognitive and neuroanatomical impairments associated with chronic exposure to levamisole-contaminated cocaine. Transl. Psychiatry 8, 235.
Vonmoos, M., Hulka, L.M., Preller, K.H., Minder, F., Baumgartner, M.R., Quednow, B.B., 2014. Cognitive impairment in cocaine users is drug-induced but partially reversible: evidence from a longitudinal study. Neuropsychopharmacology 39, 2200–2210.
Voyer, D., Voyer, S.D., 2014. Gender differences in scholastic achievement: a meta-analysis. Psychol. Bull. 140, 1174–1204.
Washio, Y., Higgins, S.T., Heil, S.H., McKerchar, T.L., Badger, G.J., Skelly, J.M., Dantona, R.L., 2011. Delay discounting is associated with treatment response among cocaine-dependent outpatients. Exp. Clin. Psychopharmacol. 19, 243–248.
Xiao, L., Bechara, A., Grenard, J., Stacy, W.A., Palmer, P., Wei, Y.L., Jia, Y., Fu, X.L., Johnson, C.A., 2009. Affective decision-making predictive of Chinese adolescent drinking behaviors. J. Int. Neuropsychol. Soc. 15, 547–557.
Xiao, L., Koritzky, G., Johnson, C.A., Bechara, A., 2013. The cognitive processes underlying affective decision-making predicting adolescent smoking behaviors in a longitudinal study. Front. Psychol. 4, 685.
Yoon, J.H., De La Garza, R., Newton, T.F., Suchting, R., Weaver, M.T., Brown, G.S., Omar, Y., Haliwa, I., 2017. A comparison of Mazur's k and area under the curve for describing steep discounters. Psychol. Rec. 67, 355–363.