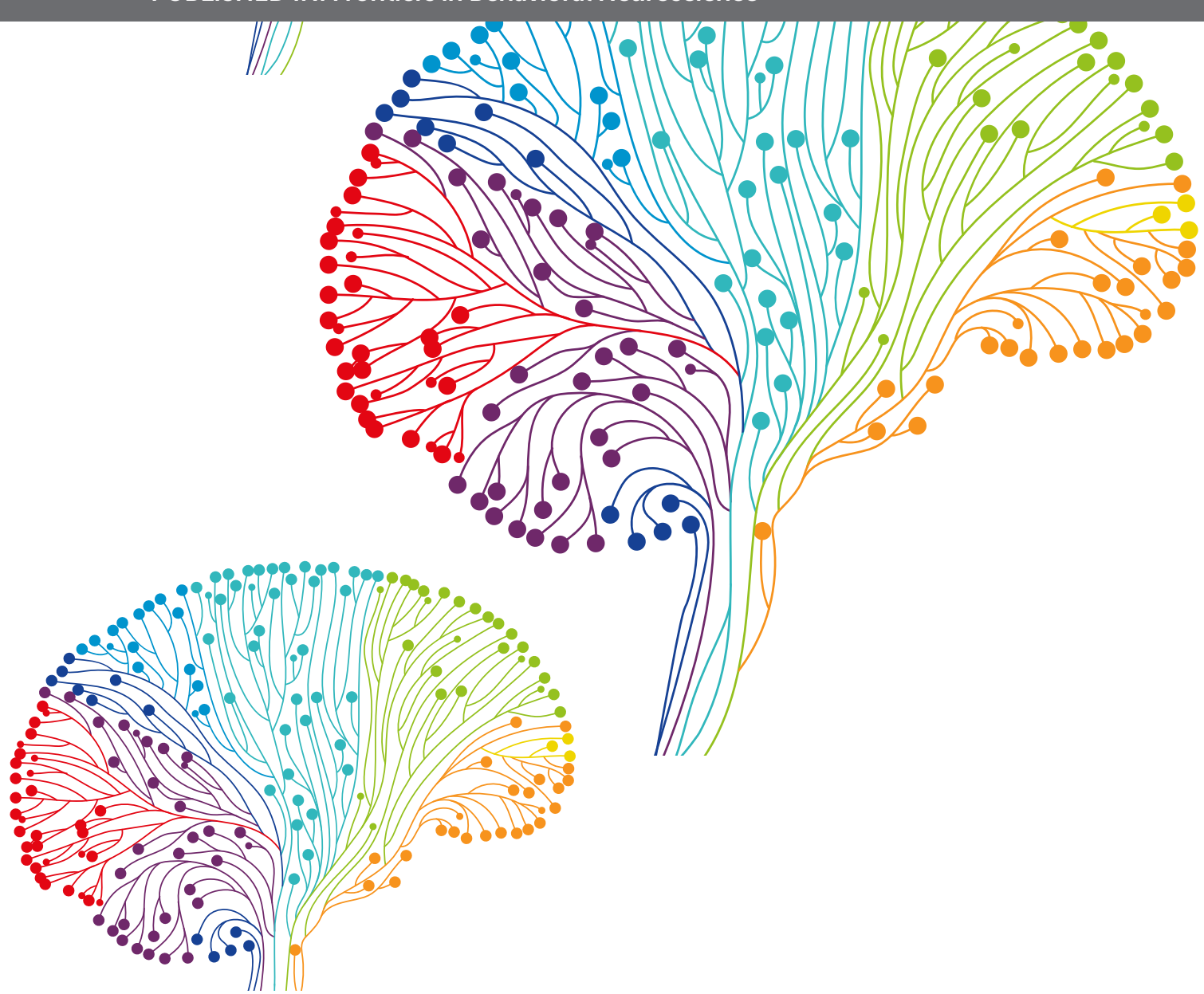
BEHAVIORAL ADDICTIONS, RISK-TAKING, AND IMPULSIVE CHOICE

EDITED BY: Marco Bortolato and Gregory J. Madden
PUBLISHED IN: Frontiers in Behavioral Neuroscience



frontiers Research Topics

ISSN 1664-8714
ISBN 978-2-88976-266-8
DOI 10.3389/978-2-88976-266-8

About Frontiers

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers Journal Series

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to Quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews.
Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: frontiersin.org/about/contact

BEHAVIORAL ADDICTIONS, RISK-TAKING, AND IMPULSIVE CHOICE

Topic Editors:
Marco Bortolato, The University of Utah, United States
Gregory J. Madden, Utah State University, United States

Citation: Bortolato, M., Madden, G. J., eds. (2022). Behavioral Addictions, Risk-Taking, and Impulsive Choice. Lausanne: Frontiers Media SA.
doi: 10.3389/978-2-88976-266-8

Table of Contents

frontiers | Frontiers in Behavioral Neuroscience

EDITORIAL
published: 09 May 2022
doi: 10.3389/fnbeh.2022.924030

Editorial: Behavioral Addictions, Risk-Taking, and Impulsive Choice

Marco Bortolato[1*†] *and Gregory J. Madden*[2*†]

[1] *Department of Pharmacology and Toxicology, University of Utah, Salt Lake City, UT, United States,* [2] *Department of Psychology, Utah State University, Logan, UT, United States*

Keywords: impulsivity, risk taking, animal models, delay discounting, probability discounting, decision making, behavioral addiction

Editorial on the Research Topic

Behavioral Addictions, Risk-Taking, and Impulsive Choice

This special topic presents theoretical and experimental work on the biopsychological mechanisms of impulsivity. While impulsivity is regarded as a core symptom in various psychiatric disorders, ranging from ADHD to disruptive disorders and behavioral addiction, current frameworks indicate that impulsivity is a multidimensional construct, which is currently interpreted as a cluster of different behavioral domains that likely reflect separate neurobiological mechanisms (Strickland and Johnson, 2020).

One of the main facets of impulsivity is maladaptive decision making, whereby immediate benefits (such as the rewarding effect of a drug or alcohol use or the escape/avoidance of physical/emotional pain) are preferred over more consequential, but delayed negative outcomes (e.g., health deficits, relationship loss). This devaluation of untoward consequences (i.e., steep delay-discounting) is borne out in the literature by meta-analyses showing robust (replicable, medium-to-large effect size) correlations between a variety of substance-use disorders and delay discounting (MacKillop et al., 2011; Amlung et al., 2017). In addition, several studies indicate that decreased delay discounting is associated with maladaptive health decision-making (e.g., Stein et al., 2016; Athamneh et al., 2021). Therefore, interventions that aim to decrease delay discounting are of some importance. The special topic paper by Stein et al. finds, for the first time, that a choice-bundling intervention reduces the extent to which cigarette smokers discount delayed gains *and* losses, the latter being analogous to loss of health, relationships, etc. Bundling interventions allow the decision-maker to make one choice and then experience a series of either smaller-sooner or larger-later rewards (depending on the initial choice). These interventions have proven effective in reducing delay discounting in human and non-human subjects (Rung and Madden, 2018; Smith et al., 2019), with the Stein et al. paper being the first to show the bundling strategy works to decrease the devaluation of delayed negative outcomes. The authors discuss bundling-based therapies that could help those at risk of substance use disorders to give greater consideration to the future outcomes of decisions made today.

Beyond interventions, there are several state-factors known to influence the rate of delay discounting (Odum et al., 2020). The special topic paper by Downey et al. reviews the human and non-human literature to evaluate if deprivation (e.g., hunger, thirst, acute drug withdrawal) is one such state variable that, when increased, increases impulsive choice. They find little uniformity in the literature, either in how deprivation is imposed (e.g., hypothetical vs. real deprivations of varying durations) or in the effect sizes these manipulations induce. They discuss the importance of better understanding deprivation effects, and how greater uniformity might be brought to the literature.

OPEN ACCESS

Edited and reviewed by:
Liana Fattore,
CNR Neuroscience Institute (IN), Italy

Correspondence:
Marco Bortolato
marco.bortolato@utah.edu
Gregory J. Madden
greg.madden@usu.edu

[†] These authors have contributed equally to this work

Specialty section:
This article was submitted to Motivation and Reward, a section of the journal Frontiers in Behavioral Neuroscience

Received: *20 April 2022*
Accepted: *26 April 2022*
Published: *09 May 2022*

Citation:
Bortolato M and Madden GJ (2022) Editorial: Behavioral Addictions, Risk-Taking, and Impulsive Choice. Front. Behav. Neurosci. 16:924030. doi: 10.3389/fnbeh.2022.924030

The special topic paper by Gilroy et al. examines the practice of excluding data because the shape of the discounting function is irregular, potentially reflecting inattention, or careless survey responding. To avoid the inadvertent exclusion of valid data, the authors explore a Latent Class Mixed Modeling approach, which classifies groups of obtained uncharacteristic patterns of choice. Their application of that approach to a publicly available dataset suggests it may prove a useful supplement to existing methods for screening out unsystematic discounting data. The paper by Grunevski et al. reveals that an independent measure of ambivalence systematically increases as participants complete survey questions that approach the point of subjective equivalence (i.e., when the smaller-sooner and larger-later outcomes are equally valued). Such measures of ambivalence are potentially useful in detecting (and excluding) data produced by careless participants, or in detecting shifting indifference points in interventions designed to reduce delay discounting.

Less is known about the correlation between delay discounting and maladaptive decision-making that does not involve substance use. The special topic paper by Weinsztok et al. provides a pre-registered systematic review and meta-analysis of 78 published studies evaluating delay discounting rates among those with a behavioral (non-substance) addiction. The clearest relation was observed among those with a gambling disorder, whereas other "addictions" (e.g., internet/smartphone, compulsive buying) have either not been adequately studied or are not consistently correlated with delay discounting. Concerns are raised about the potential for publication bias.

Gambling disorders are, unsurprisingly, also correlated with putting greater subjective value on probabilistic outcomes. The special topic paper by Schneider et al. replicates this finding in an American Indian sample of gamblers and non-gamblers. They also explore neural responses correlating with choices made in the probability discounting task. In a rat model of gambling, Vonder Haar et al. explore the effects of traumatic brain injury (TBI) on risky, suboptimal choices. They report that, despite considerable individual differences within groups, TBI rats were less sensitive to contingencies, less sensitive to recent outcomes, and demonstrated a general bias toward the riskier alternatives. Clustering the patterns of choice revealed distinct behavioral phenotypes, with TBI rats rarely demonstrating the optimal of these choice phenotypes.

Another critical dimension that can influence impulsivity is the sensitivity to environmental stress. In fact, ample evidence indicates that exposure to acute stress can modify decision making and promote the choice of rewarding options. Building on this idea, the article by Dong et al. shows that tail-clip stress increases self-administration of propofol in rats through corticotropin-releasing factor (CRF) receptor 1, a key orchestrator of the stress response. These mechanisms, which are likely supported by dopamine 1 receptors in the nucleus accumbens, point to the crosstalk between CRF and mesolimbic dopamine neurotransmission as a key process shaping the negative influence of stress on drug seeking.

In addition to neuroeconomic alterations (such as those observed in delay and probability discounting), impulsivity is likely to encompass other constructs related to sensation-seeking, boredom susceptibility, and venturesomeness (Depue and Collins, 1999). However, operationalizing these dispositions, and identifying valid animal models that may appropriately capture their neurobiological foundations, has proven complex. In their article, Festucci et al. present a novel paradigm based on an adapted version of the suspended wire bridge protocol originally developed for mice (Bortolato et al., 2009). Using this behavioral task—which measures the propensity to engage in risky actions irrespective of rewards—the authors document that early-life exposure to adults with impaired dopamine reuptake reduces venturesome-like behavior.

Overall, we believe that the contributions to this Special Topic highlight the multifaceted nature of impulsivity and open to new empirical and theoretical perspectives in the definition of this complex behavioral construct. In closing, we would like to dedicate this Special Topic to the memory of Stephen C. Fowler, who passed away far too young in June 2020, and had dedicated his entire scientific life to behavioral pharmacology. As part of his extensive scientific legacy (attested in over 160 publications, many of which in high-impact, peer-reviewed journals, including *Science, Cell*, and *PNAS*), Steve developed novel quantitative methods for the detection and analysis of motor and cognitive responses. He provided major contributions to the research field of impulsivity and addiction by studying the impact of dopaminergic agonists in several animal models of risky choice and attention deficits. He was a brilliant scientist and innovator, and a staunch advocate of the essential value of animal models in neuropsychopharmacological and behavioral research. We both had the good luck to collaborate with him, and we will always remember him as a kind, open, and generous friend. We miss him deeply.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

FUNDING

This work was funded by NIH (R21DA049530 to MB) and (R03DA052467 to GM).

REFERENCES

Amlung, M., Vedelago, L., Acker, J., Balodis, I., MacKillop, J., Joseph, S., et al. (2017). Steep delay discounting and addictive behavior: a meta-analysis of continuous associations. *Addiction* 112, 51–62. doi: 10.1111/add.13535

Athamneh, L. N., Brown, J., Stein, J. S., Gatchalian, K. M., LaConte, S. M., and Bickel, W. K. (2021). Future thinking to decrease real-world drinking in alcohol use disorder: repairing reinforcer pathology in a randomized proof-of-concept trial. *Exp. Clin. Psychopharmacol.* doi: 10.1037/pha0000460. [Epub ahead of print].

Bortolato, M., Godar, S. C., Davarian, S., Chen, K., and Shih, J. C. (2009). Behavioral disinhibition and reduced anxiety-like behaviors in monoamine oxidase B-deficient mice. *Neuropsychopharmacology* 34, 2746–2757. doi: 10.1038/npp.2009.118

Depue, R. A., and Collins, P. F. (1999). Neurobiology of the structure of personality: dopamine, facilitation of incentive motivation, and extraversion. *Behav. Brain Sci.* 22, 491–569. doi: 10.1017/S0140525X99002046

MacKillop, J., Amlung, M. T., Few, L. R., Ray, L. A., Sweet, L. H., and Munaf,ò, M. R. (2011). Delayed reward discounting and addictive behavior: a meta-analysis. *Psychopharmacology* 216, 305–321. doi: 10.1007/s00213-011-2229-0

Odum, A. L., Becker, R. J., Haynes, J. M., Galizio, A., Frye, C. C. J., Downey, H., et al. (2020). Delay discounting of different outcomes: review and theory. *J. Exp. Anal. Behav.* 113, 657–679. doi: 10.1002/jeab.589

Rung, J. M., and Madden, G. J. (2018). Experimental reductions of delay discounting and impulsive choice: a systematic review and meta-analysis. *J. Exp. Psychol. Gen.* 147, 1349–1381. doi: 10.1037/xge0000462

Smith, T., Panfil, K., Bailey, C., and Kirkpatrick, K. (2019). Cognitive and behavioral training interventions to promote self-control. *J. Exp. Psychol. Anim. Learn. Cogn.* 45, 259–279. doi: 10.1037/xan0000208

Stein, J. S., Wilson, A. G., Koffarnus, M. N., Daniel, T. O., Epstein, L. H., and Bickel, W. K. (2016). Unstuck in time: episodic future thinking reduces delay discounting and cigarette smoking. *Psychopharmacology* 233, 3771–3778. doi: 10.1007/s00213-016-4410-y

Strickland, J. C., and Johnson, M. W. (2020). Rejecting impulsivity as a psychological construct: a theoretical, empirical, and sociocultural argument. *Psychol. Rev.* 128, 336–361. doi: 10.1037/rev0000263

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Behavioral Neuroscience

ORIGINAL RESEARCH
published: 28 April 2021
doi: 10.3389/fnbeh.2021.637074

"Himalayan Bridge": A New Unstable Suspended Bridge to Investigate Rodents' Venturesome Behavior

Fabiana Festucci[1,2], *Clelia Buccheri*[1], *Anna Parvopassu*[1], *Maurizio Oggiano*[3], *Marco Bortolato*[4], *Giovanni Laviola*[1], *Giuseppe Curcio*[2] *and Walter Adriani*[1]*

[1] Center for Behavioural Sciences and Mental Health, Istituto Superiore di Sanità, Rome, Italy, [2] Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy, [3] European Mind and Metabolism Association, Rome, Italy, [4] Department of Pharmacology and Toxicology, College of Pharmacy, University of Utah, Salt Lake City, UT, United States

While both risk-taking and avoidant behaviors are necessary for survival, their imbalanced expression can lead to impulse-control and anxiety disorders, respectively. In laboratory rodents, the conflict between risk proneness and anxiety can be studied by using their innate fear of heights. To explore this aspect in detail and investigate venturesome behavior, here we used a "Himalayan Bridge," a rat-adapted version of the suspended wire bridge protocol originally developed for mice. The apparatus is composed of two elevated scaffolds connected by bridges of different lengths and stability at 1 m above a foam rubber-covered floor. Rats were allowed to cross the bridge to reach food, and crossings, pawslips, turnabouts, and latencies to cross were measured. Given the link between risky behavior and adolescence, we used this apparatus to investigate the different responses elicited by a homecage mate on the adolescent development of risk-taking behavior. Thus, 24 wild-type (WT) subjects were divided into three different housing groups: WT rats grown up with WT adult rats; control WT adolescent rats (grown up with WT adolescents), which showed a proclivity to risk; and WT rats grown up with an adult rat harboring a truncated mutation for their dopamine transporter (DAT). This latter group exhibited risk-averse responses reminiscent of lower venturesomeness. Our results suggest that the Himalayan Bridge may be useful to investigate risk perception and seeking; thus, it should be included in the behavioral phenotyping of rat models of psychiatric disorders and cognitive dysfunctions.

Keywords: dopamine, risk-taking behavior, wild-type, knock-out, adolescence, bridge length, bridge height

OPEN ACCESS

Edited by:
Fabrizio Sanna,
University of Cagliari, Italy

Reviewed by:
Maurizio Casarrubea,
University of Palermo, Italy
Robert Barnet,
College of William & Mary,
United States

***Correspondence:**
Walter Adriani
walter.adriani@iss.it

Specialty section:
This article was submitted to Motivation and Reward, a section of the journal Frontiers in Behavioral Neuroscience

Received: *02 December 2020*
Accepted: *17 February 2021*
Published: *28 April 2021*

Citation:
Festucci F, Buccheri C, Parvopassu A, Oggiano M, Bortolato M, Laviola G, Curcio G and Adriani W (2021) "Himalayan Bridge": A New Unstable Suspended Bridge to Investigate Rodents' Venturesome Behavior. Front. Behav. Neurosci. 15:637074. doi: 10.3389/fnbeh.2021.637074

INTRODUCTION

The decision-making process that leads individuals to choose between different beneficial and harmful options is at the heart of everyday life. When faced with these choices, subjects can evaluate the likely outcome of their behavior by weighing risks and rewards, and ultimately decide whether to engage in venturesome or conservation behavior. Abnormal risky decision-making, which is associated with dysregulated dopamine receptor expression, is a characterizing feature of many psychiatric disorders, such as impulse-control disorders, attention deficit hyperactivity disorder (ADHD), schizophrenia, major depression, addiction, and Parkinson's disease (Bechara et al., 2001; Ernst et al., 2003; Ludewig et al., 2003; Taylor Tavares et al., 2007; Kobayakawa et al., 2008).

Crossing a suspended bridge is considered venturesome not only because of the risk of falling but also because of the fear of heights. The acquisition of fear of heights is probably based more on tactile than visual cues because the rat is myopic and with an undifferentiated floor would be unable to make graded depth judgments; it is also likely that depth is judged in an "all-or-none" manner: low enough and safe vs. high enough to evoke fear (File et al., 1998). The fact that the fear of heights is rapidly acquired during initial exposure to the apparatus suggests that there is a genetic, innate predisposition to develop this fear. Conditioned fear, based on associating cues/contexts to unescapable aversive stimuli, or instrumental punishment, based on negative reinforcement to cancel an unwanted action with its punishment, has been used to model phobia; however, simple exposure to frights or innately scary situations has not yet been used to prove useful animal models of phobia. Therefore, this rapidly acquired fear of heights using a naturalistic test situation may prove more useful (Klein, 1980). We presently challenge rats with acute fear induced by the feeling of danger, and therefore this task is not directly comparable to any conditioned-fear task. As far as phobic behavior is concerned, however, Zelli et al. (2020) recently developed a "sudden fright" task that proved useful to highlight a phobic phenotype in dopamine transporter (DAT)-heterozygous rats. This feeling of danger causes excessive and maladaptive avoidance that contributes to the development and maintenance of anxiety disorders and prevents the extinction of fearful responses in humans (Craske et al., 2009; Lovibond et al., 2009) and rodents (Muigg et al., 2008).

The elevated plus maze (EPM) is the gold standard to assess approach–avoidance behavior in rodents, but a homologous test in humans is lacking. For this reason, Biedermann et al. (2017) translated the EPM test into a human paradigm, using a novel task in mixed reality through a combination of virtual and real-world elements. Such task allows tracking of approach–avoidance behavior that is ecologically and ethologically valid. Firstly, experimenters observed a high immersion in the mixed-reality test: participants often gasped at the beginning of the procedure and moved precariously and slow on open arms. Secondly, on a physiological level, the EPM stimulated the sympathetic nervous system; this has been demonstrated by a rise in skin conductance level (SCL), heart rate, and respiration rate. On a behavioral level, participants spent most of the time in the safe compartments of the EPM; on a subjective level, after the experiment, participants stated that they had felt more anxious on open vs. closed arms and center (safe zones). Thirdly, the authors found a high correlation between subjective and behavioral outcomes. Lastly, the authors found significant associations of behavioral measures with trait measures of acrophobia and sensation-seeking (Biedermann et al., 2017).

The goal of our study was to develop a new structure to be able to study the proclivity of rats in risk-taking. For our purpose, we were inspired by the work by Bortolato et al. (2009). To investigate the impact of monoamine oxidase (MAO) B deficiency on the emotional responses elicited by environmental cues, these authors tested MAO B knockout (KO) mice in a set of behavioral assays capturing different aspects of anxiety-related manifestation, including the wire-beam bridge test. Low levels of platelet MAO activity have been strongly associated with features of the behavioral disinhibition spectrum including impulsivity, sensation-seeking, and risk-taking. To capture these elements, the authors measured the animals' proclivity to cross an unrailed flexible bridge suspended over a 30-cm-deep gap to reach a food reward. MAO B KO mice exhibited a significantly shorter latency to access the bridge. In the time before accessing the bridge, MAO B KO mice engaged in a significantly higher sniffing frequency compared to wild-type (WT) mice. These results provide further support that MAO B KO mice display greater impulsivity, sensation-seeking, and risk-taking behaviors than WT mice (Bortolato et al., 2009). The same apparatus was used by the same group to study the combined effect of reserpine (RES), a monoamine-depleting agent, and pramipexole (PPX), a D_2 and D_3 dopamine receptor agonist, on rats' impulsive behavior. The rationale of this study relies on the hypothesis that PPX would stimulate sensation-seeking in a context of dopamine depletion. The authors found that the association of RES and PPX does not augment the proclivity of rats to cross the bridge to obtain a reward. This result suggests that the effect of RES and PPX does not reflect a generalized increase in impulsivity and venturesomeness (Orrù et al., 2020). The advantage of this task is that the animals may feel the risk of falling solely because the bridge bends. On the EPM, the platform is stable, and the subjects instinctively know that their risk of falling is minimal as long as they stay on the platform. In contrast, the present paradigm imposes a perception of current (rather than potential) danger, which requires the enactment of coping strategies.

On a neurobiological level, several studies tried to identify the brain regions responsible for the decision-making behavior. Salamone et al. (1994) found that dopamine depletion in the nucleus accumbens biased rats toward making less effortful choices in a T-maze cost–benefit procedure. Walton et al. (2002) later showed that relatively large lesions of the medial pre-frontal cortex in rats also reduced the likelihood of effortful choices. This same group also demonstrated that relatively small lesions of the anterior cingulate cortex decreased effortful choices, whereas lesions to the prelimbic/infralimbic cortex and orbitofrontal cortex did not (Walton et al., 2005). Finally, Floresco and Ghods-Sharifi (2007) showed that the amygdala may also serve as a locus of effort-based decision-making in the brain, since bilateral inactivation of the basolateral amygdala concurrent with inactivation of the contralateral anterior cingulate cortex decreases effortful behavior driven by a food reward. All brain regions currently implicated in effort-based decision-making utilize dopamine released from neurons in the ventral tegmental area as a neurotransmitter: this observation suggests a central role for dopamine in effort-based decision-making. Despite this, the specific dopamine receptor subtypes required for such responses have not been identified (Bardgett et al., 2009).

The DAT is involved in the uptake of dopamine released into the extracellular space; deficiency of DAT function can lead to a hyperdopaminergic phenotype, altering gratification, cognitive, emotional, and motor functions (Salatino-Oliveira et al., 2018). In this context, a new rat model has been developed. In these animals, the gene encoding DAT has been disrupted by using zinc finger nuclease technology: bearing a truncated DAT

(DAT-trunk) protein, KO (DAT-KO) rats develop normally but weigh less than heterozygous (HET) and WT rats. DAT-KO rats display elevated locomotor activity and restless environmental exploration associated with a transient anxiety profile, as well as a pronounced stereotypy and compulsive-like behavior (Adinolfi et al., 2019).

In this experiment, a suspended bridge (named "Himalayan" to underscore its similarity to the rope bridges extending over canyons and valleys across Nepal) was exploited to assess the potential difference in novelty-seeking and venturesomeness using a rat model for deviant adolescent trajectories. This was achieved by housing normal WT adolescent rats with either WT adult rats or with DAT-trunk adult rats. These housing arrangements were intended to represent a continuum of adolescent rearing and development ranging from "normal" (adolescent rats reared with adolescent peer rats) and "slightly abnormal" (adolescent rats housed with adult WT rats) to "highly abnormal" (adolescent rats reared with behaviorally atypical adult-DAT-trunk rats) (see Parvopassu et al., 2021). The goal of this study was to investigate how the developing behavior of adolescent WT rats was influenced by the DAT-trunk adult's actions after a period. During adolescence, rats develop behavioral skills through social interaction and play with conspecifics. Given the restricted behavioral profile expressed by DAT-trunk rats, consisting of hyperactivity and stereotypy (Cinque et al., 2018), we hypothesized that growing WT rats would have no way to develop behavioral skills due to a narrowed and altered interaction. However, since DAT-trunk cagemates were also adult, there was the need for a third "intermediate" group, which was housed with an adult but of a WT genotype. Adult WT rats express a normal behavioral repertoire but are however less prone to play with adolescents, whose development may thus take a somewhat altered trajectory. In both cases, such poor social interaction might interfere with the proneness to express, later, appropriate coping skills during a challenge. Influence on them was recently shown to yield a depressive and compulsive phenotype (Parvopassu et al., 2021).

In this way, we were able to assess whether companion affects the risk-taking proclivity, regardless of the genotype. Studies conducted in humans and other mammalian species have reported that adolescents often exhibit more risk-taking behavior than adults (Doremus-Fitzwater et al., 2010; Sturman and Moghaddam, 2011). Such differences are likely driven by neurobiological and hormonal changes that affect cognition and motivation (Doremus-Fitzwater et al., 2009). It has been suggested that these typical adolescent alterations are evolutionarily adaptive in that they cause animals to leave the nest, to mate, acquire resources (Steinberg and Belsky, 1996; Spear, 2010), and, ultimately, facilitate the transition from juvenile period to adulthood (Gore-Langton et al., 2020). It has been postulated that an imbalance between the early-maturing reward and later-maturing cognitive control systems may lead to the elevated impulsive and risk-taking behaviors of adolescents (Ernst et al., 2006; Doremus-Fitzwater et al., 2010; Sturman and Moghaddam, 2011). For these reasons, it is our opinion that WT adolescent rats grown up with WT adolescent rats will be more likely to take the risk of falling to get the food.

The apparatus consisted of an arrival point and a departure point linked by metal bridges of different lengths. This structure was placed 1 m above the floor, which was covered with foam rubber to avoid damage to subjects in case of a fall. Subjects had to cross the bridge to reach the arrival point where a food reward was available.

MATERIALS AND METHODS

Subjects

The generation of Wistar-Han DAT-KO rats was previously described elsewhere (Leo et al., 2018). The colony was maintained in a heterozygous-heterozygous breeding fashion; these animals were intercrossed for >10 generations at *Istituto Italiano di Tecnologia* (ITT, Genoa, Italy). Some progenitors were shipped to *Istituto Superiore di Sanità* (ISS, Rome, Italy), where male DAT-KO rats (and their DAT-WT siblings) were bred with outbred Wistar-Han WT females (Charles River, Italy). As such, we obtained a G0 of founders (namely, heterozygous and WT G0 subjects, respectively). From that step onward, two parallel lines were maintained with a heterozygous-heterozygous vs. a WT-WT breeding fashion. Present subjects are G4 of our ISS colony. All rats were born by "typical" breeding. In particular, WT rats were offspring by WT mothers bred with WT fathers, while HET rats were offspring by HET mothers bred with HET fathers. Animals were maintained under a 12-h reverse dark–light cycle (lights off at 7:00 a.m.) in a temperature- and humidity-controlled environment (T 21 ± 1°C, relative humidity 60 ± 10%) with food (ALTROMIN-R, Rieper SpA, Vandoies, Italy) and water provided *ad libitum*. All test procedures were performed during the dark phase of the cycle.

The experimental group consisted of 24 subjects (eight subjects per group): for the cagemates, 16 rats were male adults, eight rats were male adolescents (respectively born in February 2019 and in March 2019, all weaned at postnatal day 24), and they all weighed around 300–400 g at the beginning of the habituation session. Subjects were at least 3–4 months old at the beginning and no more than 4–5 months old at the end of the procedure.

Subjects were housed in pairs in Makrolon cages. The first group consisted of eight WT rats grown up with truncated-DAT rats (DAT^{trunk} adult companion); the second group consisted of eight WT rats grown up with WT rats (WT adult companion); the third group consisted of eight WT adolescent rats grown up with WT adolescent rats (WT peer companion).

Apparatus and Procedure

Our experiment aimed to observe the behavior differences of WT rats grown in different conditions and faced with a suspended-bridge task.

The apparatus consisted of two plastic boxes (34 × 24 × 25 cm each) with black floor and sidewalls, one of which was the starting point (A) and the other one, containing pieces of food pellet, was the endpoint (B), connected by a steel bridge that had a 5-cm width.

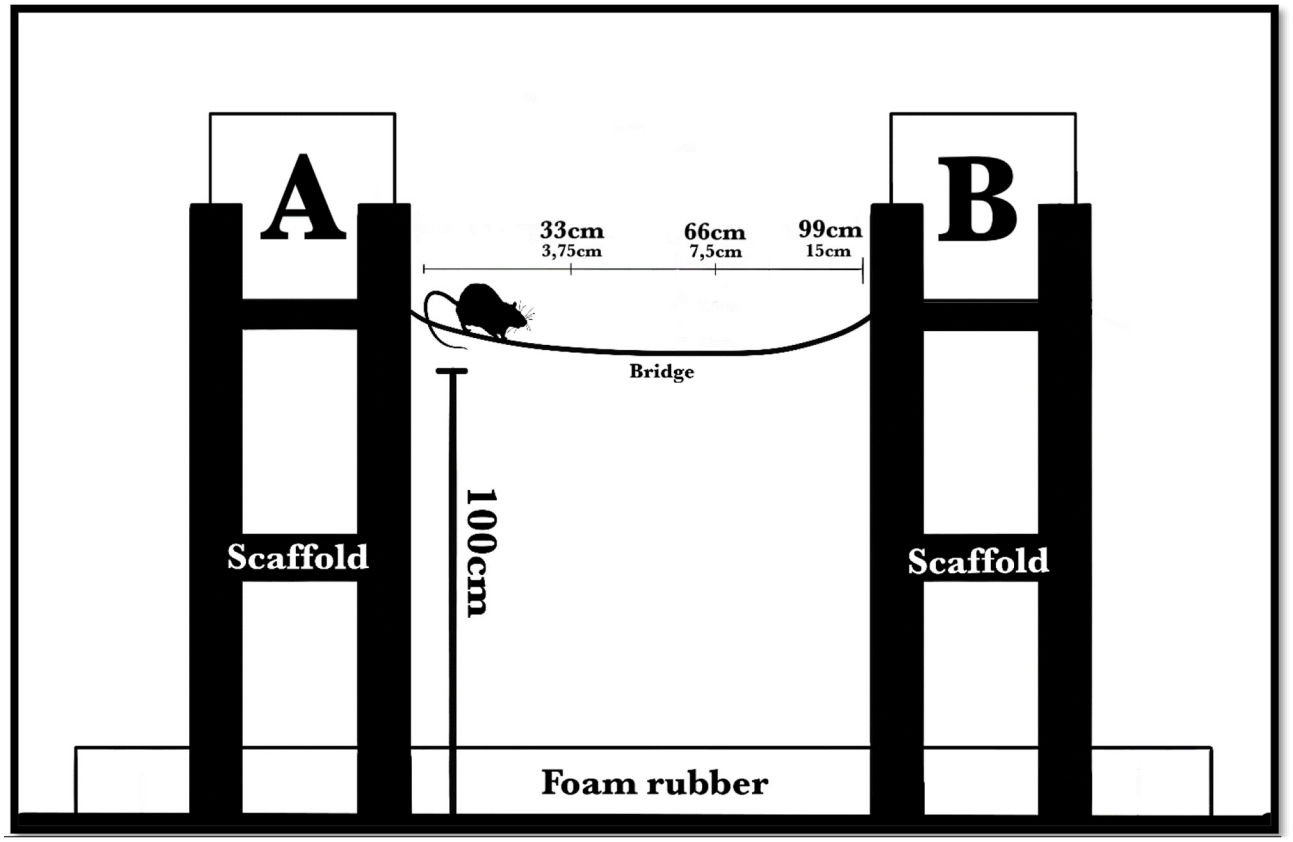


FIGURE 1 | The apparatus consisted of two plastic boxes (34 × 24 × 25 cm each leaning on the long side), one of which was at the starting point **(A)** and the other at the end point (**B**, containing pieces of food pellet), connected by a steel wire-mesh bridge that had a 5-cm width. Each box was placed on a wooden scaffold 1 m above the ground, and the room floor was covered with foam rubber to avoid damage to subjects in the event of a fall. The distance between the boxes depended on the length of the bridge used in specific phases of the procedure: first, 33 cm long, with a 3.75-cm difference in level (midway bending); second, 66 cm long, with a 7.5-cm difference in level; third, 99 cm long, with a 15-cm difference in level. Lastly, the 99-cm bridge was made unstable by means of short chains suspending it to the end scaffold; eventually, we added a "gap" between the bridge and the end scaffold, requiring a little jump as the last step.

Each box was placed on a wooden scaffold 1 m above the ground, and the room floor was covered with foam rubber to avoid damage to subjects in the event of a fall. None of the subjects ever fell. The distance between the boxes depended on the length of the bridge used in specific phases of the procedure (**Figure 1**).

To build the bridges, we used a wire-mesh metallic grid, cutting some of the internal links, so the wire-mesh became composed of rectangles (5 × 3.5 cm each). We used three stable bridges with different lengths: first, 33 cm long, with a 3.75-cm difference in level due to bending; second, 66 cm long, with a 7.5-cm difference in level; third, 99 cm long, with a 15-cm difference in level. Lastly, we made the 99-cm bridge unstable by means of short suspending chains, so that it oscillated under the animal's weight; eventually, we added a "gap" between the bridge and the endpoint to investigate the subjects' last "step" behavior in that particular situation. Each subject performed the task at least once on each bridge.

The procedure was conducted 3 days per week, for 4 weeks, on Tuesday, Wednesday, and Thursday. Each rat performed one trial per day. Animals were food-deprived at homecage on Monday morning and food was available *ad libitum* on Thursday evening. From Monday until Thursday, rats could eat only by reaching end box, to increase motivation for food. Initially, subjects underwent 2 days of habituation: they had a 25-cm steel plate to cross from "A" to "B." During the 1st week, subjects performed on the 33-cm bridge; during the 2nd week, subjects performed on the 66-cm bridge; during the 3rd week, subjects performed on the 99-cm stable bridge; during the 4th week, subjects performed on the 99-cm unstable bridge. In the latter case, during the 2nd day of exposure, we added a space between the bridge and the arrival point to increase the subjects' perception of danger. Moreover, in this way, the bridge swung more during the last "step." See **Figure 2** for the timeline.

For each trial, subjects were placed in box "A" and remained in the apparatus for a total of 5 min. During the trials, observations considered the complete crossings of the bridge (crossings), the slips during the crossing (pawslips), when the subject returned to the starting point without completing the initiated crossing (turnabout), the time elapsed between the introduction of the subject into the apparatus and the first crossing (latency).

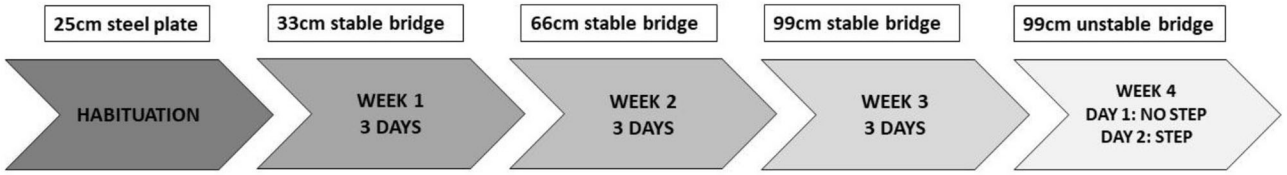


FIGURE 2 | The procedure was conducted 3 days per week for 4 weeks on Tuesday, Wednesday, and Thursday. Animals were food-deprived at homecage on Monday morning, and food was available *ad libitum* on Thursday evening. Initially, subjects underwent 2 days of habituation. They had a 25-cm steel plate to cross from "A" to "B." During the 1st week, subjects performed on the 33-cm bridge. During the 2nd week, subjects performed on the 66-cm bridge. During the 3rd week, subjects performed on the 99-cm stable bridge. During the 4th week, subjects performed on the 99-cm unstable bridge. In the latter case, during the 2nd day of exposure, we added a space between the bridge and the arrival point to increase the subjects' perception of danger. Moreover, in this way, the bridge swung more during the last "step".

The behaviors were scored by a blind observer. The observer scored every behavior (see **Tables 1–3** for the complete data), such as the number of crossings, pawslips, and turnabout, also tracking their times with a stopwatch (i.e., latencies for the crossings).

Statistical Analysis

We ran three different analyses to investigate three different conditions.

First, we investigated the subjects' performances (crossings, pawslips, turnabouts, and latencies) in the three different "distance" conditions (33-, 66-, 99-cm stable bridges) using a repeated-measure ANOVA with a $3 \times 3 \times 2$ design: "companion" (three levels: DAT^{trunk} companion, WT adult companion, WT peer companion) was a between-subjects factor; all the factors were within-subjects: "bridge" (three levels: 33 vs. 66 vs. 99 cm), "day" (two levels: day 1 vs. day 2).

Then, we investigated the subjects' performances (crossings, pawslips, turnabouts, and latencies) in the two different "stability" conditions (during the 1st day on the 99-cm stable bridge and during the 1st day on the 99-cm unstable bridge) using a repeated-measure ANOVA with a 3×2 design: "companion" (three levels: DAT^{trunk} companion, WT adult companion, WT peer companion) was a between-subjects factor; the within-subjects factor was "stability" (two levels: stable vs. unstable).

Eventually, we investigated the subjects' performances (crossings, pawslips, turnabouts, and latencies) in the "step" condition (during the 1st day vs. during the 2nd day on the 99-cm unstable bridge) using a repeated-measure ANOVA with a 3×2 design: "companion" (three levels: DAT^{trunk} companion, WT adult companion, WT peer companion) was a between-subjects factor; the within-subjects factor was "step" (two levels: no-step vs. step).

A p-value < 0.05 was considered significant. The range between $0.05 < p < 0.10$ was considered a significant trend. Tukey honestly significant difference (HSD) *post-hoc* test was then performed.

TABLE 1 | Mean (±SEM) number of the performances on the different bridges in Group 1 (WT rats grown up with DAT^{trunk} rats).

Bridge	Crossings	Pawslips	Turnabouts	Latencies (s)
33 cm, stable	4.12 ± 5.51	0.13 ± 0.35	0.38 ± 0.74	106.20 ± 47.12
66 cm, stable	3.25 ± 3.15	0.00 ± 0.00	0.13 ± 0.35	36.50 ± 29.78
99 cm, stable	2.37 ± 2.20	0.00 ± 0.00	0.00 ± 0.00	58.25 ± 44.16
99 cm, unstable	0.78 ± 0.77	0.13 ± 0.35	1.25 ± 1.28	10.00 ± 8.48
99 cm, unstable w/ gap	0.38 ± 0.74	0.50 ± 0.75	1.25 ± 1.28	11.00 ± 8.48

TABLE 2 | Mean (±SEM) number of the performances on the different bridges in Group 2 (WT rats grown up with WT rats).

Bridge	Crossings	Pawslips	Turnabouts	Latencies (s)
33 cm, stable	4.50 ± 3.07	0.38 ± 0.35	0.38 ± 0.74	97.78 ± 44.89
66 cm, stable	3.50 ± 3.33	0.00 ± 0.00	0.62 ± 0.91	40.08 ± 28.02
99 cm, stable	3.13 ± 2.29	0.13 ± 0.35	0.13 ± 0.35	74.33 ± 36.89
99 cm, unstable	1.25 ± 0.88	0.38 ± 0.51	0.88 ± 0.64	39.00 ± 23.70
99 cm, unstable w/ gap	0.75 ± 0.88	0.38 ± 0.51	1.50 ± 1.92	144.75 ± 80.78

TABLE 3 | Mean (±SEM) number of the performances on the different bridges in Group 3 (WT adolescent rats grown up with WT adolescent rats).

Bridge	Crossings	Pawslips	Turnabouts	Latencies (s)
33 cm, stable	4.50 ± 3.16	0.13 ± 0.35	0.50 ± 0.75	113.42 ± 56.27
66 cm, stable	4.38 ± 3.24	0.00 ± 0.00	0.63 ± 0.51	31.35 ± 18.12
99 cm, stable	4.13 ± 3.60	0.13 ± 0.35	0.13 ± 0.35	63.85 ± 56.30
99 cm, unstable	1.62 ± 1.30	0.00 ± 0.00	0.63 ± 0.74	32.00 ± 55.03
99 cm, unstable w/ gap	1.38 ± 0.91	0.75 ± 0.88	1.38 ± 0.91	53.67 ± 39.64

Ethical Note

All experimental procedures have been approved by the ISS animal welfare survey board on behalf of the Italian Ministry of Health (formal license 937/2018-PR and 1008/2020-PR for project D9997.110, delivered to W. Adriani). Procedures were carried out in close agreement with the directive of the European Community Council (2010/63/EEC) and with Italian law guidelines. All efforts have been made to minimize the suffering of the animals and to use as few animals as possible, according to the 3Rs principle.

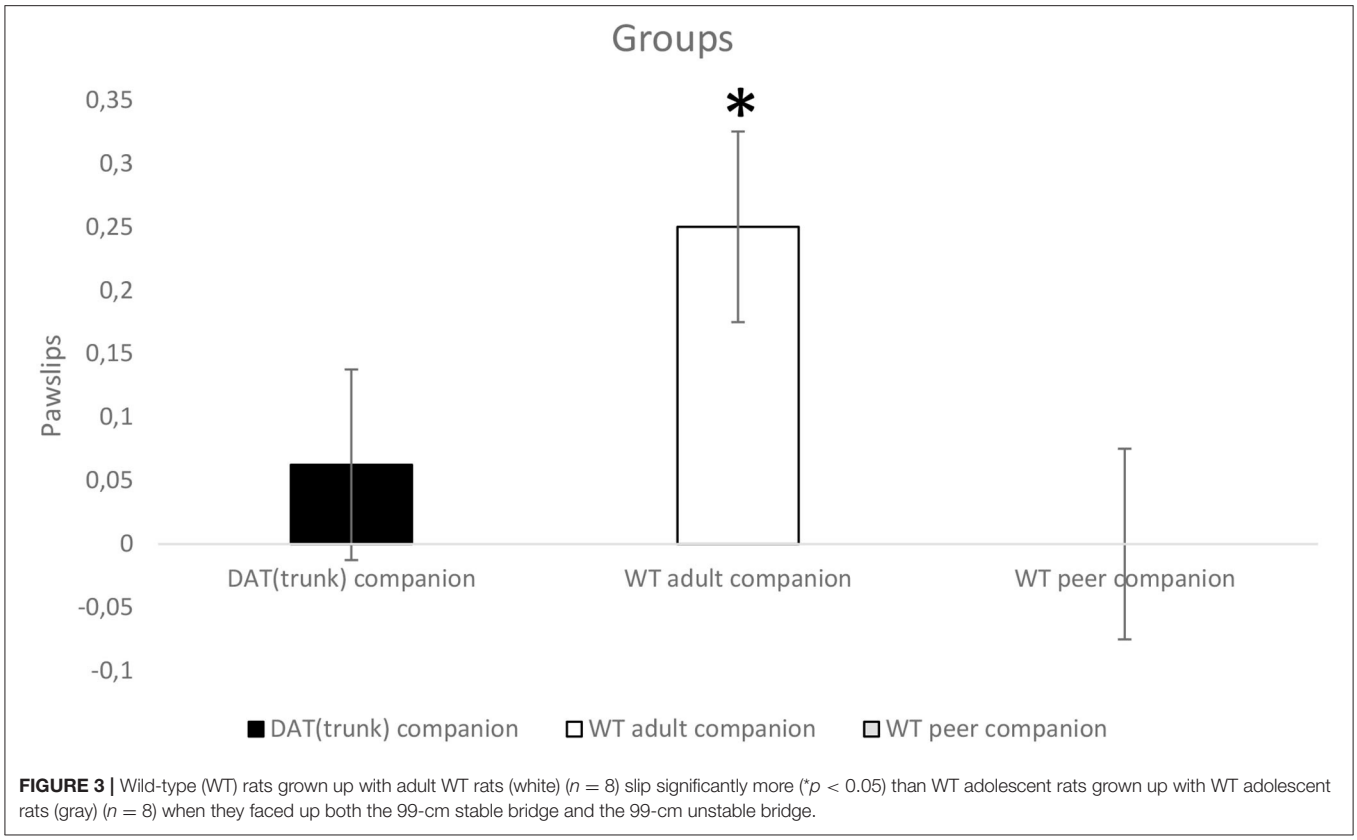


FIGURE 3 | Wild-type (WT) rats grown up with adult WT rats (white) ($n = 8$) slip significantly more (*$p < 0.05$) than WT adolescent rats grown up with WT adolescent rats (gray) ($n = 8$) when they faced up both the 99-cm stable bridge and the 99-cm unstable bridge.

RESULTS

Stable Bridges Differing for Distance

For "crossings" and "pawslips," the ANOVA does not show any significant effects. For "turnabout," a significant trend was presented ($p < 0.08$; $F_{2,42} = 2.777$) for "bridge" due to increasing lengths. Pairwise comparisons show that subjects returned to the starting point significantly more ($p < 0.05$) when they faced the 66-cm bridge than the 99-cm one. The ANOVA shows a significant effect for the "day" ($p < 0.001$; $F_{1,21} = 21.295$). Subjects returned to the starting point significantly more during each 1st day of the task weeks than during the second one. The ANOVA shows a significant interaction for "bridge * day" ($p < 0.05$; $F_{2,42} = 3.500$). The ANOVA does not show any between-subjects significant effect.

For "latency," the ANOVA shows a significant effect ($p < 0.001$; $F_{2,30} = 13.689$) for "bridge" due to increasing lengths. Pairwise comparisons show that subjects cross the 66-cm bridge significantly earlier ($p < 0.001$) than the 33-cm one. Moreover, pairwise comparisons show significant trends for the 99-cm bridge. Indeed, subjects cross the 99-cm bridge earlier than the 33-cm one ($p < 0.09$) but *later* than the 66-cm bridge ($p < 0.09$). The ANOVA shows a significant effect for the "day" ($p < 0.001$; $F_{1,15} = 41{,}934$). During each 2nd day, subjects cross the bridges significantly earlier than during each 1st day. Finally, the ANOVA shows an interaction significant effect for "bridge * day" ($p < 0.05$; $F_{2,30} = 4.859$). The ANOVA does not show any between-subjects significant effect.

Longest Bridges Differing for Stability

For "crossings," the ANOVA shows a significant "stability" effect ($p < 0.05$; $F_{1,21} = 5.402$). Subjects cross significantly more the stable bridge than the unstable one. The ANOVA does not show any between-subjects significant effect.

For "pawslips," the ANOVA does not show a within-subjects significant effect, but it shows a between-subjects significant effect ($p < 0.05$; $F_{2,21} = 3.957$). Tukey HSD *post-hoc* test shows that WT with adult companion rats slip significantly more ($p < 0.05$) than WT peer companion rats which nearly never slip at all (**Figure 3**).

For "turnabout," the ANOVA shows a significant "stability" effect ($p < 0.001$; $F_{2,21} = 18.485$). Subjects returned to the starting point significantly more when they faced the unstable bridge than the stable one. The ANOVA does not show any between-subjects significant effect.

For "latency," the ANOVA shows a significant "stability" effect ($p < 0.05$; $F_{1,14} = 6.920$). Indeed, subjects cross the unstable bridge significantly *earlier* than the stable one. The ANOVA does not show any between-subjects significant effect.

Unstable Bridges Differing for the Last Step

For "crossings," a significant trend was presented for "step" ($p < 0.07$; $F_{1,21} = 3.733$). Subjects cross the bridge without the gap more than the bridge with the gap (with need of a last step). Moreover, a significant trend was presented for a between-subjects effect (companion, $p < 0.06$; $F_{2,21} = 3.111$). Tukey HSD

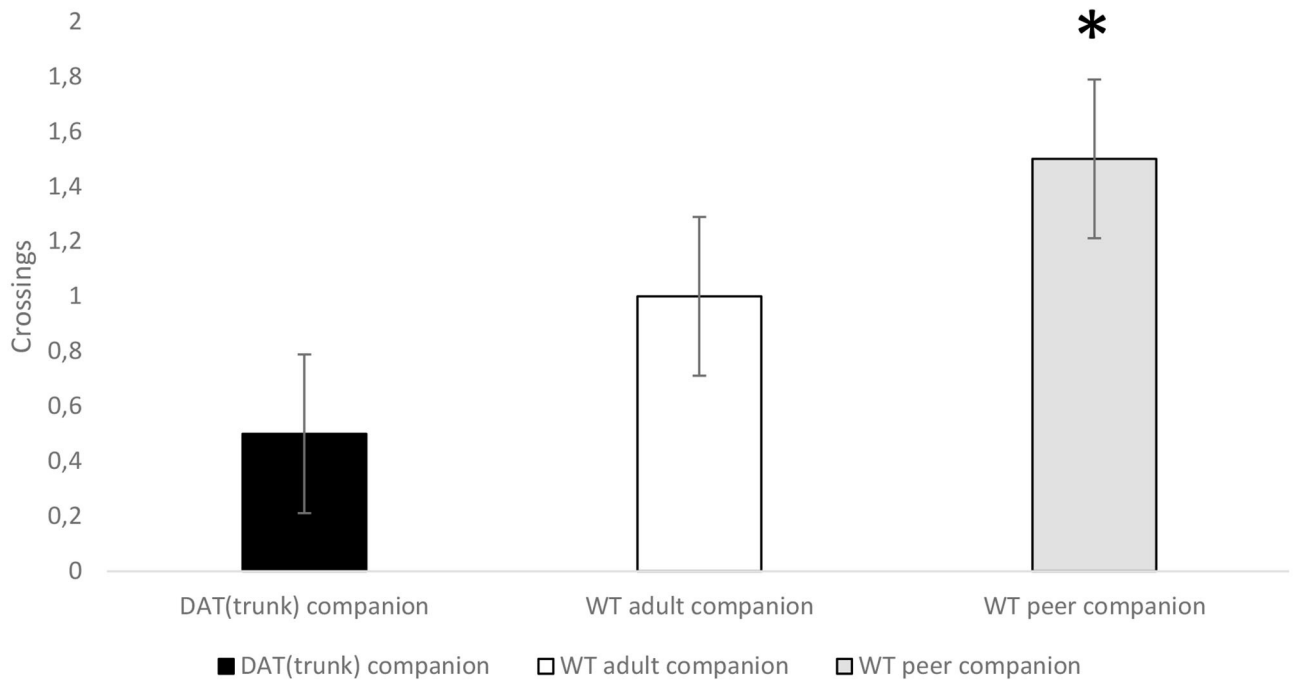


FIGURE 4 | Wild-type (WT) adolescent rats grown up with WT adolescent rats (gray) ($n = 8$) cross more (*$p < 0.06$) than WT rats grown up with DAT^{trunk} rats (black) ($n = 8$) when they faced up both the 99-cm unstable bridge without the "step" and the 99-cm unstable bridge with the "step".

post-hoc test shows that control WT peer companion rats cross more than WT with DAT^{trunk} companion rats do (**Figure 4**). More than half of the latter rats did not cross at all, yielding overall to an average below one.

For "pawslips," a significant trend was presented for "step" ($p < 0.06$; $F_{1,21} = 4.079$). Subjects slip more when they face the bridge with the step than the bridge without it. The ANOVA does not show any between-subjects significant effect.

For "turnabout," a significant trend was presented ($p < 0.09$; $F_{1,21} = 3.172$). Subjects returned to the starting point more often when they faced the bridge with the step than the bridge without it. The ANOVA does not show any between-subjects significant effect.

For "latency," the ANOVA shows a significant effect for "step" ($p < 0.05$; $F_{1,9} = 9.406$). Subjects cross the bridge without the gap significantly earlier than the bridge with the gap (with need of a last step). Moreover, the ANOVA shows a significant interaction for "step * companion" ($p < 0.05$; $F_{1,9} = 5.720$). Indeed, all groups crossed the bridge without the "step" with a lower latency.

DISCUSSION

In this study, we used an adapted protocol of a task previously developed in mice (Bortolato et al., 2009) to capture venturesomeness-related behaviors. Bridges of various kinds allowed rats to reach a food reward by making a choice: either take risks of falling in order to reach the food or waive the food and stay safe. Specifically, we explored the phenotypic differences of WT rats spending adolescence in different circumstances to understand if the companion of a diverse nature could influence the rats' risk-taking behavior.

We can affirm that all the subjects have shown rapid habituation to the apparatus, since they crossed both the 66 and the 99-cm bridges with shorter latency compared to the 33-cm one. Furthermore, due to such rapid habituation, subjects crossed the different bridges with lower latency on the 2nd day of exposure than on the first. Finally, they noticed the different bridges' length since they crossed the 99-cm bridge with a higher latency than the 66-cm one. Although they have become accustomed to the precarious situation, they hesitated to immediately cross the 99-cm bridge.

As for "stability" of the longer bridge, subjects crossed the stable bridge more times than the unstable one perhaps due to the oscillation of the latter. On this occasion, WT with adult companion rats slipped more often than WT peer companion and WT with DAT^{trunk} companion rats. A probable interpretation of this finding is that the latter was more scared and crossed more quickly, or did not cross at all; while the former took their time and crossed more calmly, suggesting some problems with motor coordination. In general, subjects crossed the unstable bridge with lower latency than the stable one, denoting again a quick habituation. However, they went back more often while crossing the unstable bridge probably because, at first, they did not expect it to swing. The fact that the

unstable bridge was crossed with lower latency seems strange, but a possible explanation is that, as soon as they perceived it to swing and felt in danger, rats hurried up to complete the crossing, thus yielding overall to a lower latency.

Finally, all subjects crossed the bridge without the "gap" more often than the bridge with the gap and need of a last "step" probably because of the increased swing of the latter. Besides, subjects crossed the bridge without the "gap" in less time. When they were preparing to make the first step by placing the two forepaws on the bridge, they probably perceived the increased oscillation compared to the day just before, and this delayed their stepping and/or caused a turnabout. This gap-induced increased oscillation also explains the greater number of pawslips observed. Turnabouts are also particularly numerous on the bridge with the "step."

WT with DAT^{trunk} companion rats immediately showed a restless environmental exploration. Compared to the other groups, the WT with DAT^{trunk} companion rats made fewer crossings on average, regardless of the length of the bridge. Moreover, even if they crossed the bridge, after eating some food pellets, they rarely went back through the bridge to the starting point, but they spent more time exploring the endpoint box. Avoiding the bridge, they displayed a risk-averse and more anxious behavior compared to both WT adult companion rats and control WT peer companion rats. A "restless exploration" is a typical feature of KO rats (Adinolfi et al., 2019); therefore, we can say that the observing of truncated-DAT rats by growing WT rats influenced the WT rats' developing phenotype. Besides, control WT peer companion rats crossed more than other groups on average. Particularly when they faced the unstable bridge, WT peer companion rats crossed significantly more than WT with DAT^{trunk} companion rats did, confirming the link between normal adolescence and enhanced risk-taking behavior (Gore-Langton et al., 2020).

Given the results, we can state that different types of companions influenced the development of WT rats' risk-taking behavior. WT peer companion rats showed a risk-taking behavior proclivity, while the WT with DAT^{trunk} companion rats seemed to feel unsafe, showing a continuous environmental exploration. Furthermore, it is interesting to highlight that WT peer companion rats continually crossed back and forth from the start point to endpoint and *vice versa* over and over, although the food reward was only in the endpoint, while the WT with DAT^{trunk} companion rats often did not cross at all, and rarely crossed back again to return to the start point—they preferred to stay at the end point to eat and greatly explore.

In our opinion, these apparatus and procedure could be useful to investigate risk-taking behavior. Indeed, to cross the bridge, each subject has to take the risk of falling because of a sudden bending of the bridge and cope with the feeling in danger for this unavoidable situation. In this context, such procedure can be combined with other tests to create a statistically valid battery of tests to study animal behavior, perception, and cognitive functions. As for limitations, the apparatus can be cumbersome, and the procedure can be dangerous to the animals. The experimenters should be careful in the choice of appropriate floor covering to avoid harm for the subject in case of fall.

In conclusion, we used this paradigm to investigate the risky behavior of rats and the influence that diverse companions at adolescence could have on it. We believe that the use of our "Himalayan Bridge" could be extended to model other behavioral anomalies like those observed in some human psychiatric disorders and cognitive dysfunctions.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

All experimental procedures have been approved by the ISS animal welfare survey board, on behalf of the Italian Ministry of Health (formal license 937/2018-PR and 1008/2020-PR for project D9997.110, delivered to WA). Procedures were carried out in close agreement with the directive of the European Community Council (2010/63/EEC) and with the Italian law guidelines. All efforts have been made to minimize the suffering of animals and to use as few animals as possible, according to the 3Rs principle.

AUTHOR CONTRIBUTIONS

MB designed the study. FF, CB, and AP carried out the behavioral experiment and then analyzed all behavioral data. FF and CB wrote the first draft of the paper together. WA, GL, MO, and GC commented critically. All authors together contributed to its final version.

ACKNOWLEDGMENTS

We are grateful to the master's student Martina Pepe for her precious help. We thank Raul Gainetdinov and Damiana Leo who developed and kindly provided the progenitors of the DAT rat colony, Stella Falsini for all management issues, and Antonio Di Virgilio for animal care and welfare.

REFERENCES

Adinolfi, A., Zelli, S., Leo, D., Carbone, C., Mus, L., Illiano, P., et al. (2019). Behavioral characterization of DAT-KO rats and evidence of asocial-like phenotypes in DAT-HET rats: The potential involvement of norepinephrine system. *Behav. Brain Res.* 359, 516–527. doi: 10.1016/j.bbr.2018.11.028

Bardgett, M. E., Depenbrock, M., Downs, N., Points, M., and Green, L. (2009). Dopamine modulates effort-based decision making in rats. *Behav. Neurosci.* 123, 242–251. doi: 10.1037/a0014625

Bechara, A., Dolan, S., Denburg, N., Hindes, A., Anderson, S. W., and Nathan, P. E. (2001). Decision-making deficits, linked to dysfunctional ventromedial prefrontal cortex, revealed in alcohol and stimulant abusers. *Neuropsychologia* 39, 376–389. doi: 10.1016/S0028-3932(00)00136-6

Biedermann, S. V., Biedermann, D. G., Wenzlaff, F., Kurjak, T., Nouri, S., Auer, M. K., et al. (2017). An elevated plus-maze in mixed reality for studying human anxiety-related behavior. *BMC Biol*. 15:125. doi: 10.1186/s12915-017-0463-6

Bortolato, M., Godar, S. C., Davarian, S., Chen, K., and Shih, J. C. (2009). Behavioral disinhibition and reduced anxiety-like behaviors in monoamine oxidase B-deficient mice. *Neuropsychopharmacology* 34, 2746–2757. doi: 10.1038/npp.2009.118

Cinque, S., Zoratto, F., Poleggi, A., Leo, D., Cerniglia, L., Cimino, S., et al. (2018). Behavioral phenotyping of dopamine transporter knockout rats: compulsive traits, motor stereotypies, and anhedonia. *Front. Psychiatry* 22:43. doi: 10.3389/fpsyt.2018.00043

Craske, M. G., Rauch, S. L., Ursano, R., Prenoveau, J., Pine, D. S., and Zinbarg, R. E. (2009). What is an anxiety disorder? *Depress. Anxiety* 26, 1066–1085. doi: 10.1002/da.20633

Doremus-Fitzwater, T. L., Varlinskaya, E. I., and Spear, L. P. (2009). Effects of pretest manipulation on elevated plus-maze behavior in adolescent and adult male and female Sprague-Dawley rats. *Pharmacol. Biochem. Behav*. 92, 413–423. doi: 10.1016/j.pbb.2009.01.006

Doremus-Fitzwater, T. L., Varlinskaya, E. I., and Spear, L. P. (2010). Motivational systems in adolescence: possible implications for age differences in substance abuse and other risk-taking behaviors. *Brain Cogn*. 72, 114–123. doi: 10.1016/j.bandc.2009.08.008

Ernst, M., Kimes, A. S., London, E. D., Matochik, J. A., Eldreth, D., Tata, S., et al. (2003). Neural substrates of decision making in adults with attention deficit hyperactivity disorder. *Am. J. Psychiatry* 160, 1061–1070. doi: 10.1176/appi.ajp.160.6.1061

Ernst, M., Pine, D. S., and Hardin, M. (2006). Triadic model of the neurobiology of motivated behavior in adolescence. *Psychol. Med*. 36, 299–312. doi: 10.1017/S0033291705005891

File, S. E., Gonzalez, L. E., and Gallant, R. (1998). Role of the basolateral nucleus of the amygdala in the formation of a phobia. *Neuropsychopharmacology* 19, 397–405. doi: 10.1016/S0893-133X(98)00035-9

Floresco, S. B., and Ghods-Sharifi, S. (2007). Amygdala-prefrontal cortical circuitry regulates effort-based decision making. *Cereb. Cortex* 17, 251–260. doi: 10.1093/cercor/bhj143

Gore-Langton, J. K., Werner, D. F., and Spear, L. P. (2020). The effects of age, sex, and handling on behavioral parameters in the multivariate concentric square field™ test. *Physiol. Behav*. 229:113243. doi: 10.1016/j.physbeh.2020.113243

Klein, D. F. (1980). Anxiety reconceptualized. *Compr. Psychiatry* 21, 411–427. doi: 10.1016/0010-440X(80)90043-7

Kobayakawa, M., Koyama, S., Mimura, M., and Kawamura, M. (2008). Decision making in Parkinson's disease: analysis of behavioral and physiological patterns in the Iowa gambling task. *Movement Disord*. 23, 547–552. doi: 10.1002/mds.21865

Leo, D., Sukhanov, I., Zoratto, F., Illiano, P., Caffino, L., Sanna, F., et al. (2018). Pronounced hyperactivity, cognitive dysfunctions and BDNF dysregulation in dopamine transporter knockout rats. *J. Neurosci*. 38, 1959–1972. doi: 10.1523/JNEUROSCI.1931-17.2018

Lovibond, P. F., Mitchell, C. J., Minard, E., Brady, A., and Menzies, R. G. (2009). Safety behaviours preserve threat beliefs: protection from extinction of human fear conditioning by an avoidance response. *Behav. Res. Ther*. 47, 716–720. doi: 10.1016/j.brat.2009.04.013

Ludewig, K., Paulus, M. P., and Vollenweider, F. X. (2003). Behavioural dysregulation of decision-making in deficit but not nondeficit schizophrenia patients. *Psychiatry Res*. 119, 293–306. doi: 10.1016/S0165-1781(03)00103-3

Muigg, P., Hetzenauer, A., Hauer, G., Hauschild, M., Gaburro, S., Frank, E., et al. (2008). Impaired extinction of learned fear in rats selectively bred for high anxiety–evidence of altered neuronal processing in prefrontal-amygdala pathways. *Eur. J. Neurosci*. 28, 2299–2309. doi: 10.1111/j.1460-9568.2008.06511.x

Orrù, M., Strathman, H. J., Floris, G., Scheggi, S., Levant, B., and Bortolato, M. (2020). The adverse effects of pramipexole on probability discounting are not reversed by acute D_2 or D_3 receptor antagonism. *Eur. Neuropsychopharmacol*. 32, 104–119. doi: 10.1016/j.euroneuro.2020.01.005

Parvopassu, A., Oggiano, M., Festucci, F., Curcio, G., Alleva, E., and Adriani, W. (2021). Altering the development of the dopaminergic system through social play in rats: implications for anxiety, depression, hyperactivity, and compulsivity. *Neurosci. Letters* (submitted).

Salamone, J. D., Cousins, M. S., and Bucher, S. (1994). Anhedonia or anergia? Effects of haloperidol and nucleus accumbens dopamine depletion on instrumental response selection in a T-maze cost/benefit procedure. *Behav. Brain Res*. 65, 221–229. doi: 10.1016/0166-4328(94)90108-2

Salatino-Oliveira, A., Rohde,. L. A., and Hutz, M. H. (2018). The dopamine transporter role in psychiatric phenotypes. *Am. J. Med. Genet. B Neuropsychiatr. Genet*. 177, 211–231. doi: 10.1002/ajmg.b.32578

Spear, L. P. (2010). *The Behavioral Neuroscience of Adolescence*. New York, NY: WW Norton and Company.

Steinberg, L., and Belsky, J. (1996). "An evolutionary perspective on psychopathology in adolescence, " in *Rochester Symposium on Developmental Psychopathology, Vol. 7 "Adolescence: Opportunities and Challenges*", eds D. Cicchetti and S. L.Toth (Rochester, NY: University of Rochester Press), 93–124.

Sturman, D. A., and Moghaddam, B. (2011). The neurobiology of adolescence: changes in brain architecture, functional dynamics, and behavioral tendencies. *Neurosci. Biobehav. Rev*. 35, 1704–1712. doi: 10.1016/j.neubiorev.2011.04.003

Taylor Tavares, J. V., Clark, L., Cannon, D. M., Erickson, K., Drevets, W. C., and Sahakian, B. J. (2007). Distinct profiles of neurocognitive function in unmedicated unipolar depression and bipolar II depression. *Biol. Psychiatry* 62, 917–924. doi: 10.1016/j.biopsych.2007.05.034

Walton, M. E., Bannerman, D. M., and Rushworth, M. F. (2002). The role of rat medial frontal cortex in effort-based decision making. *J. Neurosci*. 22, 10996–11003. doi: 10.1523/JNEUROSCI.22-24-10996.2002

Walton, M. E., Croxson, P. L., Rushworth, M. F., and Bannerman, D. M. (2005). The mesocortical dopamine projection to anterior cingulate cortex plays no role in guiding effort-related decisions. *Behav. Neurosci*. 119, 323–328. doi: 10.1037/0735-7044.119.1.323

Zelli, S., Brancato, A., Mattioli, F., Pepe, M., Alleva, E., Carbone, C., et al. (2020). A new "sudden fright paradigm" to explore the role of (epi)genetic modulations of the DAT gene in fear-induced avoidance behavior. *Genes Brain Behav*. 2020:e12709. doi: 10.1111/gbb.12709

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Behavioral Neuroscience

SYSTEMATIC REVIEW
published: 26 November 2021
doi: 10.3389/fnbeh.2021.786358

Delay Discounting in Established and Proposed Behavioral Addictions: A Systematic Review and Meta-Analysis

*Sarah Weinsztok[1], Sarah Brassard[2], Iris Balodis[2], Laura E. Martin[1,3,4] and Michael Amlung[1,5]**

[1] Cofrin Logan Center for Addiction Research and Treatment, University of Kansas, Lawrence, KS, United States, [2] Peter Boris Centre for Addictions Research, McMaster University, Hamilton, ON, United States, [3] Department of Population Health, University of Kansas Medical Center, Kansas City, KS, United States, [4] Hoglund Biomedical Imaging Center, University of Kansas Medical Center, Kansas City, KS, United States, [5] Department of Applied Behavioral Science, University of Kansas, Lawrence, KS, United States

Steep delay discounting, or a greater preference for smaller-immediate rewards over larger-delayed rewards, is a common phenomenon across a range of substance use and psychiatric disorders. Non-substance behavioral addictions (e.g., gambling disorder, internet gaming disorder, food addiction) are of increasing interest in delay discounting research. Individual studies have reported steeper discounting in people exhibiting various behavioral addictions compared to controls or significant correlations between discounting and behavioral addiction scales; however, not all studies have found significant effects. To synthesize the published research in this area and identify priorities for future research, we conducted a pre-registered systematic review and meta-analysis (following PRISMA guidelines) of delay discounting studies across a range of behavioral addiction categories. The final sample included 78 studies, yielding 87 effect sizes for the meta-analysis. For studies with categorical designs, we found statistically significant, medium-to-large effect sizes for gambling disorder (Cohen's d = 0.82) and IGD (d = 0.89), although the IGD effect size was disproportionately influenced by a single study (adjusted d = *0.53* after removal). Categorical internet/smartphone studies were non-significant (d = 0.16, p = 0.06). Aggregate correlations in dimensional studies were statistically significant, but generally small magnitude for gambling (r = 0.22), internet/smartphone (r = 0.13) and food addiction (r = 0.12). Heterogeneity statistics suggested substantial variability across studies, and publication bias indices indicated moderate impact of unpublished or small sample studies. These findings generally suggest that some behavioral addictions are associated with steeper discounting, with the most robust evidence for gambling disorder. Importantly, this review also highlighted several categories with notably smaller effect sizes or categories with too few studies to be included (e.g., compulsive buying, exercise addiction). Further research on delay discounting in behavioral addictions is warranted, particularly for categories with relatively few studies.

Keywords: delay discounting, behavioral addiction, systematic review, meta-analysis, behavioral economics

OPEN ACCESS

Edited by:
Gregory J. Madden, Utah State University, United States

Reviewed by:
Todd McKerchar, Jacksonville State University, United States
Jeffrey Stein, Fralin Biomedical Research Institute, Virginia Tech Carilion, United States

***Correspondence:**
Michael Amlung
mamlung@ku.edu

Specialty section:
This article was submitted to Motivation and Reward, a section of the journal Frontiers in Behavioral Neuroscience

Received: *30 September 2021*
Accepted: *03 November 2021*
Published: *26 November 2021*

Citation:
Weinsztok S, Brassard S, Balodis I, Martin LE and Amlung M (2021) Delay Discounting in Established and Proposed Behavioral Addictions: A Systematic Review and Meta-Analysis. Front. Behav. Neurosci. 15:786358. doi: 10.3389/fnbeh.2021.786358

INTRODUCTION

Delay discounting refers to the tendency to devalue rewards as a function of the delay to their receipt (Rachlin and Green, 1972; Madden and Bickel, 2010; Odum, 2011). In behavioral economics, delay discounting is an index used to conceptualize the overvaluation of smaller, immediate rewards over larger, delayed rewards (Bickel et al., 2014), Delay discounting is generally assessed by providing an individual with a series of choices between a small amount of a commodity (e.g., money, cigarettes, food) which is available immediately vs. a larger amount of the given commodity only obtainable after a certain delay (e.g., "would you prefer $40 today or $200 in 6 months?"). Researchers systematically vary either the commodity amount or the magnitude of the immediate and delayed rewards (e.g., $40 today or $200 in 6 months, $75 today or $200 in 6 months). Researchers will also vary the length of the delay (e.g., 1 month, 6 months, 1 year). Varying reward amount and delay to the larger reward across trials produces an indifference point, i.e., the amount at which the delayed reward has equivalent subjective value to the immediate reward. Plotting these indifference points across different delays generates a discounting curve with the steepness of this curve reflecting the degree of discounting. Delay discounting has been considered a measure of impulsivity in the past; however, recently researchers have begun to debate whether this is appropriate (see Strickland and Johnson, 2021, for a more thorough analysis of this issue). While resolving this debate is outside the scope of the current review, we will avoid use of the term impulsive to describe steep discounting.

Delay discounting tasks (DDTs) may be administered via a survey with a pre-established number of questions in which the reward values and delay length varies across questions like the monetary choice questionnaire (MCQ; Kirby et al., 1999). They may also be adjusting intertemporal choice tasks administered on a computer or mobile device in which the delay lengths or the reward value automatically adjusts up or down (titrates) based on the participant's response to the previous choice. Still others provide a single choice between a smaller, immediate reward and a larger, delayed reward (i.e., "single-shot" discounting tasks). The magnitude of the immediate and delayed rewards, the length of the delays, the number of choices offered, and the commodity of interest all may differ across tasks; thus, sizeable heterogeneity exists across published delay discounting data sets.

To assess individual and group differences in delay discounting, theoretical [k, log(k), effective delay 50] or atheoretical (area under the curve, impulsive choice ratio) measures may be derived from the data. The k parameter is derived from exponential, hyperbolic, or hyperboloid discounting functions and quantifies the degree of discounting observed. Effective delay 50 (ED50) is the inverse measure of k (Yoon and Higgins, 2008) and reflects the delay at which the subjective value of the delayed reward loses 50% of its value. Traditionally, most delay discounting curves are best fit by hyperbolic or hyperboloid functions that can account for preference reversals, in other words, the phenomenon observed in which an initial preference for the smaller, immediate reward shifts to the larger, delayed reward as the delays to both the immediate and delayed reward are increased (Green et al., 1994; McKerchar et al., 2009; Odum, 2011). Quantifying the area under the curve or the proportion of choices made for the immediate reward (impulsive choice ratio) are alternative, atheoretical methods of assessing discounting (Myerson et al., 2001; Mitchell et al., 2005).

Despite differences in calculating delay discounting and deriving discounting parameters, discounting rates appear to be elevated across a wide range of addictive disorders. Because of the consistency of excessive delay discounting observed across a variety of disorders and unhealthy behaviors, delay discounting has been proposed as a trans-disease or transdiagnostic process (e.g., Bickel et al., 2012; Amlung et al., 2019). Several reviews and meta-analyses have synthesized this body of literature, primarily focusing on substance use disorders (e.g., MacKillop et al., 2011; Amlung et al., 2017) and other psychiatric and neurodevelopmental disorders (e.g., Jackson and MacKillop, 2016; Amlung et al., 2019; Lempert et al., 2019). While there is still ongoing debate as to whether measures of delay discounting can be considered a transdiagnostic process (see Bailey et al., 2021, for a recent critique), reviewing the growing body of literature on delay discounting and non-substance behavioral addictions can contribute to this discussion.

The "Substance-Related and Addictive Disorders" category in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (*DSM-5;* American Psychiatric Association, 2013) DSM-5, introduced "behavioral addictions," with gambling disorder recognized as the first "non-substance-related" disorder (American Psychiatric Association, 2013). In addition to gambling, many different behavior patterns have been proposed as behavioral addictions [for a comprehensive account of criteria, see Rosenberg and Feder, 2014, including, videogaming, smartphone and internet use, food consumption, sex, and compulsive buying (Holden, 2001)]. While initially pleasurable, increasing priority of these behaviors over others can lead to dysregulation, as an individual experiences negative consequences and impaired control. The DSM-5 substance-related disorders work group examined Internet gaming and other non-substance-related behaviors (e.g., shopping) other than gambling. While they found a large literature base for internet gaming, the work group concluded that additional research was still needed, and that research on other behaviors was even more preliminary (Hasin et al., 2013). Other APA working groups for addictions examined sex and eating, finding insufficient peer-reviewed evidence to classify these behaviors as addictive disorders (American Psychiatric Association, 2013). However, the state of the research demonstrated similar phenomenological and neurobiological substrates between gambling and substance use disorders, warranting the inclusion of the new classification (Frascella et al., 2010). Currently, gambling disorder is the only behavioral condition included in this category in the DSM-5, although internet gaming disorder (IGD) is now included in the ICD-11 (World Health Organization, 2018) and listed in Section III of the DSM-5 as a condition requiring additional study.

There is increasing concern that symptom-based models of addictive disorders can lead to a pathologizing of common

behaviors, thereby reducing the relevance and credibility of the diagnosis (Kardefelt-Winther et al., 2017). Some have argued that the lack of a theoretical framework for behavioral addictions, such as those which exist for substance-related addictions, is cause for concern and that research on behavioral addictions should be guided by process-based as opposed to criteria-based approaches (Billieux et al., 2015). However, phenomenological, clinical, and neurobiological similarities do exist between gambling disorder and proposed behavioral addictions. For example, many risky behaviors such as gambling, hypersexuality, compulsive shopping and excessive eating have been linked to Parkinson's disease and are related to dopamine receptor functioning, thereby suggesting a common biological pathway (e.g., Evans et al., 2009). Additionally, the clinical presentation is often that of these conditions co-occurring and individuals often seek help for these behaviors at clinics, despite no specific diagnosis or treatment for them. For these reasons, we believe that an improved understanding of these conditions is warranted.

While excessive use or engagement in a particular activity may not be enough to categorize that behavior as pathological (Billieux et al., 2015), examining these behaviors through a behavioral economic lens may provide more insight into underlying processes that warrant further investigation. A systematic review of both established and proposed behavioral addictions research is an important step toward compiling existing evidence across these behaviors to better understand the phenomena. We make these caveats because most categories of behavioral addiction present in the current review are not listed in the DSM-5; however, whether these disorders should be considered diagnosable behavioral addictions is beyond the scope of the review.

Delay discounting rates in gambling disorder and IGD have been the focus of separate meta-analyses (MacKillop et al., 2011; Amlung et al., 2017; Cheng et al., 2021; Yao et al., 2021); however, no review has synthesized findings across all proposed behavioral addictions. Therefore, the purpose of the current study was to conduct a systematic review and meta-analysis of published studies comparing delay discounting rates between individuals with non-substance behavioral addictions and healthy controls or studies assessing dimensional associations between delay discounting and quantity/frequency or severity of the behavioral addiction presented. Secondary purposes included updating and synthesizing the novel research on gambling disorder conducted since previous meta-analyses and comparing rates of delay discounting across behavioral addictions. A final purpose, based on the results of the review and meta-analysis, is identifying areas that warrant further study.

METHODS

Literature Search and Study Selection

The current systematic review and meta-analysis was pre-registered with PROSPERO (#CRD42021257164) and followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA; Page et al., 2021) standards. Searches of PubMed and PsycInfo databases were conducted to identify studies using an all-text search strategy with keywords listed in **Supplementary Table 1**. Database searches were conducted through June 25, 2021 and were not restricted by year or journal (except for English language). The returned records were uploaded to Covidence[1] (Level 10, Melbourne, Australia), an online software used to help streamline the systematic review process. To be included, studies had to meet the following criteria: (i) published in an English language peer-reviewed journal, (ii) assessed one or more types of behavioral addiction among human participants, (iii) included at least one measure of delay discounting, (iv) included either a comparison of a behavioral addiction group and a control group OR a correlation coefficient measuring the association between delay discounting and the behavioral addiction of interest. Because a formal diagnosis of "behavioral addiction" does not exist for every present category, studies were included if the authors measured engagement with the activity using an empirically validated psychometric scale that differentiated between non-problematic and problematic, excessive, or pathological use or engagement. The full study selection procedure is outlined in **Figure 1**.

The articles were screened for inclusion first by abstract, then by the full text, by two independent raters (SW and MA) with conflicts resolved by consensus rating at each stage. A total of 78 studies met inclusion criteria. The number of unique effect sizes in each behavioral addiction category were as follows: gambling = 53 (28 categorical, 25 dimensional), IGD = 15 (13 categorical, 2 dimensional), internet/smartphone = 16 (6 categorical, 10 dimensional), food addiction = 6 (1 categorical, 5 dimensional), and compulsive and pathological buying = 2 (1 categorical, 1 dimensional). Characteristics of included studies are presented in **Supplementary Table 2**. Three studies

[1] www.covidence.org

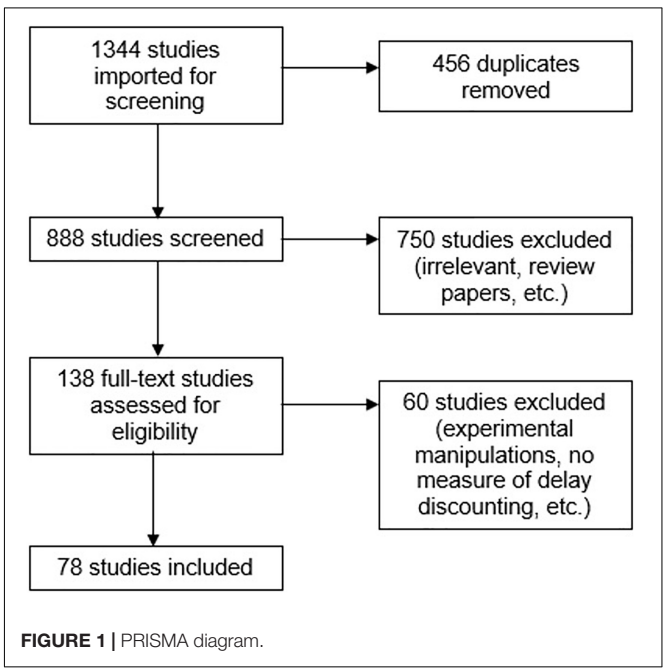


FIGURE 1 | PRISMA diagram.

(Williams, 2012; Wölfling et al., 2020; Acuff et al., 2021) included more than one behavioral addiction category in their assessments; effect sizes from each category were included in the meta-analysis. Kräplin et al. (2020) examined a combined group of non-substance-based addictions but did not differentiate between specific categories of behavioral addictions; thus, it was omitted from the analysis.

Data Extraction

Study characteristics, task parameters, addiction scales, and participant demographics were coded for each study. Means, standard deviations, and group ns were extracted for each categorical study. If means were not reported in text but a figure presenting these values was available, we used WebPlotDigitizer[2] to estimate the mean and standard deviation from the high-resolution figure. Standard error values were converted to standard deviation prior to data entry. For dimensional studies, correlation values and sample sizes were extracted. In cases where data were not available in the published paper or **Supplementary Materials**, we contacted the authors to request data (4/5 contacted authors provided data). When reporting AUC and indifference points, a larger value indicates shallower discounting. The reverse is true for k, log(k), ln(k), or ICR. Therefore, to maintain consistency across studies, the direction of effect sizes from studies using area under the curve (AUC) or indifference points were reversed prior to analysis. Extracted data were checked for accuracy by two authors.

Meta-Analytic Approach

Quantitative meta-analysis was conducted in Comprehensive Meta-Analysis Software Version 3.0 (Biostat, Englewood, NJ). Separate meta-analyses were conducted for each design type (categorical, dimensional) using a random-effects model. First, we estimated the aggregate effect size collapsed across all addiction types to examine the overall effect size for differences in discounting between groups or correlations with behavior addiction variables. Next, we examined each addiction category separately and calculated between-groups heterogeneity statistics to determine if effect sizes significantly differed across addiction type. Only categories with 4 or more effect sizes were included in this subgroup analysis; however, the findings of the remaining studies are described in narrative review. Several indices of effect size heterogeneity were calculated. Cochran's Q reflects the sum of squared differences between individual weighted study effects and the overall mean. I^2 captures the proportion of variation within study effect sizes explained by heterogeneity. Of note, Borenstein et al. (2009) emphasized that Q is less reliable with small sample sizes while I^2 is not affected by sample size. Therefore, given the variability in number of studies per category, both statistics were reported to be comprehensive. A "one-study-removed" analysis quantified the impact of individual studies on the aggregate results (Tukey, 1958). Differences in effect sizes across different delay discounting measures were examined in a moderator analysis. This analysis was first conducted at the aggregate level for categorical and dimensional studies (collapsed across behavioral addiction type), and then repeated within each type individually. For the latter analysis, only categories with at least 4 effect sizes per level of the moderator were examined. Due to low statistical power for the funnel plot indices with small sample sizes, publication bias indices were only examined for categories with 10 or more effect sizes (Sterne et al., 2000). Indices included Orwin's modified fail-safe N using a criterion of 50% reduction in aggregate effect size (Orwin, 1983) and examination of the funnel plots using the two-tailed Begg-Mazumdar test (Begg and Mazumdar, 1994) and the one-tailed Egger's test (Egger et al., 1997). Finally, adjusted estimates of effect size were generated using the Duval and Tweedie (2000) trim and fill approach.

[2]https://apps.automeris.io/wpd/

RESULTS

Complete demographic variables, task parameters, and other relevant characteristics from the included studies are provided in **Supplementary Table 1**. For those studies that did report race or ethnicity, most of the participants identified as White and non-Hispanic. For studies that reported gender, an average of 36.2% of participants reported as female. While most DDTs employed hypothetical outcomes, 9 studies provided real rewards to participants. Aside from Buono et al. (2017), all included studies used money as the only target commodity. The most common delay discounting measures used were *k* (or a log or natural log transformation of *k*) and AUC. Eleven studies utilized less-common measures such as impulsive choice ratio (ICR), total number of choices for the immediate reward, a discounting factor, indifference point, or some other derived proportion of choices of immediate and delayed rewards.

Results of the aggregate and subgroup meta-analyses for categorical and dimensional studies are presented in **Table 1** and effect sizes by study are presented in forest plots (**Figures 2**, **3**). See **Supplementary Table 3** for complete effect size data by individual studies.

Categorical Studies

The aggregate meta-analysis for categorical studies included 47 effect sizes yielding an overall Cohen's *d* of 0.76 ($p < 0.0001$), reflecting a medium-to-large effect size difference in discounting between the behavioral addiction groups and control groups. Results of the one-study-removed analysis revealed that no single study had a disproportionate impact on the aggregate effect size. There was substantial heterogeneity in the aggregate analysis, as indicated by both Cochran's Q and I^2 statistics (**Table 1**). Gambling, IGD, and internet/smartphone categories had sufficient effect sizes for subgroup analyses (findings of food addiction and compulsive buying categories are described in narrative review below). Gambling and IGD yielded comparable aggregate effect sizes (*d*s = 0.82 and 0.89, respectively) that were highly significant (*p*s < 0.0001; see **Figure 2**). However, the one-study-removed analysis revealed that the IGD category was markedly influenced by a single study (Raiha et al., 2020). Removal of this study reduced the aggregate effect size from $d = 0.82$ to 0.59. Both categories had statistically

TABLE 1 | Meta-analytic results.

Category	*k*	*N*	*d* or *r*	*p*	95% CI	OSR	*Q*	P_q	I^2
Categorical designs									
Aggregate effect	47	5,393	0.76	<0.0001	0.58–0.93	0.70–0.78	268.27	<0.0001	82.85
Gambling	28	2,252	0.82	<0.0001	0.60–1.04	0.76–0.88	113.02	<0.0001	76.11
Internet gaming disorder	13	641	0.89	<0.0001	0.53–1.24	0.68–0.94	65.76	<0.0001	81.75
Internet smartphone	6	2,500	0.16	0.141	−0.05–0.37	0.02–0.28	10.54	0.061	52.57
Dimensional designs									
Aggregate effect	40	13,441	0.19	<0.0001	0.15–0.23	0.18–0.20	198.94	<0.0001	80.40
Gambling	25	7,129	0.22	<0.0001	0.16–0.27	0.20–0.23	10.40	<0.0001	75.64
Internet smartphone	10	3,479	0.13	0.0001	0.06–0.20	0.10–0.16	10.40	0.0006	81.92
Food addiction	5	2,833	0.12	0.003	0.04–0.20	0.12–0.19	13.11	0.011	63.48

k, # of effect sizes; N, total number of unique individuals; d, Cohen's d effect size statistic for categorical designs; r, Pearson's correlation coefficient for dimensional designs; p, statistical significance of effect size; OSR, range of effect sizes obtained from one-study-removed jackknife analysis; Heterogeneity statistics from the fixed effects analysis: Q, Cochran's Q-test of homogeneity; P_q, p-value corresponding to Cochran's Q; I^2, proportion of variability due to heterogeneity.

significant heterogeneity (see **Table 1**). In contrast to the findings for gambling and IGD, the aggregate effect size for internet/smartphone studies was small in magnitude and not statistically significant ($d = 0.16$, $p = 0.141$).

Dimensional Designs

Before presenting the results for dimensional designs, an important detail to consider when aggregating correlations across studies is whether the sample was restricted to participants meeting clinical criteria or an established cutoff (e.g., participants diagnosed with gambling disorder or reporting a history of gambling problems) or a non-restricted sample of participants (i.e., a general sample of community volunteers or university students). The latter sample type presumably represents the full range of possible scores on the addiction scales, while the former may be subject to restricted range on the scales. All studies within the internet/smartphone and food addiction categories were non-restricted/general samples; eight of the 25 gambling studies were restricted to participants meeting clinical criteria for pathological gambling, gambling disorder, or reporting problems with gambling (see **Supplementary Table 3**).

The aggregate analysis of studies using dimensional designs included 40 effect sizes. The overall correlation across studies was small magnitude ($r = 0.19$, $p < 0.0001$). The one-study-removed analysis indicated minimal influence of individual studies on the overall effect size (*r* 0.18–0.20). Cochran's Q and I^2 statistics indicated substantial heterogeneity across studies (**Table 1**). Gambling, internet/smartphone, and food addiction had sufficient effect sizes for subgroup analysis (IGD and compulsive buying are summarized below). The effect size for gambling studies ($r = 0.22$) was moderately larger than the other two categories (*r* 0.12–0.13), with the caveat that all effect sizes are considered small magnitude (see **Figure 3**). As with the aggregate analysis, there was significant heterogeneity within each category (**Table 1**).

Delay Discounting Measure Type

A moderator analysis was conducted to examine differences in effect size between types of delay discounting measures. Following a similar procedure as previous meta-analyses (e.g., Amlung et al., 2017), individual effect sizes were coded as either using the MCQ or a multi-item DDT. This latter category was considerably heterogeneous; however, there were insufficient studies with specific types of discounting tasks (e.g., adjusting amount vs. titration vs. experiential) to examine these individually. Therefore, the moderator analysis considered whether the MCQ yielded significantly different effect sizes compared to other "non-MCQ" discounting measures. At the aggregate level collapsing across all behavioral addiction types, there were no significant differences between MCQ and non-MCQ for categorical studies (MCQ $d = 0.64$, $k = 21$; non-MCQ $d = 0.85$, $k = 26$; $Q = 1.43$, $p = 0.233$) or dimensional studies (MCQ $r = 0.19$, $k = 18$; non-MCQ $r = 0.19$, $k = 21$; $Q = 0.05$, $p = 0.819$). Importantly, although the Cohen's *d* for categorical studies was somewhat larger than MCQ studies, the between-study heterogeneity statistic was non-significant. There were also no significant differences between MCQ and non-MCQ measures when behavioral addiction types were examined separately (*p*s = 0.23–0.95). Thus, the moderator analysis provided evidence of similar effect sizes regardless of the type of discounting measure administered.

Publication Bias

Publication bias indices were examined for two categorical design categories (gambling and IGD) and two dimensional design categories (gambling and internet/smartphone). Results are provided in **Table 2**. Owrin's modified fail safe *N*-values for gambling categorical and dimensional studies indicated that 30 and 26 non-significant studies (respectively) would be needed to reduce the aggregate effect size by 50%. A smaller number of studies would be needed for IGD categorical ($k = 13$) and internet/smartphone dimensional ($k = 11$) to yield a similar 50% reduction. Kendall's tau and Egger's intercepts were significant for all but one category (gambling dimensional). The trim and fill approach identified missing effect sizes for the gambling and internet/smartphone categories (see funnel plots in **Supplementary Figure 1**). After imputation, the adjusted effect size was reduced for both categories (gambling: 0.22–0.16 and

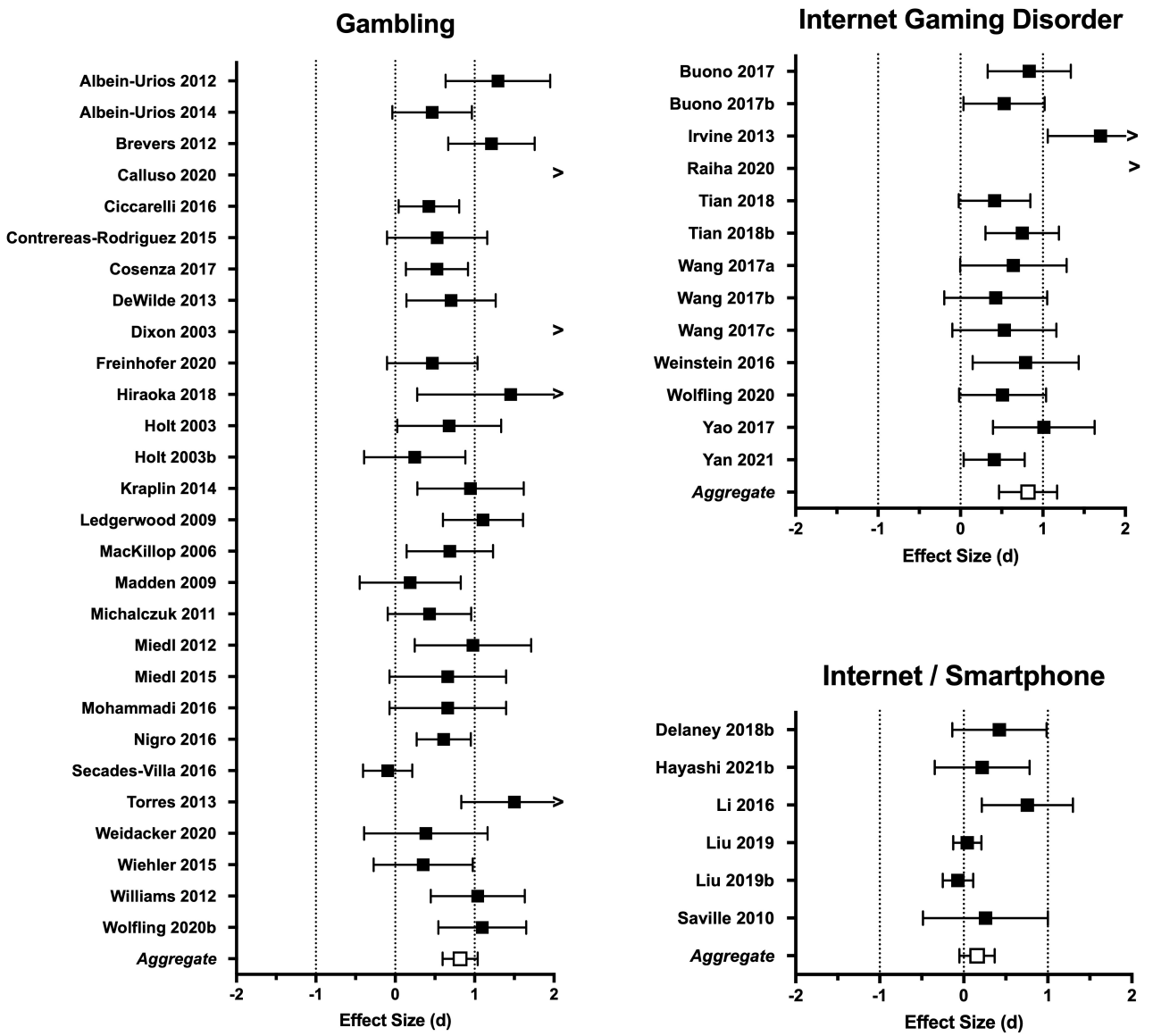


FIGURE 2 | Forest plots depicting effect sizes for categorical studies. Individual data points reflect effect size (Cohen's d) and 95% confidence intervals. The aggregate effect size generated by the random-effects model is provided at the bottom of each forest plot. Complete data is provided in **Supplementary Table 3**.

0.13–0.08 for internet/smartphone). Of note, the lower bound of 95% confidence intervals for the adjusted internet/smartphone category approached 0.0, essentially indicating a non-significant aggregate effect size.

Narrative Review of Studies Not in Meta-Analysis

Compulsive and pathological buying was the focus of only two included studies. Nicolai and Moshagen (2017) compared rates of delay discounting using AUC (for which greater values indicate a larger area, thus, less steep discounting) with severity of pathological buying using the pathological buying scale (PBS). The resulting correlation was −0.15, indicating that greater delay discounting was associated with increased severity on the PBS. Williams (2012) used a two-choice impulsivity program (TCIP) to examine discounting between a group of healthy controls and a group of individuals who met the proposed DSM criteria for impulse control disorder (ICD) for compulsive buying. Taking the sum of impulsive choices across groups, the mean and standard deviation for the compulsive buying group was 20.56 (13.82), and for the healthy controls group was 8.5 (9.33). Thus, individuals in the compulsive buying group selected more immediate choices on the TCIP than individuals in the control group.

In addition to the four dimensional food addiction studies included in the meta-analysis (Davis et al., 2011), employed a categorical design comparing individuals who met the Yale

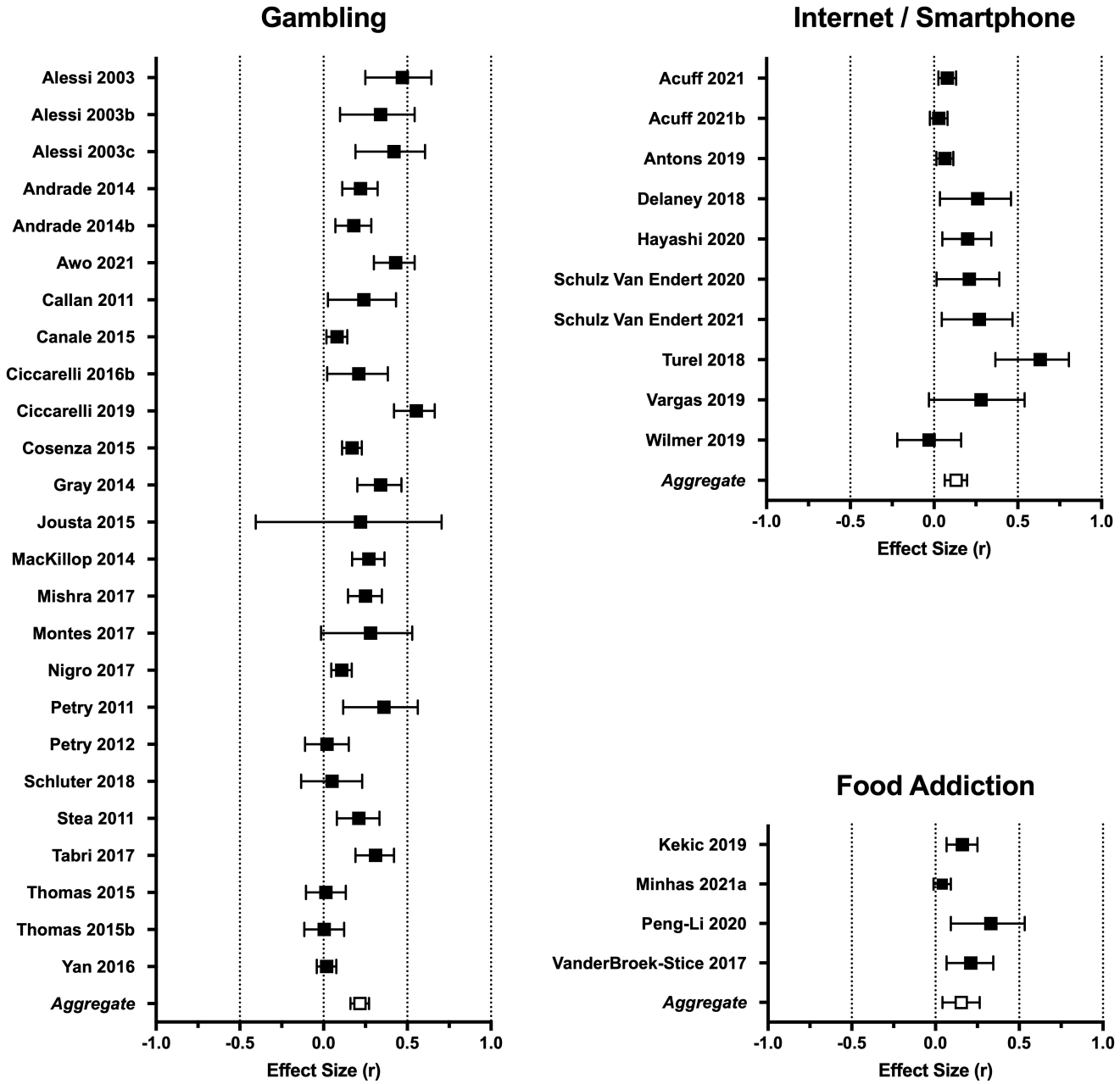


FIGURE 3 | Forest plots depicting effect sizes for dimensional studies. Individual data points reflect effect size (Pearson's r) and 95% confidence intervals. The aggregate effect size generated by the random-effects model is provided at the bottom of each forest plot. Complete data is provided in **Supplementary Table 3**.

Food Addiction Scale (YFAS) diagnostic scoring criteria for food addiction to a group of controls. The mean and standard deviation of indifference points for the food addiction group was 231.7 (138.2) and for the control group was 306.5 (123.2), indicating that individuals in the food addiction group generally had steeper delay discounting rates than controls.

Two studies focusing on IGD employed dimensional designs. Acuff et al. (2021) correlated delay discounting (using ICR) with severity of responses on the Gaming Addiction Scale (GAS). The resulting Pearson *r* correlation was 0.031. Bailey et al. (2013) also correlated ICR with severity responses on a revised version of the Problematic Video Game Play (PVP) Scale, reporting a correlation of 0.12.

DISCUSSION

The results of this meta-analysis show that individuals across a range of behavioral addictions exhibit similar patterns of steeper delay discounting both compared to controls and as a

TABLE 2 | Publication bias indices.

Category	Orwin's *N*	Kendall's tau	Egger's intercept	Trim and fill # studies	Adjusted effect (CI)
Categorical designs					
Gambling	29	0.29*	4.21*	0	–
Internet gaming disorder	13	0.45*	6.28*	0	–
Dimensional designs					
Gambling	26	0.27	2.73*	6	0.16 (0.10–0.22)
Internet smartphone	11	0.49*	2.16*	4	0.08 (0.01–0.15)

*Orwin's N, Orwin's modified fail-safe N assuming a 50% reduction in effect size. *Statistical significance ($p < 0.05$) of Kendall's Tau (two-tailed) and Egger's Intercept (one-tailed). CI, 95% confidence interval; Publication bias indices were not calculated for categories with less than 10 effect sizes (see **Supplementary Table 3**).*

function of the severity of the behavioral addiction. We found statistically significant results for the two aggregate analyses and significant effects for most behavioral addictions categories. However, several categories returned larger effect sizes than others. The effect sizes from the analysis of categorical studies in gambling and IGD categories were medium-to-large magnitude (although IGD was strongly influenced by a single study), while the effect size for internet/smartphone addiction was smaller and not statistically significant. The effect sizes from the analysis of continuous measures returned a somewhat different pattern of results. Although the category-specific effect sizes for gambling, food, and internet/smartphone addiction were statistically significant, the aggregate correlation for gambling was larger than for internet/smartphone or food addiction. One possible explanation for these discrepancies is that the scales used in the internet/smartphone addiction studies require additional validation and perhaps are not identifying certain behavior patterns that more well-validated scales, such as those for gambling and IGD, can ascertain. Due to the current ubiquity of mobile devices, additional scale validation and delay discounting research in this area is warranted.

Gambling disorder has been a category of focus in two prior meta-analyses (MacKillop et al., 2011; Amlung et al., 2017). Synthesizing research on continuous associations, Amlung et al. (2017) calculated a Pearson r effect size statistic of 0.16. In the current meta-analysis, the overall effect size statistic of gambling studies using dimensional designs was slightly larger ($r = 0.22$). MacKillop et al. (2011) calculated effect size statistics for studies with categorical designs. The overall effect size for the clinical group was 0.79, and for the subclinical group was 0.41, whereas the Cohen's d in the current meta-analysis was 0.82. The number of gambling disorder studies using categorical designs increased from 7 total in MacKillop et al., 2011 to 28 studies in the current analysis. A smaller number of dimensional studies were added (4 more than Amlung et al., 2017); however, the change in total sample size was substantial, increasing from 2,940 to 7,129. It is plausible that modest increase in aggregate effect size was due, in part, to greater precision from larger sample sizes. In sum, the addition of updated gambling studies results in somewhat larger effect sizes for both dimensional and categorical designs.

The relationship between delay discounting rate and presence of IGD has been a focus of prior meta-analyses (Cheng et al., 2021; Yao et al., 2021). Cheng et al. (2021) focused only on categorical designs. While the present review was originally designed to examine dimensional designs, there were not enough to be included in the meta-analysis. Cheng et al. (2021) calculated an overall effect size statistic for studies that used k-values to analyze discounting rate (k) of Hedges' $g = 0.76$, and for studies that used AUC of $g = 1.44$. Similarly, Yao et al. (2021) included categorical designs but also focused on a range of decision-making deficits beyond discounting. The effect size statistic (g) for delay discounting was 0.58 while $d = 0.68$ in our analysis after removal of the highly influential result from Raiha et al., 2020. Both results indicate steeper discounting in participants with IGD. Updating past meta-analyses with sufficient new research advances our understanding of the relationship between delay discounting and the present disorders. Indeed, we found that recent research has further strengthened the relationship between gambling disorder and IGD and steep delay discounting.

Food addiction and obesity, while occasionally conflated, are in fact distinctly separate constructs (Gordon et al., 2018). Thus, the results from the food addiction category should not be compared to the results of the meta-analysis on delay discounting among individuals with obesity conducted by Amlung et al. (2016). Indeed, apart from Davis et al. (2011) in which the inclusion criteria for participation was a body mass index (BMI) in the obese range, the average BMI in most studies in the food addiction category was in the normal weight range. While a positive association was found across most studies between food addiction severity and BMI, this was not the focus of the present review and future research examining the relationship between BMI, food addiction, and delay discounting is warranted.

The paucity of compulsive or pathological buying studies, food addiction studies using categorical designs, and IGD studies using dimensional designs prevented us from calculating aggregate effect sizes. While the narrative summary of these studies generally suggests steeper discounting associated with presence of these behavioral addictions, we are unable to evaluate the reliability of these findings or directly compare the results to the other categories included in the meta-analysis. Replications and extensions of the current research in these areas is integral. Additionally, it is worth highlighting that in the search for studies to include in the current systematic review and meta-analysis, several categories proposed as behavioral addictions (e.g., sex, love, work, indoor tanning, kleptomania) returned no results (see **Supplementary Table 1**). These too are areas of importance for future research.

The current review and meta-analysis raises several additional questions for future research. First, because not all categories included in the current review are officially recognized as behavioral addictions, whether some of these categories are over-pathologized should be a topic of continued research and discourse (Billieux et al., 2015). By definition, "impulsivity" inherently pathologizes behavior patterns that may not necessarily be maladaptive. Such a concern can be raised for all behaviors labeled "impulsive." A functional and theoretical approach to describing behavior patterns often characterized as facets of impulsivity—specifically, steep delay discounting—is integral to our understanding of the importance of and limitations to this line of research.

The considerable heterogeneity across studies within each category limits the generality of these findings. While the use of a random-effects model addresses this limitation to some extent, the differences in the discounting tasks and behavioral addiction scales used may have impacted the results. Additionally, while we did not include groups of subjects for whom there was an explicit comorbid substance use or other psychiatric disorder, we did not exclude all studies in which there were possible comorbidities with behavioral addictions. Many behavioral addictions likely include co-morbidity with substance use disorders which may be difficult or impossible to disentangle based on participant descriptions, thus, these comorbidities may have confounded the results in unknown ways.

We could not always identify the specific procedures of the DDTs. However, the results of the moderator analysis indicated similar effect sizes in studies using the MCQ compared to non-MCQ measures. This is consistent with prior meta-analyses reporting no significant differences between MCQ and non-MCQ multi-item tasks (e.g., MacKillop et al., 2011; Amlung et al., 2017). Providing details of delay discounting methods in future studies may help in determining whether more specific types of discounting task used may function as a moderator between discounting rates and the independent variable of interest. Though the exact task procedures in the included studies were not always clear, it is worth discussing the potential implications of the use of monetary rewards as the only target commodity for all included studies except one (Buono et al., 2017). Individuals with substance use disorder tend to discount their substance of choice (e.g., cigarettes, crack/cocaine, cannabis, alcohol) more steeply than monetary rewards (e.g., Bickel et al., 1999; Coffey et al., 2003; Johnson et al., 2010; Moody et al., 2017). Buono et al. (2017) examined discounting of monetary rewards and video game time among high-, medium-, and low-frequency video game players. Results indicated that AUC was lower (i.e., steeper discounting) across all groups when the commodity was video game play compared to money. Although these findings are from a single study, they do underscore the need for additional investigation of commodity effects in behavioral addictions.

To our knowledge, this is the first systematic review and meta-analysis comparing rates of delay discounting across multiple categories of behavioral addictions. In sum, the results revealed that there is generally a relationship between steepness of delay discounting rates and severity of behavioral addiction (except for internet/smartphone addiction); however, the magnitude of these relationships varies across categories. Several categories included in the review are not listed as addictions in the DSM-5 (food addiction, internet/smartphone addiction, compulsive/pathological buying) and thus warrant caution when interpreting results. Additionally, some scales used to assess the presence and severity of a given behavioral addiction are not as well-validated as others, which may have contributed to the smaller effect sizes in the internet/smartphone category. Importantly, the present review highlights the need for additional research to deepen our understanding of the relationship between discounting and behavioral addiction.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

MA, SB, and IB: study conception. SW and MA: study selection, data analysis, and manuscript development. SW: data extraction. IB, SB, and LM: manuscript edits and feedback. All authors: approval of final manuscript.

FUNDING

This research was supported, in part, by funding from the National Institute on Alcohol Abuse and Alcoholism (R01AA027255, PI: MA), the University of Kansas New Faculty General Research Fund, the Cofrin Logan Center for Addiction Research and Treatment, the University of Kansas College of Liberal Arts and Sciences, and the Peter Boris Centre for Addictions Research.

ACKNOWLEDGMENTS

We thank William Davis and Alyssa Biles for contributions to study coding and data extraction. We are grateful to Damien Brevers, Simon Dymond, Kathrin Weidacker, James MacKillop, and Meenu Minhas for providing additional data from their published papers. We acknowledge that the University of Kansas resides on the ancestral territory of several tribal nations, including the Kaw Osage, and Shawnee peoples. This land acknowledgment recognizes that Indigenous peoples are traditional guardians of the land and that there is an enduring relationship between Native peoples and these traditional territories.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnbeh.2021.786358/full#supplementary-material

REFERENCES

Acuff, S. F., Pilatti, A., Collins, M., Hides, L., Thingujam, N. S., Chai, W. J., et al. (2021). Reinforcer pathology of internet-related behaviors among college students: Data from six countries. *Exp. Clin. Psychopharmacol.* 2021:ha0000459. doi: 10.1037/pha0000459

Albein-Urios, N., Martinez-González, J. M., Lozano, Ó, and Verdejo-Garcia, A. (2014). Monetary delay discounting in gambling and cocaine dependence with personality comorbidities. *Addict. Behav.* 39, 1658–1662. doi: 10.1016/j.addbeh.2014.06.001

Albein-Urios, N., Martinez-González, J. M., Lozano, Ó, Clark, L., and Verdejo-García, A. (2012). Comparison of impulsivity and working memory in cocaine addiction and pathological gambling: Implications for cocaine-induced neurotoxicity. *Drug Alcohol Depend.* 126, 1–6. doi: 10.1016/j.drugalcdep.2012.03.008

Alessi, S., and Petry, N. M. (2003). Pathological gambling severity is associated with impulsivity in a delay discounting procedure. *Behav. Proces.* 64, 345–354. doi: 10.1016/S0376-6357(03)00150-5

American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders: DSM-5*. Arlington, VA: American Psychiatric Association.

Amlung, M., Marsden, E., Holshausen, K., Morris, V., Patel, H., Vedelago, L., et al. (2019). Delay discounting as a transdiagnostic process in psychiatric disorders: a meta-analysis. *JAMA Psychiatry* 76, 1176–1186. doi: 10.1001/jamapsychiatry.2019.2102

Amlung, M., Petker, T., Jackson, J., Balodis, I., and MacKillop, J. (2016). Steep discounting of delayed monetary and food rewards in obesity: a meta-analysis. *Psychol. Med.* 46, 2423–2434. doi: 10.1017/S0033291716000866

Amlung, M., Sweet, L. H., Acker, J., Brown, C. L., and MacKillop, J. (2014). Dissociable brain signatures of choice conflict and immediate reward preferences in alcohol use disorders. *Addict. Biol.* 19, 743–753. doi: 10.1111/adb.12017

Amlung, M., Vedelago, L., Acker, J., Balodis, I., and MacKillop, J. (2017). Steep delay discounting and addictive behavior: A meta-analysis of continuous associations. *Addiction* 112, 51–62. doi: 10.1111/add.13535

Andrade, L. F., and Petry, N. M. (2014). White problem gamblers discount delayed rewards less steeply than their African American and Hispanic counterparts. *Psychol. Addict. Behav.* 28:599. doi: 10.1037/a0036153

Antons, S., Mueller, S. M., Wegmann, E., Trotzke, P., Schulte, M. M., and Brand, M. (2019). Facets of impulsivity and related aspects differentiate among recreational and unregulated use of Internet pornography. *J. Behav. Addict.* 8, 223–233. doi: 10.1556/2006.8.2019.22

Awo, L. O., Amazue, L. O., and Oko, C. A. (2021). Moderating Effect of Impulsivity on the Association Between Entrapment and Problem Gambling. *J. Gambl. Stud.* 2021, 1–13. doi: 10.1007/s10899-021-10047-w

Bailey, A. J., Romeu, R. J., and Finn, P. R. (2021). The problems with delay discounting: a critical review of current practices and clinical applications. *Psychol. Med.* 2021, 1–8. doi: 10.1017/S0033291721002282

Bailey, K., West, R., and Kuffel, J. (2013). What would my avatar do? Gaming, pathology, and risky decision making. *Front. Psychol.* 4:609. doi: 10.3389/fpsyg.2013.00609

Begg, C. B., and Mazumdar, M. (1994). Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994, 1088–1101. doi: 10.2307/2533446

Bickel, W. K., Jarmolowicz, D. P., Mueller, E. T., Koffarnus, M. N., and Gatchalian, K. M. (2012). Excessive discounting of delayed reinforcers as a trans-disease process contributing to addiction and other disease-related vulnerabilities: emerging evidence. *Pharmacol. Therapeut.* 134, 287–297. doi: 10.1016/j.pharmthera.2012.02.004

Bickel, W. K., Johnson, M. W., Koffarnus, M. N., MacKillop, J., and Murphy, J. G. (2014). The behavioral economics of substance use disorders: reinforcement pathologies and their repair. *Annu. Rev. Clin. Psychol.* 10, 641–677. doi: 10.1146/annurev-clinpsy-032813-153724

Bickel, W. K., Odum, A. L., and Madden, G. J. (1999). Impulsivity and cigarette smoking: delay discounting in current, never, and ex-smokers. *Psychopharmacology* 146, 447–454. doi: 10.1007/PL00005490

Billieux, J., Schimmenti, A., Khazaal, Y., Maurage, P., and Heeren, A. (2015). Are we overpathologizing everyday life? A tenable blueprint for behavioral addiction research. *J. Behav. Addict.* 4, 119–123. doi: 10.1556/2006.4.2015.009

Borenstein, M., Hedges, L. V., Higgins, J. P., and Rothstein, H. R. (2009). *Introduction to Meta-Analysis*. Hoboken, NJ: John Wiley & Sons. doi: 10.1002/9780470743386

Brevers, D., Cleeremans, A., Verbruggen, F., Bechara, A., Kornreich, C., Verbanck, P., et al. (2012). Impulsive action but not impulsive choice determines problem gambling severity. *PLoS One* 7:e50647. doi: 10.1371/journal.pone.0050647

Buono, F. D., Sprong, M. E., Lloyd, D. P., Cutter, C. J., Printz, D. M., Sullivan, R. M., et al. (2017). Delay discounting of video game players: comparison of time duration among gamers. *Cyberpsychol. Behav. Soc. Network.* 20, 104–108. doi: 10.1089/cyber.2016.0451

Callan, M. J., Shead, N. W., and Olson, J. M. (2011). Personal relative deprivation, delay discounting, and gambling. *J. Personal. Soc. Psychol.* 101:955. doi: 10.1037/a0024778

Calluso, C., Pettorruso, M., Tosoni, A., Carenti, M. L., Cannito, L., Martinotti, G., et al. (2020). Cognitive dynamics of intertemporal choice in gambling disorder. *Addict. Behav.* 109:106463. doi: 10.1016/j.addbeh.2020.106463

Canale, N., Vieno, A., Griffiths, M. D., Rubaltelli, E., and Santinello, M. (2015). Trait urgency and gambling problems in young people by age: The mediating role of decision-making processes. *Addict. Behav.* 46, 39–44. doi: 10.1016/j.addbeh.2015.02.020

Cheng, Y.-S., Ko, H.-C., Sun, C.-K., and Yeh, P.-Y. (2021). The relationship between delay discounting and Internet addiction: A systematic review and meta-analysis. *Addict. Behav.* 2020:106751. doi: 10.1016/j.addbeh.2020.106751

Ciccarelli, M., Cosenza, M., D'Olimpio, F., Griffiths, M. D., and Nigro, G. (2019). An experimental investigation of the role of delay discounting and craving in gambling chasing behavior. *Addict. Behav.* 93, 250–256. doi: 10.1016/j.addbeh.2019.02.002

Ciccarelli, M., Malinconico, R., Griffiths, M. D., Nigro, G., and Cosenza, M. (2016). Reward preferences of pathological gamblers under conditions of uncertainty: An experimental study. *J. Gambl. Stud.* 32, 1175–1189. doi: 10.1007/s10899-016-9593-y

Coffey, S. F., Gudleski, G. D., Saladin, M. E., and Brady, K. T. (2003). Impulsivity and rapid discounting of delayed hypothetical rewards in cocaine-dependent individuals. *Exp. Clin. Psychopharmacol.* 11:18. doi: 10.1037/1064-1297.11.1.18

Contreras-Rodríguez, O., Albein-Urios, N., Perales, J. C., Martínez-Gonzalez, J. M., Vilar-López, R., Fernández-Serrano, M. J., et al. (2015). Cocaine-specific neuroplasticity in the ventral striatum network is linked to delay discounting and drug relapse. *Addiction* 110, 1953–1962. doi: 10.1111/add.13076

Cosenza, M., and Nigro, G. (2015). Wagering the future: Cognitive distortions, impulsivity, delay discounting, and time perspective in adolescent gambling. *J. Adolesc.* 45, 56–66. doi: 10.1016/j.adolescence.2015.08.015

Cosenza, M., Griffiths, M. D., Nigro, G., and Ciccarelli, M. (2017). Risk-taking, delay discounting, and time perspective in adolescent gamblers: An experimental study. *J. Gambl. Stud.* 33, 383–395. doi: 10.1007/s10899-016-9623-9

Davis, C., Curtis, C., Levitan, R. D., Carter, J. C., Kaplan, A. S., and Kennedy, J. L. (2011). Evidence that 'food addiction'is a valid phenotype of obesity. *Appetite* 57, 711–717. doi: 10.1016/j.appet.2011.08.017

De Wilde, B., Goudriaan, A., Sabbe, B., Hulstijn, W., and Dom, G. (2013). Relapse in pathological gamblers: A pilot study on the predictive value of different impulsivity measures. *J. Behav. Addict.* 2, 23–30. doi: 10.1556/jba.2.2013.1.4

Delaney, D., Stein, L., and Gruber, R. (2018). Facebook addiction and impulsive decision-making. *Addict. Res. Theory* 26, 478–486. doi: 10.1080/16066359.2017.1406482

Dixon, M. R., Marley, J., and Jacobs, E. A. (2003). Delay discounting by pathological gamblers. *J. Appl. Behav. Anal.* 36, 449–458. doi: 10.1901/jaba.2003.36-449

Duval, S., and Tweedie, R. (2000). Trim and fill: a simple funnel-plot–based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 56, 455–463. doi: 10.1111/j.0006-341X.2000.00455.x

Egger, M., Smith, G. D., Schneider, M., and Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. *BMJ* 315, 629–634. doi: 10.1136/bmj.315.7109.629

Evans, A. H., Strafella, A. P., Weintraub, D., and Stacy, M. (2009). Impulsive and compulsive behaviors in Parkinson's disease. *Mov. Disord.* 24, 1561–1570. doi: 10.1002/mds.22505

Frascella, J., Potenza, M. N., Brown, L. L., and Childress, A. R. (2010). Shared brain vulnerabilities open the way for nonsubstance addictions: carving addiction at a new joint? *Ann. N Y. Acad. Sci.* 1187, 294–315. doi: 10.1111/j.1749-6632.2009.05420.x

Freinhofer, D., Schwartenbeck, P., Thon, N., Eigenberger, T., Aichhorn, W., Lenger, M., et al. (2020). Deficient decision making in pathological gamblers correlates with gray matter volume in medial orbitofrontal cortex. *Front. Psychiatry* 11:109. doi: 10.3389/fpsyt.2020.00109

Gordon, E. L., Ariel-Donges, A. H., Bauman, V., and Merlo, L. J. (2018). What is the evidence for "food addiction?" A systematic review. *Nutrients* 10:477. doi: 10.3390/nu10040477

Gray, J. C., and MacKillop, J. (2014). Genetic basis of delay discounting in frequent gamblers: examination of a priori candidates and exploration of a panel of dopamine-related loci. *Brain Behav.* 4, 812–821. doi: 10.1002/brb3.284

Green, L., Fristoe, N., and Myerson, J. (1994). Temporal discounting and preference reversals in choice between delayed outcomes. *Psychonomic Bull. Rev.* 1, 383–389. doi: 10.3758/BF03213979

Hasin, D. S., O'Brien, C. P., Auriacombe, M., Borges, G., Bucholz, K., Budney, A., et al. (2013). DSM-5 criteria for substance use disorders: recommendations and rationale. *Am. J. Psychiatry* 170, 834–851. doi: 10.1176/appi.ajp.2013.12060782

Hayashi, Y. (2020). Attitude moderates the relation between frequency of media multitasking in the classroom and delay discounting. *Psychol. Record* 2020, 1–8. doi: 10.1007/s40732-020-00443-w

Hayashi, Y., and Washio, Y. (2020). Text-message dependency, executive function, and impulsivity in college students: A cluster analysis. *Cyberpsychol. Behav. Soc. Network.* 23, 794–799. doi: 10.1089/cyber.2019.0743

Hiraoka, K. (2018). Gambling and Delay Discounting in Japanese Students. *Japan. Psychol. Res.* 60, 156–161. doi: 10.1111/jpr.12192

Holden, C. (2001). 'Behavioral' Addictions: Do They Exist? *Science* 294, 980–982. doi: 10.1126/science.294.5544.980

Irvine, M. A., Worbe, Y., Bolton, S., Harrison, N. A., Bullmore, E. T., and Voon, V. (2013). Impaired decisional impulsivity in pathological videogamers. *PLoS One* 8:e75914. doi: 10.1371/journal.pone.0075914

Jackson, J. N., and MacKillop, J. (2016). Attention-deficit/hyperactivity disorder and monetary delay discounting: a meta-analysis of case-control studies. *Biol. Psychiatry Cognit. Neurosci. Neuroimaging* 1, 316–325. doi: 10.1016/j.bpsc.2016.01.007

Johnson, M. W., Bickel, W. K., Baker, F., Moore, B. A., Badger, G. J., and Budney, A. J. (2010). Delay discounting in current and former marijuana-dependent individuals. *Exp. Clin. Psychopharmacol.* 18:99. doi: 10.1037/a0018333

Joutsa, J., Voon, V., Johansson, J., Niemelä, S., Bergman, J., and Kaasinen, V. (2015). Dopaminergic function and intertemporal choice. *Translat. Psychiatry* 5, e491–e491. doi: 10.1038/tp.2014.133

Kardefelt-Winther, D., Heeren, A., Schimmenti, A., van Rooij, A., Maurage, P., Carras, M., et al. (2017). How can we conceptualize behavioural addiction without pathologizing common behaviours? *Addiction* 112, 1709–1715. doi: 10.1111/add.13763

Kekic, M., McClelland, J., Bartholdy, S., Chamali, R., Campbell, I. C., and Schmidt, U. (2020). Bad things come to those who do not wait: Temporal discounting is associated with compulsive overeating, eating disorder psychopathology and food addiction. *Front. Psychiatry* 10:978. doi: 10.3389/fpsyt.2019.00978

Kirby, K. N., Petry, N. M., and Bickel, W. K. (1999). Heroin addicts have higher discount rates for delayed rewards than non-drug-using controls. *J. Exp. Psychol. General* 128:78. doi: 10.1037/0096-3445.128.1.78

Kräplin, A., Dshemuchadse, M., Behrendt, S., Scherbaum, S., Goschke, T., and Bühringer, G. (2014). Dysfunctional decision-making in pathological gambling: pattern specificity and the role of impulsivity. *Psychiatry Res.* 215, 675–682. doi: 10.1016/j.psychres.2013.12.041

Kräplin, A., Höfler, M., Pooseh, S., Wolff, M., Krönke, K.-M., Goschke, T., et al. (2020). Impulsive decision-making predicts the course of substance-related and addictive disorders. *Psychopharmacology* 237, 2709–2724. doi: 10.1007/s00213-020-05567-z

Ledgerwood, D. M., Alessi, S. M., Phoenix, N., and Petry, N. M. (2009). Behavioral assessment of impulsivity in pathological gamblers with and without substance use disorder histories versus healthy controls. *Drug Alcohol Depend.* 105, 89–96. doi: 10.1016/j.drugalcdep.2009.06.011

Lempert, K. M., Steinglass, J. E., Pinto, A., Kable, J. W., and Simpson, H. B. (2019). Can delay discounting deliver on the promise of RDoC? *Psychol. Med.* 49, 190–199. doi: 10.1017/S0033291718001770

Li, Q., Tian, M., Taxer, J., Zheng, Y., Wu, H., Sun, S., et al. (2016). Problematic internet users' discounting behaviors reflect an inability to delay gratification, not risk taking. *Cyberpsychol. Behav. Soc. Networking* 19, 172–178. doi: 10.1089/cyber.2015.0295

Liu, S.-J., Lan, Y., Wu, L., and Yan, W.-S. (2019). Profiles of impulsivity in problematic internet users and cigarette smokers. *Front. Psychol.* 10:772. doi: 10.3389/fpsyg.2019.00772

MacKillop, J., Amlung, M. T., Few, L. R., Ray, L. A., Sweet, L. H., and Munafò, M. R. (2011). Delayed reward discounting and addictive behavior: a meta-analysis. *Psychopharmacology* 216, 305–321. doi: 10.1007/s00213-011-2229-0

MacKillop, J., Miller, J. D., Fortune, E., Maples, J., Lance, C. E., Campbell, W. K., et al. (2014). Multidimensional examination of impulsivity in relation to disordered gambling. *Exp. Clin. Psychopharmacol.* 22:176. doi: 10.1037/a0035874

Madden, G. J., and Bickel, W. K. (2010). *Impulsivity: The behavioral and neurological science of discounting*. Washington, D.C: American Psychological Association.

Madden, G. J., Petry, N. M., and Johnson, P. S. (2009). Pathological gamblers discount probabilistic rewards less steeply than matched controls. *Exp. Clin. Psychopharmacol.* 17:283. doi: 10.1037/a0016806

McKerchar, T. L., Green, L., Myerson, J., Pickford, T. S., Hill, J. C., and Stout, S. C. (2009). A comparison of four models of delay discounting in humans. *Behav. Proces.* 81, 256–259. doi: 10.1016/j.beproc.2008.12.017

Michalczuk, R., Bowden-Jones, H., Verdejo-Garcia, A., and Clark, L. (2011). Impulsivity and cognitive distortions in pathological gamblers attending the UK National Problem Gambling Clinic: a preliminary report. *Psychol. Med.* 41, 2625–2635. doi: 10.1017/S003329171100095X

Miedl, S. F., Peters, J., and Büchel, C. (2012). Altered neural reward representations in pathological gamblers revealed by delay and probability discounting. *Arch. General Psychiatry* 69, 177–186. doi: 10.1001/archgenpsychiatry.2011.1552

Miedl, S. F., Wiswede, D., Marco-Pallarés, J., Ye, Z., Fehr, T., Herrmann, M., et al. (2015). The neural basis of impulsive discounting in pathological gamblers. *Brain Imaging Behav.* 9, 887–898. doi: 10.1007/s11682-015-9352-1

Minhas, M., Murphy, C. M., Balodis, I. M., Acuff, S. F., Buscemi, J., Murphy, J. G., et al. (2021a). Multidimensional elements of impulsivity as shared and unique risk factors for food addiction and alcohol misuse. *Appetite* 159:105052. doi: 10.1016/j.appet.2020.105052

Minhas, M., Murphy, C. M., Balodis, I. M., Samokhvalov, A. V., and MacKillop, J. (2021b). Food addiction in a large community sample of Canadian adults: prevalence and relationship with obesity, body composition, quality of life and impulsivity. *Addiction* 2021:15446. doi: 10.1111/add.15446

Mishra, S., and Lalumière, M. L. (2017). Associations between delay discounting and risk-related behaviors, traits, attitudes, and outcomes. *J. Behav. Decision Making* 30, 769–781. doi: 10.1002/bdm.2000

Mitchell, J. M., Fields, H. L., D'Esposito, M., and Boettiger, C. A. (2005). Impulsive responding in alcoholics. *Alcohol. Clin. Exp. Res.* 29, 2158–2169. doi: 10.1097/01.alc.0000191755.63639.4a

Mohammadi, B., Hammer, A., Miedl, S. F., Wiswede, D., Marco-Pallarés, J., Herrmann, M., et al. (2016). Intertemporal choice behavior is constrained by brain structure in healthy participants and pathological gamblers. *Brain Struct. Funct.* 221, 3157–3170. doi: 10.1007/s00429-015-1093-9

Montes, K. S., and Weatherly, J. N. (2017). Differences in the gambling behavior of online and non-online student gamblers in a controlled laboratory environment. *J. Gambl. Stud.* 33, 85–97. doi: 10.1007/s10899-016-9613-y

Moody, L. N., Tegge, A. N., and Bickel, W. K. (2017). Cross-commodity delay discounting of alcohol and money in alcohol users. *Psychol. Record* 67, 285–292. doi: 10.1007/s40732-017-0245-0

Myerson, J., Green, L., and Warusawitharana, M. (2001). Area under the curve as a measure of discounting. *J. Exp. Anal. Behav.* 76, 235–243. doi: 10.1901/jeab.2001.76-235

Nicolai, J., and Moshagen, M. (2017). Dissociating pathological buying from obsessive-compulsive symptoms using delay discounting. *Zeitschrift Psychol.* 2017:a000308. doi: 10.1027/2151-2604/a000308

Nigro, G., and Cosenza, M. (2016). Living in the now: Decision-making and delay discounting in adolescent gamblers. *J. Gambl. Stud.* 32, 1191–1202. doi: 10.1007/s10899-016-9595-9

Nigro, G., Cosenza, M., and Ciccarelli, M. (2017). The blurred future of adolescent gamblers: Impulsivity, time horizon, and emotional distress. *Front. Psychol.* 8:486. doi: 10.3389/fpsyg.2017.00486

Odum, A. L. (2011). Delay discounting: I'm a *k,* you're a *k*. *J. Exp. Anal. Behav.* 96, 427–439. doi: 10.1901/jeab.2011.96-423

Orwin, R. G. (1983). A fail-safe N for effect size in meta-analysis. *J. Educat. Statist.* 8, 157–159. doi: 10.3102/10769986008002157

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., et al. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 372, n71. doi: 10.1136/bmj.n71

Peng-Li, D., Sørensen, T. A., Li, Y., and He, Q. (2020). Systematically lower structural brain connectivity in individuals with elevated food addiction symptoms. *Appetite* 155:104850. doi: 10.1016/j.appet.2020.104850

Petry, N. M. (2001). Pathological gamblers, with and without substance use disorders, discount delayed rewards at high rates. *J. Abnorm. Psychol.* 110:482. doi: 10.1037/0021-843X.110.3.482

Petry, N. M. (2012). Discounting of probabilistic rewards is associated with gambling abstinence in treatment-seeking pathological gamblers. *J. Abnorm. Psychol.* 121:151. doi: 10.1037/a0024782

Rachlin, H., and Green, L. (1972). Commitment, choice and self-control 1. *J. Exp. Anal. Behav.* 17, 15–22. doi: 10.1901/jeab.1972.17-15

Raiha, S., Yang, G., Wang, L., Dai, W., Wu, H., Meng, G., et al. (2020). Altered Reward Processing System in Internet Gaming Disorder. *Front. Psychiatry* 11:599141. doi: 10.3389/fpsyt.2020.599141

Rosenberg, K. P., and Feder, L. C. (2014). *Behavioral addictions: Criteria, evidence, and treatment*. Florida, FL: Academic Press.

Saville, B. K., Gisbert, A., Kopp, J., and Telesco, C. (2010). Internet addiction and delay discounting in college students. *Psychol. Record* 60, 273–286. doi: 10.1007/BF03395707

Schluter, M. G., Kim, H. S., and Hodgins, D. C. (2018). Obtaining quality data using behavioral measures of impulsivity in gambling research with Amazon's Mechanical Turk. *J. Behav. Addict.* 7, 1122–1131. doi: 10.1556/2006.7.2018.117

Schulz van Endert, T. (2021). Addictive use of digital devices in young children: Associations with delay discounting, self-control and academic performance. *PLoS One* 16:e0253058. doi: 10.1371/journal.pone.0253058

Schulz van Endert, T., and Mohr, P. N. (2020). Likes and impulsivity: Investigating the relationship between Actual smartphone use and delay discounting. *PLoS One* 15:e0241383. doi: 10.1371/journal.pone.0241383

Secades-Villa, R., Martínez-Loredo, V., Grande-Gosende, A., and Fernández-Hermida, J. R. (2016). The relationship between impulsivity and problem gambling in adolescence. *Front. Psychol.* 7:1931. doi: 10.3389/fpsyg.2016.01931

Stea, J. N., Hodgins, D. C., and Lambert, M. J. (2011). Relations between delay discounting and low to moderate gambling, cannabis, and alcohol problems among university students. *Behav. Proc.* 88, 202–205. doi: 10.1016/j.beproc.2011.09.002

Sterne, J. A., Gavaghan, D., and Egger, M. (2000). Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. *J. Clin. Epidemiol.* 53, 1119–1129. doi: 10.1016/S0895-4356(00)00242-0

Strickland, J. C., and Johnson, M. W. (2021). Rejecting impulsivity as a psychological construct: A theoretical, empirical, and sociocultural argument. *Psychol. Rev.* 128:336. doi: 10.1037/rev0000263

Tabri, N., Shead, N. W., and Wohl, M. J. (2017). Me, Myself, and Money II: Relative deprivation predicts disordered gambling severity via delay discounting, especially among gamblers who have a financially focused self-concept. *J. Gambl. Stud.* 33, 1201–1211. doi: 10.1007/s10899-017-9673-7

Thomas, K. B., Derenne, A., and Weatherly, J. N. (2015). Delay and probability discounting in the context of gambling function and expectancies. *J. Gambl. Iss.* 30, 35–56. doi: 10.4309/jgi.2015.30.6

Tian, M., Tao, R., Zheng, Y., Zhang, H., Yang, G., Li, Q., et al. (2018). Internet gaming disorder in adolescents is linked to delay discounting but not probability discounting. *Comput. Hum. Behav.* 80, 59–66. doi: 10.1016/j.chb.2017.10.018

Torres, A., Catena, A., Megías, A., Maldonado, A., Cándido, A., Verdejo-García, A., et al. (2013). Emotional and non-emotional pathways to impulsive behavior and addiction. *Front. Hum. Neurosci.* 7:43. doi: 10.3389/fnhum.2013.00043

Tukey, J. (1958). Bias and confidence in not quite large samples. *Ann. Math. Statist.* 29:614.

Turel, O., He, Q., Brevers, D., and Bechara, A. (2018). Delay discounting mediates the association between posterior insular cortex volume and social media addiction symptoms. *Cognit. Affect. Behav. Neurosci.* 18, 694–704. doi: 10.3758/s13415-018-0597-1

VanderBroek-Stice, L., Stojek, M. K., Beach, S. R., and MacKillop, J. (2017). Multidimensional assessment of impulsivity in relation to obesity and food addiction. *Appetite* 112, 59–68. doi: 10.1016/j.appet.2017.01.009

Vargas, T., Maloney, J., Gupta, T., Damme, K. S., Kelley, N. J., and Mittal, V. A. (2019). Measuring facets of reward sensitivity, inhibition, and impulse control in individuals with problematic Internet use. *Psychiatry Res.* 275, 351–358. doi: 10.1016/j.psychres.2019.03.032

Wang, Y., Hu, Y., Xu, J., Zhou, H., Lin, X., Du, X., et al. (2017a). Dysfunctional prefrontal function is associated with impulsivity in people with internet gaming disorder during a delay discounting task. *Front. Psychiatry* 8:287. doi: 10.3389/fpsyt.2017.00287

Wang, Y., Wu, L., Wang, L., Zhang, Y., Du, X., and Dong, G. (2017b). Impaired decision-making and impulse control in Internet gaming addicts: evidence from the comparison with recreational Internet game users. *Addict. Biol.* 22, 1610–1621. doi: 10.1111/adb.12458

Wang, Y., Wu, L., Zhou, H., Lin, X., Zhang, Y., Du, X., et al. (2017c). Impaired executive control and reward circuit in Internet gaming addicts under a delay discounting task: independent component analysis. *Eur. Arch. Psychiatry Clin. Neurosci.* 267, 245–255. doi: 10.1007/s00406-016-0721-6

Weidacker, K., Johnston, S. J., Mullins, P. G., Boy, F., and Dymond, S. (2020). Impulsive decision-making and gambling severity: The influence of γ-amino-butyric acid (GABA) and glutamate-glutamine (Glx). *Eur. Neuropsychopharmacol.* 32, 36–46. doi: 10.1016/j.euroneuro.2019.12.110

Weinstein, A., Abu, H. B., Timor, A., and Mama, Y. (2016). Delay discounting, risk-taking, and rejection sensitivity among individuals with internet and video gaming disorders. *J. Behav. Addict.* 5, 674–682. doi: 10.1556/2006.5.2016.081

Wiehler, A., Bromberg, U., and Peters, J. (2015). The role of prospection in steep temporal reward discounting in gambling addiction. *Front. Psychiatry* 6:112. doi: 10.3389/fpsyt.2015.00112

Williams, A. D. (2012). Are compulsive buyers impulsive? Evidence of poor response inhibition and delay discounting. *J. Exp. Psychopathol.* 3, 794–806. doi: 10.5127/jep.025211

Wilmer, H. H., Hampton, W. H., Olino, T. M., Olson, I. R., and Chein, J. M. (2019). Wired to be connected? Links between mobile technology engagement, intertemporal preference and frontostriatal white matter connectivity. *Soc. Cognit. Affect. Neurosci.* 14, 367–379. doi: 10.1093/scan/nsz024

Wölfling, K., Duven, E., Wejbera, M., Beutel, M., and Müller, K. (2020). Discounting delayed monetary rewards and decision making in behavioral addictions–A comparison between patients with gambling disorder and internet gaming disorder. *Addict. Behav.* 108:106446. doi: 10.1016/j.addbeh.2020.106446

World Health Organization (2018). *International classification of diseases for mortality and morbidity statistics*. Geneva: World Health Organization.

Yan, W.-S., Chen, R.-T., Liu, M.-M., and Zheng, D.-H. (2021). Monetary Reward Discounting, Inhibitory Control, and Trait Impulsivity in Young Adults With

Internet Gaming Disorder and Nicotine Dependence. *Front. Psychiatry* 12:28. doi: 10.3389/fpsyt.2021.628933

Yan, W.-S., Zhang, R.-R., Lan, Y., Li, Y.-H., and Sui, N. (2016). Comparison of impulsivity in non-problem, at-risk and problem gamblers. *Sci. Rep.* 6, 1–8. doi: 10.1038/srep39233

Yao, Y. W., Zhang, J. T., Fang, X. Y., Liu, L., and Potenza, M. N. (2021). Reward-related decision-making deficits in internet gaming disorder: a systematic review and meta-analysis. *Addiction* 2021:15518. doi: 10.1111/add.15518

Yao, Y.-W., Chen, P.-R., Chiang-shan, R. L., Hare, T. A., Li, S., Zhang, J.-T., et al. (2017). Combined reality therapy and mindfulness meditation decrease intertemporal decisional impulsivity in young adults with Internet gaming disorder. *Comput. Hum. Behav.* 68, 210–216. doi: 10.1016/j.chb.2016.11.038

Yoon, J. H., and Higgins, S. T. (2008). Turning *k* on its head: comments on the use of ED50 in delay discounting research. *Drug Alcohol Depend.* 95, 169–172. doi: 10.1016/j.drugalcdep.2007.12.011

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Behavioral Neuroscience

ORIGINAL RESEARCH
published: 02 December 2021
doi: 10.3389/fnbeh.2021.775209

The Antagonism of Corticotropin-Releasing Factor Receptor-1 in Brain Suppress Stress-Induced Propofol Self-Administration in Rats

Zhanglei Dong[1†], Gaolong Zhang[1†], Saiqiong Xiang[1], Chenchen Jiang[2], Zhichuan Chen[1,3], Yan Li[4], Bingwu Huang[1], Wenhua Zhou[5], Qingquan Lian[1*] and Binbin Wu[1*]*

[1] Department of Anesthesiology, Perioperative and Pain Medicine, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou, China, [2] Clinical Research Unit, The Second Affiliated and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou, China, [3] Medical School, Institution of Reproductive Medicine, Nantong University, Nantong, China, [4] Department of Neurology, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou, China, [5] Zhejiang Provincial Key Lab of Addiction, Ningbo Kangning Hospital, School of Medicine, Ningbo Universtiy, Ningbo, China

OPEN ACCESS

Edited by:
Marco Bortolato,
The University of Utah, United States

Reviewed by:
Georgina Maria Renard,
University of Santiago, Chile
Adam Prus,
Northern Michigan University,
United States

***Correspondence:**
Wenhua Zhou
whzhou@vip.163.com
Qingquan Lian
lianqingquanmz@163.com
Binbin Wu
wbb19880117@163.com
orcid.org/0000-0001-7953-0992

[†] These authors have contributed equally to this work

Specialty section:
This article was submitted to Motivation and Reward, a section of the journal Frontiers in Behavioral Neuroscience

Received: 13 September 2021
Accepted: 22 October 2021
Published: 02 December 2021

Citation:
Dong Z, Zhang G, Xiang S, Jiang C, Chen Z, Li Y, Huang B, Zhou W, Lian Q and Wu B (2021) The Antagonism of Corticotropin-Releasing Factor Receptor-1 in Brain Suppress Stress-Induced Propofol Self-Administration in Rats. Front. Behav. Neurosci. 15:775209. doi: 10.3389/fnbeh.2021.775209

Propofol addiction has been detected in humans and rats, which may be facilitated by stress. Corticotropin-releasing factor acts through the corticotropin-releasing factor (CRF) receptor-1 (CRF1R) and CRF2 receptor-2 (CRF2R) and is a crucial candidate target for the interaction between stress and drug abuse, but its role on propofol addiction remains unknown. Tail clip stressful stimulation was performed in rats to test the stress on the establishment of the propofol self-administration behavioral model. Thereafter, the rats were pretreated before the testing session at the bilateral lateral ventricle with one of the doses of antalarmin (CRF1R antagonist, 100–500 ng/site), antisauvagine 30 (CRF2R antagonist, 100–500 ng/site), and RU486 (glucocorticoid receptor antagonist, 100–500 ng/site) or vehicle. The dopamine D1 receptor (D1R) in the nucleus accumbens (NAc) was detected to explore the underlying molecular mechanism. The sucrose self-administration establishment and maintenance, and locomotor activities were also examined to determine the specificity. We found that the establishment of propofol self-administration was promoted in the tail clip treated group (the stress group), which was inhibited by antalarmin at the dose of 100–500 ng/site but was not by antisauvagine 30 or RU486. Accordingly, the expression of D1R in the NAc was attenuated by antalarmin, dose-dependently. Moreover, pretreatments fail to change sucrose self-administration behavior or locomotor activities. This study supports the role of CRF1R in the brain in mediating the central reward processing through D1R in the NAc and provided a possibility that CRF1R antagonist may be a new therapeutic approach for the treatment of propofol addiction.

Keywords: stress, CRF, D1 receptor, propofol, addiction

INTRODUCTION

Propofol is an intravenous anesthetic mainly used for anesthesia induction and sedation in more than 50 countries. However, with the sedative and relaxing effect of propofol, its recreational abuse and dependence have risen (Earley and Finver, 2013). The abuse and misuse of propofol have recently become a social problem in many countries, and anesthesiologists are the main potential abusers, who usually suffered great pressure from daily clinical work (Wischmeyer et al., 2007; Fry et al., 2015; Park et al., 2015). We have demonstrated propofol as a substance for addiction in animals with the self-administration model, which was mediated by dopamine D1 receptor (D1R) in the nucleus accumbens (NAc) (Lian et al., 2013). We also found that propofol self-administration behavior was prompted by glucocorticoid—a stress hormone released from the hypothalamic-pituitary-adrenal (HPA) axis under the regulation of D1R in the NAc in rats (Wu et al., 2016, 2018). This effect can be attenuated by the intraperitoneal injection of RU486, an antagonist of the glucocorticoid receptor (GR) (Wu et al., 2016). However, whether the corticotropin-releasing factor (CRF) participates in the modulation of propofol self-administration behavior remains to be elucidated.

Previous studies demonstrated that stress increased the susceptibility of an individual to drug abuse (Sinha, 2008). The self-administration of psychomotor stimulants in animals were escalated after intermittent exposure to various stressors such as amphetamines and cocaine (Newman et al., 2018). The neuropeptide of CRF is a key modulator of physiological endocrine and behavior during stress, as well as the first identified central initiator of the classic HPA axis stress neuroendocrine response (Roberto et al., 2017). The CRF-containing system not only includes the HPA axis, but many findings also confirmed that stress-induced drug seeking can be mediated by extrahypothalamic CRF sites in the brain (Lasheras et al., 2015). As such, CRF has been a candidate target for the interaction between stress and drug abuse, playing a critical role in stress-escalated drug taking (Koob and Volkow, 2010; Newman et al., 2018).

Corticotropin-releasing factor signaling *via* CRF receptor-1 (CRF1R) and CRF receptor-2 (CRF2R), and is a preferential agonist for CRF1R over CRF2R. Corticotropin-releasing factor receptors widely signal throughout the brain, such as the ventral tegmental area (VTA), NAc, amygdala, and bed nucleus of the stria terminalis (Baumgartner et al., 2021). It was reported that the CRF-induced increase in the activity of dopamine (DA) neurons in the VTA might enhance release in the NAc, which potentiates drug-seeking behaviors and the response to reward (Wanat et al., 2008). To investigate the modulation of CRF in the central system for addiction, the ventricle injection of CRF was adopted in many studies. Both acute and chronic blockade of CRF1R by the lateral ventricle injection of CRF1R antagonist attenuated cocaine-induced DA release in the NAc (Lodge and Grace, 2005). Antagonizing CRF1R but not CRF2R blocked morphine-induced conditioned place preference (CPP) (Lasheras et al., 2015). These findings include the results of pharmacological and transgenic studies, indicating that CRF1R and CRF2R have differential roles in regulating addiction behavioral response (Valdez et al., 2004; Roberto et al., 2017). Corticotropin-releasing factor receptor-1 and CRF2R messenger RNA (mRNA) were detected in the VTA and NAc in rodents (Wischmeyer et al., 2007), in which both areas are pivotal in reward processing and drug abuse (Liu et al., 2020). Multiple studies suggested that drugs of abuse implement reward effects by increasing DA release in the NAc, where the dopaminergic afferent can be received from the VTA (Koob, 1999), and also, it was reported that CRF increases dopamine release in the NAc through CRF receptors (Lemos et al., 2012). Based on these findings, we assumed that CRF might regulate propofol self-administration behavior through the CRF receptors in the mesolimbic DA system.

In the present study, we adopted tail clip pretreatment to explore the effects of stress on propofol self-administration model establishment. After that, the role of CRF receptor and GR in the brain on propofol self-administration behaviors was examined with the tail clip-induced propofol self-administration model by the microinjection of antalarmin (a CRF1R antagonist), antisauvagine 30 (a CRF2R antagonist), and RU486 (an antagonist of GR) at the bilateral lateral ventricle. In addition, the pre-treatments on the expressions of D1R in the NAc, sucrose self-administration, and locomotor activities were also researched.

MATERIALS AND METHODS

Animals

Adult male Sprague-Dawley rats weighing 300–350 g (14-week-old) were purchased from the Experimental Animal Center of Wenzhou Medical University. All procedures were consistent with the Guide for the Care and Use of Laboratory Animals and were approved by the Animal Care and Use Committee of Wenzhou Medical University. All operations were performed under anesthesia with sodium pentobarbital, and efforts were made to minimize the number of animals and suffering. The rats were housed in a temperature-controlled room individually under a 12-h light/dark cycle at 22–24°C, with free access to food and water. Only the rats that were successfully implanted with chronic indwelling catheters *via* the jugular vein and guide cannulae in the bilateral lateral ventricle were randomly assigned to continue the subsequent experiments.

Drugs

Propofol in this study was obtained from Astra Zeneca (10 mg/ml, Diprivan, Italy), and was prepared daily for self-administration behavioral training. A single dose of 1.7 mg/kg/injection was used for the training as described in previous studies (McAulliffe et al., 2006). The CRF1R antagonist antalarmin (Axon Medchem, the Netherlands), CRF2R antagonist (Tocris Bioscience, Ellisville, MO, United States),

Abbreviations: CRF, corticotropin-releasing factor; CRF1R, CRF1 receptor; CRF2R, CRF2 receptor; GR, glucocorticoid receptor; D1R, dopamine D1 receptor; D2R, dopamine D2 receptor; FR1, fixed ratio 1; NAc, nucleus accumbens; VTA, ventral tegmental area; mPFC, medial prefrontal cortex; CPP, conditioned place preference.

and GR antagonist RU486 (Sigma-Aldrich, St-Louis, MO, United States) were dissolved in artificial cerebrospinal fluid (ACSF) (Zhongxing Chemical Reagent Co., Ltd., Zhejiang, China) (122.5 mM NaCl, 3.5 mM KCl, 25 mM NaHCO3, 1 mM NaH2PO4, 2.5 mM CaCl2, 1 mM MgCl2, 20 mM glucose, 1 mM ascorbic acid (pH: 7.40, 295-305 mOsm) (Yarur et al., 2020). The doses of the agents adopted in the present study were determined on previous behavioral studies (Blacktop et al., 2011; Taslimi et al., 2018).

Surgeries

The implantations of intravenous catheters were performed as described previously (Zhou et al., 2007). The rats were implanted with the chronically indwelling intravenous catheters under sodium pentobarbital anesthesia (40 mg/kg) and the catheter were flushed daily with 0.2 ml saline-heparin solution to maintain the patency. Meanwhile, the rats were treated with penicillin B once a day through the implanted catheter to prevent infection during the recovery period for at least 7 days. The intra-lateral ventricle injections (A/P −0.8 mm, M/L ± 1.4 mm, D/V—3.5 mm) were done through bilaterally implanted guide cannulae (20 gauge, Small Parts Inc., United States) (Biagioni et al., 2006).

Tail Clip Procedure

The acute pain induced by the tail clip test was according to a tail clip procedure described in a previously published study (Goebel-Stengel et al., 2014; Lee et al., 2017). The rats were put in a custom-made acrylic cylinder and given 10 min to accustom themselves to the new environment. An alligator clip exerting a force of 2.5 N was manually applied to the tail at a position approximately 2.5 cm proximal to the tail tip to induce pain for 2 min. The force was measured by attaching a flexible force sensor to the tail (FSR-400, Interlink Electronics, CA, United States). We observed that the tail clip pretreatment did not cause any apparent physical damage in the rats.

Intra-Lateral Ventricle Microinjection Procedure

To evaluate the effects of the agents on the establishment and maintenance of tail clip-induced propofol self-administration behavior, sucrose self-administration, and locomotor activities, the rats were treated with ACSF (vehicle), antalarmin (100 and 500 ng/site), antisauvagine 30 (100 and 500 ng/site), or RU486 (100 and 500 ng/site) 10 min before the behavior test session. The microinjection in the lateral ventricle was delivered through the previous indwelling infusion cannula with a microinjection pump (MD-1001, Bioanalytical System Inc., West Lafayette, IN, United States) in a volume of 0.25 μL over 5 min.

Self-Administration Apparatus

The apparatus for propofol self-administration (Ningbo Addiction Research and Treatment Center, Zhejiang, China) behavior training has been described in a previous study (Dong et al., 2021). Briefly, the apparatus was accompanied with custom-made operant boxes that sized 30 cm × 30 cm × 30 cm and equipped with two nose-poke operanda (active nose-poke and inactive nose-poke) located 5 cm above the floor with a yellow LED light inside each nose-poke hole. The rats were trained for the self-administration of propofol through the jugular injection with a 5-ml syringe that was attached to a special pump at the speed of 1.2 ml/min. The rats would receive a propofol infusion of 1.7 mg/kg after one active nose-poke as a reward (fixed ratio 1, FR1), which was paired with a 5-s extinguishing of the house light and the noise from the propofol infusion pump. No injection was given after an inactive nose-poke. Each active nose-poke was followed by a 30-s time-out period, no injection or reward would be given even if nose-poke occurred, both house light and the lights in the active and inactive nose-poke hole remained illuminated when active or inactive nose-poke occurred during the time-out period, and the numbers of nose-poke would be recorded. All the behavioral training sessions were automatically recorded by the computer.

Propofol Self-Administration Training

The rats were trained under a fixed ratio 1 (FR1) schedule with a daily 3-h training session for 14 consecutive days, and the training session ended when the 3-h training time or 100 propofol infusions was reached. The numbers of active nose-poke and propofol infusion increased to a stable stage as the training proceeded till a successive 14-day training, and the inactive nose-poke decreased to a minimal level. The successful establishment of the propofol self-administration behavior model was determined by the variability of less than 10% in the last three sessions (Filip and Frankowska, 2007). The rats that did not reach the criteria were excluded in this step. There were 25 rats trained for establishing propofol self-administration behavior model with (the stress group, n = 12) or without tail-clip stimulation (the control group, n = 12), and one rat was ruled out. Another 58 rats received a 2 min tail-clip stressful stimulation 30 min before propofol self-administration training, and two rats were excluded. Finally, there were 56 rats randomly assigned to the groups that received a lateral ventricle injection of ACSF, antalarmin, antisauvagine 30, or RU486 (the vehicle group, n = 8; the antalarmin group n = 8; the antisauvagine 30 group, n = 8; the RU486 group, n = 8).

Specific Experiments

Experiment 1: To explore the role of CRF1R in the brain on the stress-induced propofol self-administration behavior model, the rats that received tail clip-induced propofol self-administration training were microinjected at the bilateral lateral ventricle with ACSF (vehicle) or antalarmin (100 and 500 ng/site) 10 min prior to the behavior test session on day 15.

Experiment 2: To investigate the role of central CRF2R on stress-induced propofol self-administration behavior, the tail clip-induced propofol self-administration training rats were randomly assigned to the groups that received microinjection at the bilateral lateral ventricle with ACSF (vehicle) or antisauvagine 30 (100 and 500 ng/site), 10 min prior to the behavior test session on day 15.

Experiment 3: To evaluate the effects of GR on the tail clip-induced propofol self-administration behavior, the training

rats received ACSF (vehicle) or RU486 (100 and 500 ng/site) pretreatment 10 min prior to the behavior test session on day 15.

Sucrose Self-Administration Training

The rats were trained for sucrose self-administration daily for food reward under an FR1 schedule during a 0.5-h session consecutively for 7 days ($n = 6$). The paradigm for sucrose self-administration was similar to the paradigm of propofol, but the reward was changed to a 45-mg sucrose pellet (Dustless precision pellets, Bio-Serv, United States) that was delivered *via* a special cup after an active nose-poke, and inactive nose-pokes did not result in any programmed consequence. The sessions ended after either 0.5 h or if 100 pellets occurred, and the behavioral training sessions were automatically recorded by a computer. All rats reached the criteria of the successful establishment of the sucrose self-administration behavioral model. The rats were trained to establish a sucrose self-administration behavior model with (the stress group, $n = 6$) or without tail clip stimulation (the control group, $n = 6$) for 2 min to investigate the effects of the tail clip stressful stimulation on the establishment of sucrose self-administration behavioral model. The other 42 rats that received the 2-min tail clip stimulation 30 min before daily sucrose self-administration training were microinjected with ACSF (vehicle), antalarmin, antisauvagine 30, or RU486 at the bilateral lateral ventricle injection on day 8 to examine the maintenance of the sucrose self-administration behavioral model (the vehicle group, $n = 6$; the antalarmin group $n = 6$; the antisauvagine 30 group, $n = 6$; the RU486 group, $n = 6$).

Locomotor Activity

The testing of the locomotor activity was performed in an experimental box with the size 30 cm × 40 cm × 50 cm, and was equipped with an image tracking and processing system. The rats received tail clip stressful pretreatment and a microinjection of ACSF (vehicle), antalarmin, antisauvagine 30, or RU486 at the bilateral lateral ventricle as described above prior to the locomotor activity testing, which was followed by a 1-h acclimation and a 3-h test session. The path length of the rats was monitored by a digital camera on the top of the experimental box and recorded automatically by the camera tracking system (the vehicle group, $n = 6$; the antalarmin group $n = 6$; the antisauvagine 30 group, $n = 6$; the RU486 group, $n = 6$).

Western Blot Analysis

The NAc was removed immediately after the completion of the propofol self-administration test on day 15 ($n = 4$). The rats were deeply anesthetized with sodium pentobarbital (40 mg/kg) and then were euthanized by decapitation. The brain was removed and the NAc was dissected out (Paxinos and Waston, 2007). The total protein was extracted from the NAc and the protein concentration was measured with a bicinchoninic acid (BCA) protein assay kit (Beyotime, Shanghai, China). After being denatured at 100°C for 10 min, 40 μg protein was loaded on sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) for electrophoretic separation, which was followed by the transfer to polyvinylidene fluoride (PVDF) membranes and non-specific binding site blocked with 5% skim milk (Merk) for 2 h at room temperature (RT). The band was incubated in primary D1 antibody (rabbit, 1:1,000, Abcam, Cambridge, MA, United States) at 4°C overnight, and in the secondary antibody (goat anti-rabbit, 1:5,000, Bioworld, Minnesota, United States) that was diluted in tris-buffered saline (TBST) for 2 h at RT. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was adopted as the internal control. Finally, the band was visualized with an enhanced chemiluminescence (ECL) solution (GE Healthcare, Chicago, IL, United States) and photomicrographed with Image Quant LAS 4000 mini (GE Healthcare, Chicago, IL, United States).

Statistical Analysis

The continuous data were presented as mean ± SD, and the normality of data distribution was tested. For the normally distributed data, one-way ANOVA was adopted for the analyses between multiple groups when the data also meets the homogeneity of variance, and Dunnett's *post hoc* test was used for multiple comparisons. The data of the repeated measurements were analyzed with the two-way ANOVA of repeated measures. The Kruskal–Wallis test was used for data that were non-normally distributed. Statistical calculations were performed with SPSS 25.0 (SPSS Inc., Chicago, United States), and p-value < 0.05 was considered significant.

RESULTS

Stress Stimulation Facilitated the Establishment of Propofol Self-Administration Behavior Under the FR1 Schedule

Figure 1 shows the rats in both stress group that suffered tail clip stressful pretreatment and the control group that did not receive the tail clip stimulation successfully established propofol self-administration behavior within 14 days, presenting a significant increase in the active nose-poke response and propofol infusions, and a decrease in the inactive response. However, the numbers of active nose-poke responses and propofol infusions were higher in the stress group than the control group (**Figure 1A**, active nose-poke response, $F = 8.975$, $p < 0.001$; **Figure 1B**, infusion, $F = 4.882$, $p < 0.001$), but the number of inactive nose-poke responses was not significantly different between the two groups (**Figure 1C**, $F = 1.875$, $p = 0.16$) with significant differences. The results suggested that the establishment of propofol self-administration under the FR1 schedule was facilitated by the tail clip stressful pretreatment.

Different Effects of the Bilateral Microinjection of Antalarmin, Antisauvagine 30, and RU486 at the Lateral Ventricle on Stress-Induced Propofol Self-Administration Behavior

The rats that were trained to have propofol self-administration behavior with the tail clip stressful pretreatment were either

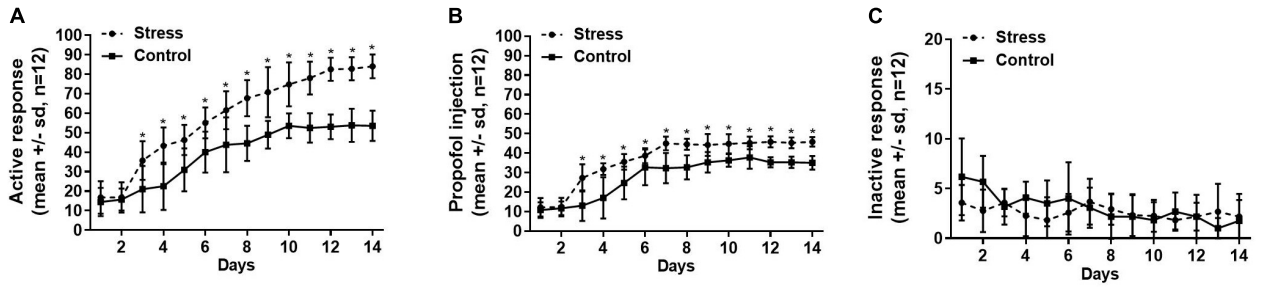


FIGURE 1 | The numbers of active nose-poke responses **(A)**, propofol infusions **(B)**, and inactive nose-poke responses **(C)** were compared between the stress group (with tail clip pretreatment) and the control group (without tail clip pretreatment) by using the two-way ANOVA of repeated measures, showing that the active nose-poke responses and propofol infusions were higher in the stress group than the control group (active nose-poke response $p < 0.001$, infusion $p < 0.001$, $n = 12$), and the number of inactive nose-poke response was not significantly different in both groups ($p = 0.16$). SD, standard deviation, $^*p < 0.05$.

microinjected with ACSF (vehicle) or antalarmin (100 and 500 ng/site) at the bilateral lateral ventricle 10 min before the propofol self-administration behavior testing session on day 15. It was found that antalarmin dose-dependently attenuated the numbers of active nose-poke responses and propofol infusions compared with the vehicle group (**Figure 2A**, active nose-poke response, $H = 15.965$, $p < 0.001$; infusion, $F = 65.653$, $p < 0.001$), but the inactive nose-poke was not significantly affected ($F = 1.195$, $p = 0.32$). Whereas, no significant difference was found after the rats were pretreated with antisauvagine 30 (100 and 500 ng/site) in either active nose-poke (**Figure 2B**, $F = 0.062$, $p = 0.94$), propofol infusions ($F = 0.997$, $p = 0.39$) or inactive nose-poke ($F = 0.057$, $p = 0.95$) compared with the vehicle group. These results indicated that CRF1R but not CRF2R in the brain participated in the process of propofol self-administration modulation.

To further explore the role of central GR on tail clip-induced propofol self-administration behavior, the rats were bilaterally intra-lateral ventricle microinjected with the vehicle or RU486 (100 and 500 ng/site). All the pretreatments failed to alter the numbers of active nose-poke responses (**Figure 2C**, $F = 0.051$, $p = 0.95$), propofol infusions ($F = 1.460$, $p = 0.26$), or inactive nose-poke responses ($F = 0.551$, $p = 0.59$).

The Expressions of D1R in the NAc Were Attenuated by Bilateral Lateral Ventricle Microinjection of Antalarmin, Not Antisauvagine 30 or RU486

The expressions of D1R in the NAc were detected after the completion of the tail clip pretreated propofol self-administration behavior testing session on day 15. The ANOVA analysis found that antalarmin significantly inhibited the expression of D1R in the NAc at the doses of both 100 and 500 ng/site (**Figure 3A**, $F = 28.267$, $p < 0.001$). However, there was no significant difference detected in the groups that were pretreated with antisauvagine 30 (**Figure 3B**, $F = 0.087$, $p = 0.92$) or RU486 compared with the vehicle group (**Figure 3C**, $F = 3.631$, $p = 0.070$).

Stress Stimulation Failed to Affect the Establishment of the Sucrose Self-Administration Behavioral Model Under the FR1 Schedule

The establishment of sucrose self-administration in the stress group and the control group was shown in **Figure 4**. The numbers of active nose-poke responses and sucrose pellets (food tray) increased as the training proceeded and stabilized at a high level in both the stress and control groups, and the inactive nose-poke responses decreased to a minimal level after the 7-day training. We found that neither active nose-poke response (**Figure 4A**, $F = 0.109$, $p = 0.88$), food tray (**Figure 4B**, $F = 0.330$, $p = 0.76$), nor inactive nose-poke response (**Figure 4C**, $F = 0.743$, $p = 0.62$) was changed in the stress group compared with the control group.

Microinjection of Antalarmin, Antisauvagine 30, or RU486 at Lateral Ventricle Did Not Alter Sucrose Self-Administration Behavior or Locomotor Activities

The effects of the microinjections of antalarmin, antisauvagine 30, or RU486 at the bilateral lateral ventricle on sucrose self-administration and general locomotor activities were examined to further confirm the specificity of these pretreatments on propofol self-administration. The sucrose self-administration test was carried out on day 8. The results showed that all of the pretreatments failed to affect the numbers of active nose-poke responses (**Figure 5**, antalarmin, $F = 0.669$, $p = 0.53$; antisauvagine 30, $F = 2.110$, $p = 0.16$; RU486, $F = 1.522$, $p = 0.25$), food tray (antalarmin, $F = 1.116$, $p = 0.35$; antisauvagine 30, $F = 0.166$, $p = 0.85$; RU486, $F = 0.077$, $p = 0.93$), and inactive response (antalarmin, $F = 0.227$, $p = 0.80$; antisauvagine 30, $F = 0.155$, $p = 0.86$; RU486, $F = 0.069$, $p = 0.93$). Meanwhile, no pretreatments changed the general locomotor activities in the tail clip-stimulated rats as judged by the path length (**Figure 6**, antalarmin, $F = 0.757$, $p = 0.49$; antisauvagine 30, $H = 114.047$, $p = 0.98$; RU486, $F = 0.651$, $p = 0.54$).

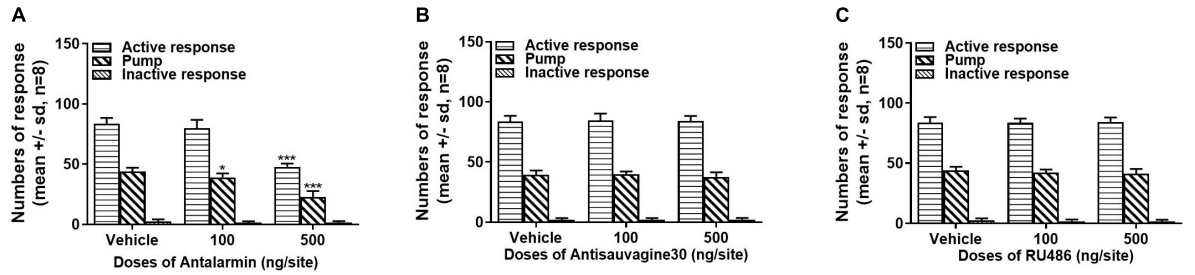


FIGURE 2 | (A) Intra-lateral ventricle injection of corticotropin-releasing factor (CRF) receptor-1 (CRF1R) antagonist antalarmin attenuated active nose-poke responses and propofol infusions in a dose-dependent manner (active nose-poke response $p < 0.001$, infusion $p < 0.001$, $n = 8$) in the rats who received tail clip stimulation before daily training and the testing session, while the numbers of inactive nose-poke responses did not show a significance compared with the vehicle group ($p = 0.32$). **(B)** Intra-lateral ventricle pretreatment of the CRF receptor-2 (CRF2R) antagonist antisauvagine 30 did not alter the active nose-poke responses ($p = 0.94$), propofol infusions ($p = 0.39$), or inactive nose-poke response ($p = 0.95$). **(C)** The pretreatment with the glucocorticoid receptor (GR) antagonist RU486 at the lateral ventricle was unlikely to affect the active nose-poke responses ($p = 0.95$), propofol infusions ($p = 0.26$), or inactive nose-poke responses ($p = 0.59$). The normally distributed data were analyzed by one-way ANOVA with Dunnett's *post hoc* test for multiple comparisons, otherwise were analyzed with a Kruskal–Wallis test. SD, standard deviation.*$p < 0.05$, ***$p < 0.001$.

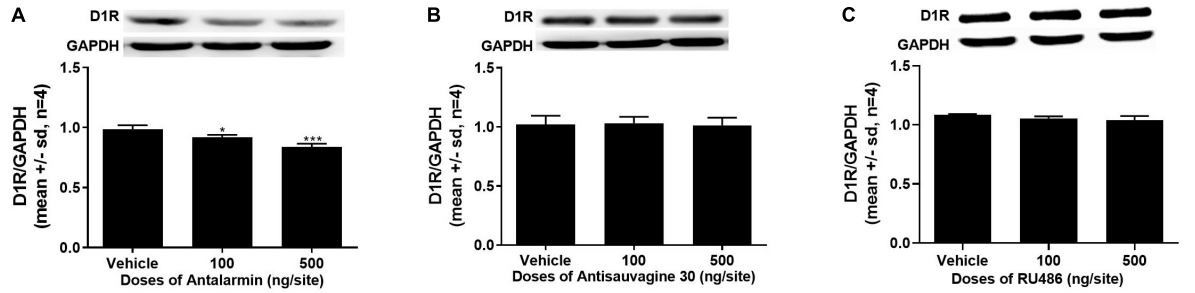


FIGURE 3 | (A) The bilaterally intra-lateral ventricle injection of antalarmin significantly attenuated the expression of dopamine D1 receptor (D1R) in the nucleus accumbens (NAc) at the doses of 100 ng/site ($p = 0.016$) and 500 ng/site ($p < 0.001$) in the rats who received tail clip stimulation prior to daily training and the testing session ($n = 4$). **(B)** The expression of D1R in the NAc was not altered by the pretreatment of antisauvagine 30 at the bilateral lateral ventricle ($p = 0.92$). **(C)** The pretreatment with RU486 at the bilateral lateral ventricle did not significantly change the D1R expression in the NAc ($p = 0.070$). The data was analyzed with one-way ANOVA with Dunnett's *post hoc* test for multiple comparisons. SD, standard deviation. *$p < 0.05$, ***$p < 0.001$.

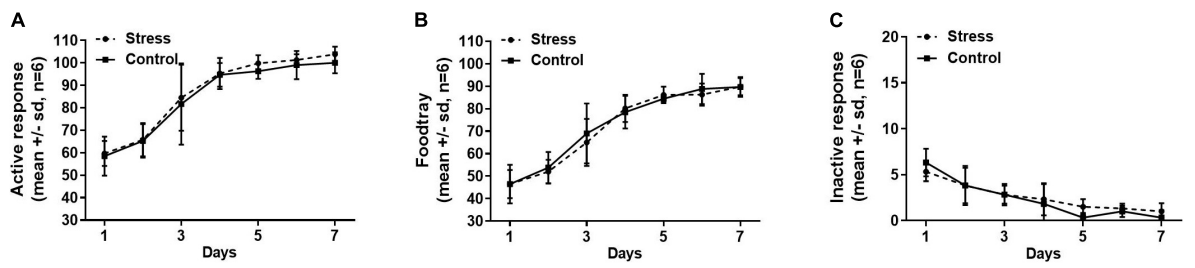


FIGURE 4 | The numbers of active nose-poke responses **(A)**, food tray **(B)**, and inactive nose-poke responses **(C)** were compared between the stress group and the control group, indicating that neither the active nose-poke responses ($p = 0.88$), food tray ($p = 0.76$), nor the number of inactive nose-poke responses ($p = 0.62$) was affected by the tail clip stressful stimulation. The data were analyzed with repeated measures of ANOVA. SD, standard deviation.

DISCUSSION

In this study, it was found that the establishment of the propofol self-administration behavioral model was facilitated by tail clip stressful stimulation prior to the daily training session, which can be inhibited by the central administration of the antagonist of CRF1R antalarmin but was not affected by antisauvagine 30 or RU486 at the bilateral lateral ventricle. The detected expression of D1R in the NAc has been approved to be a crucial concern in mediating propofol self-administration behavior to explore potential molecular mechanisms (Lian et al., 2013). Our findings show that the expression of D1R in the NAc was notably attenuated by antalarmin but not by antisauvagine 30 or RU486. We also found that the establishment and maintenance of the sucrose self-administration behavioral model or general locomotor activities were not affected

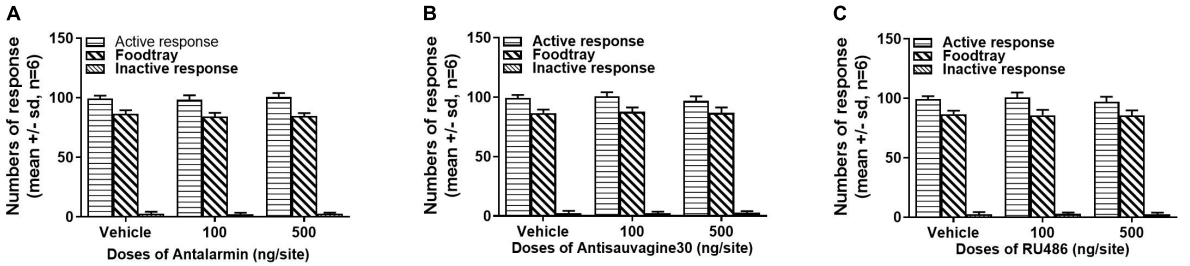


FIGURE 5 | The intra-lateral ventricle injection of antalarmin **(A)**, antisauvagine 30 **(B)**, or RU486 **(C)** bilaterally were unlikely to affect the numbers of active nose-poke responses, food tray, and inactive nose-poke responses in the rats who received tail clip stressful stimulation. The normally distributed data were analyzed with one-way ANOVA, otherwise was analyzed with a Kruskal–Wallis test. SD, standard deviation.

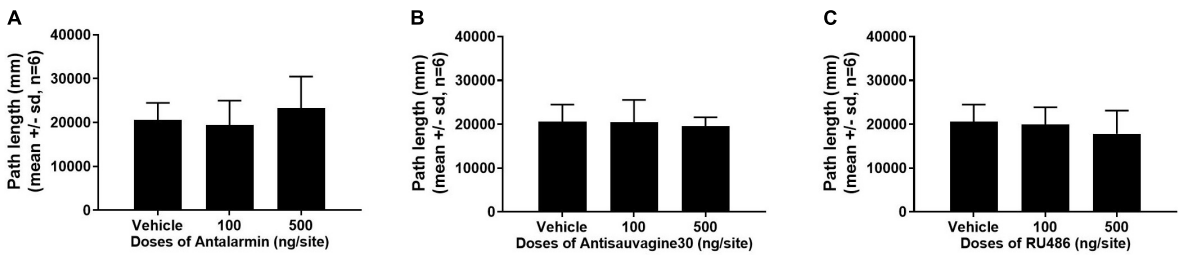


FIGURE 6 | The pretreatment with antalarmin **(A)**, antisauvagine 30 **(B)**, or RU486 **(C)** at the bilateral lateral ventricle did not cause any difference that reached significance of the numbers of active nose-poke responses, food tray, and inactive nose-poke responses in the rats that receive tail clip stressful stimulation compared with the vehicle group. The normally distributed data were analyzed with one-way ANOVA, otherwise was analyzed with a Kruskal–Wallis test. SD, standard deviation.

by all the pretreatments. Taken together, these findings support the role of CRF1R in the central nervous system in promoting propofol self-administration behavior, which may act through D1R in the NAc.

Addiction is conceptualized as a cycle of increasing the dysregulation of brain reward and anti-reward mechanisms that would result in a negative emotional state, subsequently contributing to compulsive drug-seeking behaviors (Koob, 2010). These counter-adaptive processes were hypothesized to be mediated by reward pathways and the brain stress systems. The neuropeptide CRF exerts a salient role in the neuronal networks for drug abuse initiation, escalation, and relapse (Newman et al., 2018). Previous research suggested that the chronic administration of drugs with dependence potential dysregulated the stress response mediated by CRF (Koob, 2010). The CRF was not only included in the HPA axis but also in the extrahypothalamic stress system in the brain. Also, the extrahypothalamic stress system includes the areas of VTA, NAc, and medial prefrontal cortex (mPFC) (Kelly and Fudge, 2018). The central administration of CRF at the ventricles reinstated heroin (Shaham et al., 1997), cocaine (Erb et al., 2006), and alcohol (Lê et al., 2002) seeking. Moreover, these reinstatements of drugs mimic the activation of behavioral responses to stress in rodents were blocked by competitive CRF receptor antagonists (Koob, 2010).

It is well known that the VTA and its dopaminergic projection to the NAc is one of the most important substrates for drug reward (Wischmeyer et al., 2007). Corticotropin-releasing factor was demonstrated to mediate the interaction between glutamatergic projection and dopaminergic neurons (Wise and Morales, 2010); induce glutamate release activates the mesocorticolimbic dopamine system (Wang et al., 2005); promote mesocorticolimbic DA release in the areas including the NAc; and cause lasting neural changes that may induce stress-escalated drug consumption (Park et al., 2015; Steger et al., 2020). Corticotropin-releasing factor plays roles through CRF1R and CRF2R but binds CRF1R with a 10-fold greater affinity compared with CRF2R (Hupalo et al., 2019). Previous studies implied that CRF1R but not CRF2R was involved in cocaine self-administration and morphine-induced CPP (Boyson et al., 2011; Lasheras et al., 2015). The NAc received dopaminergic projection from the VTA where CRF1R and CRF2R co-expressed on the dopaminergic neurons in rodents (Van Pett et al., 2000; Tan et al., 2017). The antagonism of CRF1R but not CFR2R in the VTA decreased footshock-induced reinstatement of cocaine seeking in rats and reduced the induction of locomotor cross-sensitization to cocaine (Blacktop et al., 2011; Boyson et al., 2014). As consistent with the above findings, the central administration of CRF1R antagonist antalarmin inhibited the tail clip-induced propofol self-administration but not the CRF2R antagonist antisauvagine 30, and activating CRF1R mimic the effect of footshock stress on reinstatement, and activation of the CRF2R did not (Blacktop et al., 2011). Both the acute and chronic blockade of CRF1R by the lateral ventricle injection with CRF1R antagonists attenuated cocaine-induced DA release in the NAc (Lodge and Grace, 2005). Despite the evidence above, the role

of CRF1R and CRF2R on DA releasing remains controversial. Some studies indicated that CRF2R also was involved in the mediation of cocaine reinstatement, and the neuronal process of releasing DA and glutamate in the VTA (Wise and Morales, 2010). The footshock-induced reinstatement of cocaine-seeking was reported to be decreased by the VTA perfusion of CRF2R antagonists but not selective CRF1R antagonists (Mantsch et al., 2016), and cocaine induced a significant increase of VTA DA extracellular levels in the repeated stress rats at the presence of CRF1R antagonists (Sotomayor-Zárate et al., 2015). This discrepancy was ascribed to the distinct mechanisms underlying different abused drugs, and we speculate that the activation of CRF on the mesolimbic DA system might go through CRF1R but not CRF2R (Almela et al., 2012), all these needs to be further determined.

The mPFC is another vital site in the brain that contributes to drug addiction, innervating the VTA with glutamatergic efferent and receiving dopaminergic afferent (Tzschentke and Schmidt, 2003; Keramatian et al., 2019). Corticotropin-releasing factor receptor-1 is considered as the primary functional receptor subtype in the prefrontal cortex (PFC) (Perrin et al., 1995). We speculate that the mPFC may be inactivated after the central administration of the selective CRF1R antagonist antalarmin, and then causes the subsequent inhibition of dopaminergic neurons in the VTA, thereby resulting in the reduction in DA release in the NAc. In addition, CRF was reported to induce the rapid phosphorylation of the cyclic-AMP response element-binding protein (CREB) *via* the activation of CRF1R, while CRF2R played no discernable role (Stern et al., 2011). Along with the signaling pathway, NMDAR-D1R/ERK/CREB in the NAc was indicated to regulate reward-seeking behaviors (Kirschmann et al., 2014), and our previous findings stated that propofol self-administration behavior was regulated by ERK1/2 in the NAc (Wang et al., 2016). Therefore, we presume that the mediation of CRF1R on the D1R/ERK1/2/CREB signal pathway may be underlying the molecular mechanisms. This postulation is supported by our results in this study that the expression of D1R in the NAc was significantly inhibited by CRF1R antagonist antalarmin, but the effects on the expression on ERK1/2 and CREB needs to be examined in the following study. Although the tail clip-induced propofol self-administration behavior and expression of D1R in the NAc were not affected by the central pretreatment of RU486 in this study, our published study reported that both were attenuated by the systemic administration of RU486 (Wu et al., 2016). We believe that the difference in the approaches of agent delivery, doses, and the methods in establishing the propofol self-administration model might lead to the distinction on D1R expression in the NAc and propofol self-administration behavior.

Corticotropin-releasing factor receptors also take part in food addiction. The pretreatment with antalarmin reduced the stress-induced reinstatement of palatable food-seeking (Ghitza et al., 2006), but some other studies reported that the antagonism of CRF1R with R121919 or CP-154526 did not affect the response to food (Goeders and Guerin, 2000; Roberto et al., 2017). And we also found that sucrose self-administration was not affected by either tail clip stressful stimulation or the pretreatments of antalarmin, antisauvagine 30, or RU486. This seems to be contradictory between the previous findings and our study, which might be ascribed to the different food addiction testing models and the distinction of the mechanisms underlying the stage of self-administration and reinstatement in food addiction.

The limitations of this study should be mentioned. As previous studies indicated, the DA release in the NAc and VTA is regulated by CRF and may be a potential for CRF receptor mediating propofol self-administration behavior, we only detected the D1R expression in the NAc, but the changes of dopamine concentration and the downstream signal pathway of D1R in the NAc were not examined. Beyond that, the neuroadaptation in the VTA that is modulated by the glutamatergic afferent from the mPFC, the interactions between the presynaptic glutamate afferent, and the CRF receptor on postsynaptic on dopaminergic neurons in the VTA is also unclear. All these questions will be elucidated in the future.

CONCLUSION

In conclusion, this study provides clear evidence that propofol self-administration behavior was facilitated by stressful stimulation, which could be inhibited by the central antagonism of CRF1R, not CRF2R or GR, and the neuronal process is mediated by the DA D1R in the NAc. This study emphasizes the role of CRF1R in the central reward processing and moreover, indicated that the CRF1R antagonist may provide a new therapeutic approach for the treatment of propofol addiction.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The animal study was reviewed and approved by the Animal Care and Use Committee of Wenzhou Medical University.

AUTHOR CONTRIBUTIONS

BW, QL, and WZ were responsible for the study concept, design and assisted the interpretation of findings. ZD, GZ, SX, ZC, and BH contributed to the acquisition of animal data. BW and CJ performed the data analysis. BW, ZD, CJ, and YL drafted the manuscript. All authors critically reviewed content and approved version for final publication.

FUNDING

This research was supported by projects of the Natural Science Foundation of Zhejiang Province (Y22H092508), the National Natural Science Foundation of China (81801320), and the Medical Health Science and Technology Project of Zhejiang Province (2022RC050).

REFERENCES

Almela, P., Navarro-Zaragoza, J., García-Carmona, J. A., Mora, L., Hidalgo, J., Milanés, M. V., et al. (2012). Role of corticotropin-releasing factor (CRF) receptor-1 on the catecholaminergic response to morphine withdrawal in the nucleus accumbens (NAc). *PLoS One* 7:e47089. doi: 10.1371/journal.pone.0047089

Baumgartner, H. M., Schulkin, J., and Berridge, K. C. (2021). Activating Corticotropin-Releasing Factor Systems in the Nucleus Accumbens, Amygdala, and Bed Nucleus of Stria Terminalis: incentive Motivation or Aversive Motivation? *Biol. Psychiatry* 89, 1162–1175. doi: 10.1016/j.biopsych.2021.01.007

Biagioni, F., Busceti, C. L., Molinaro, G., Battaglia, G., Giorgi, F. S., Ruggieri, S., et al. (2006). Dopamine stimulation *via* infusion in the lateral ventricle. *Ann. N. Y. Acad. Sci.* 1074, 337–343. doi: 10.1196/annals.1369.031

Blacktop, M., Seubert, C., Baker, D. A., Ferda, N., Lee, G., Graf, E. N., et al. (2011). Augmented cocaine seeking in response to stress or CRF delivered into the ventral tegmental area following long-access self-administration is mediated by CRF receptor type 1 but not CRF receptor type 2. *J. Neurosci.* 31, 11396–11403. doi: 10.1523/JNEUROSCI.1393-11.2011

Boyson, C. O., Holly, E. N., Shimamoto, A., Albrechet-Souza, L., Weiner, L. A., DeBold, J. F., et al. (2014). Social stress and CRF-dopamine interactions in the VTA: role in long-term escalation of cocaine self-administration. *J. Neurosci.* 34, 6659–6667. doi: 10.1523/JNEUROSCI.3942-13.2014

Boyson, C. O., Miguel, T. T., Quadros, I. M., Debold, J. F., and Miczek, K. A. (2011). Prevention of social stress-escalated cocaine self-administration by CRF-R1 antagonist in the rat VTA. *Psychopharmacology* 218, 257–269. doi: 10.1007/s00213-011-2266-8

Dong, Z., Huang, B., Jiang, C., Chen, J., Lin, H., Lian, Q., et al. (2021). The adenosine A2A receptor activation in nucleus accumbens suppress cue-induced reinstatement of propofol self-administration in rats. *Neurochem. Res.* 46, 1081–1091. doi: 10.1007/s11064-021-03238-9

Earley, P. H., and Finver, T. (2013). Addiction to propofol: a study of 22 treatment cases. *J. Addict. Med.* 7, 169–176. doi: 10.1097/ADM.0b013e3182872901

Erb, S., Petrovic, A., Yi, D., and Kayyali, H. (2006). Central injection of CRF reinstate cocaine seeking in rats after postinjection delays of up to 3h: an influence of time and environmental context. *Psychopharmacology* 187, 112–120. doi: 10.1007/s00213-006-0392-5

Filip, M., and Frankowska, M. (2007). Effects of GABA(B) receptor agents on cocaine priming, discrete contextual cue and food induced relapse. *Eur. J. Pharmacol.* 571, 166–173. doi: 10.1016/j.ejphar.2007.05.069

Fry, R. A., Fry, L. E., and Castanelli, D. J. (2015). A restrospective survey of substance abuse in anaesthetists in Australia and New Zealand from 2004 to 2013. *Anaesth. Intensive Care* 43, 111–117. doi: 10.1177/0310057X1504300117

Ghitza, U. E., Gray, S. M., Epstein, D. H., Rice, K. C., and Shaham, Y. (2006). The anxiogenic drug yohimbine reinstates palatable food seeking in a rat relapse model: a role of CRF1 receptors. *Neuropsychopharmacology* 31, 2188–2196. doi: 10.1038/sj.npp.1300964

Goebel-Stengel, M., Stengel, A., Wang, L., and Taché, Y. (2014). Orexigenic response to tail pinch: role of brain NPY(1) and corticotropin releasing factor receptor. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 306, R164–R174. doi: 10.1152/ajpregu.00335.2013

Goeders, N. E., and Guerin, G. F. (2000). Effects of the CRH receptor antagonist CP-154,526 on intravenous cocaine self-administration in rats. *Neuropsychopharmacology* 23, 577–586.

Hupalo, S., Bryce, C. A., Bangasser, D. A., Berridge, C. W., Valentino, R. J., and Floresco, S. B. (2019). Corticotropin-releasing factor (CRF) circuit modulation of cognition and motivation. *Neurosci. Biobehav. Rev.* 103, 50–59. doi: 10.1016/j.neubiorev.2019.06.010

Kelly, E. A., and Fudge, J. L. (2018). The neuroanatomic complexity of the CRF and DA systems and their interface: what we still don't know. *Neurosci. Biobehav. Rev.* 90, 247–259. doi: 10.1016/j.neubiorev.2018.04.014

Keramatian, A., Alaei, H., Eidi, A., and Radahmadi, M. (2019). Electrical stimulation mPFC affects morphine addiction by changing glutamate concentration in the ventral tegmental area. *Metab. Brain Dis.* 34, 1171–1180. doi: 10.1007/s11011-019-00426-z

Kirschmann, E. K., Mauna, J. C., Willis, C. M., Foster, R. L., Chipman, A. M., and Thiels, E. (2014). Appetitive cue-evoked ERK signaling in the nucleus accumbens requires NMDA and D1 dopamine receptor activation and regulates CREB phosphorylation. *Learn. Mem.* 21, 606–615. doi: 10.1101/lm.035113.114

Koob, G. F. (1999). The role of the striatopallidal and extended amygdala systems in drug addiction. *Ann. N. Y. Acad. Sci.* 877, 445–460. doi: 10.1111/j.1749-6632.1999.tb09282.x

Koob, G. F. (2010). The role of CRF and CRF-related peptides in the dark side of addiction. *Brain Res.* 1314, 3–14. doi: 10.1016/j.brainres.2009.11.008

Koob, G. F., and Volkow, N. D. (2010). Neurocircuitry of addiction. *Neuropsychopharmacology* 35, 217–238. doi: 10.1038/npp.2009.110

Lasheras, M. S., Laorden, M. L., Milanés, M. V., and Núñez, C. (2015). Corticotropin-releasing factor 1 receptor mediates the activity of the reward system evoked by morphine-induced conditioned place preference. *Neuropharmacology* 95, 168–180. doi: 10.1016/j.neuropharm.2014.12.021

Lê, A. D., Harding, S., Juzytsch, W., Fletcher, P. J., and Shaham, Y. (2002). The role of corticotropin-releasing factor in the median raphe nucleus in relapse to alcohol. *J. Neurosci.* 22, 7844–7849. doi: 10.1523/JNEUROSCI.22-18-07844.2002

Lee, S., Hwang, E., Lee, D., and Choi, J. H. (2017). Plus-train simulation of primary somatosensory cortex blocks pain perception in tail clip test. *Exp. Neurobiol.* 26, 90–96. doi: 10.5607/en.2017.26.2.90

Lemos, J. C., Wanat, M. J., Smith, J. S., Reyes, B. A., Hollon, N. G., Van Bockstaele, E. J., et al. (2012). Severe stress switches CRF action in the nucleus accumbens from appetitive to aversive. *Nature* 490, 402–406. doi: 10.1038/nature11436

Lian, Q., Wang, B., Zhou, W., Jin, S., Xu, L., Huang, Q., et al. (2013). Self-administration of propofol is mediated by dopamine D1 receptor in nucleus accumbens in rats. *Neuroscience* 231, 373–383. doi: 10.1016/j.neuroscience.2012.11.002

Liu, Y., Jean-Richard-Dit-Bressel, P., Yau, J. Q., Willing, A., Prasad, A. A., Power, J. M., et al. (2020). The Mesolimbic dopamine activity signatures of relapse to alcohol-seeking. *J. Neurosci.* 40, 6409–6427. doi: 10.1523/JNEUROSCI.0724-20.2020

Lodge, D. J., and Grace, A. A. (2005). Acute and chronic corticotropin-releasing factor 1 receptor blockade inhibits cocaine-induced dopamine release: correlation with dopamine neurons activity. *J. Pharmacol. Exp. Ther.* 314, 201–206. doi: 10.1124/jpet.105.084913

Mantsch, J. R., Baker, D. A., Funk, D., Lê, A. D., and Shaham, Y. (2016). Stress-induced reinstatement of drug seeking: 20 years of progress. *Neuropsychopharmacology* 41, 335–356. doi: 10.1038/npp.2015.142

McAulliffe, P. F., Gold, M. S., Bajpai, L., Merves, M. L., Frost-Pineda, K., Pomm, R. M., et al. (2006). Second-hand exposure to aerosolized intravenous anesthetics propofol and fentanyl may cause sensitization and subsequent opiate addiction among anesthesiologist and surgeons. *Med. Hypotheses* 66, 874–882. doi: 10.1016/j.mehy.2005.10.030

Newman, E. L., Leonard, A. Z., Arena, D. T., de Almeida, R. M. M., and Miczek, K. A. (2018). Social defeat stress and escalation of cocaine and alcohol consumption: focus on CRF. *Neurobiol. Stress* 9, 151–165. doi: 10.1016/j.ynstr.2018.09.007

Park, H. J., Shin, J. Y., Kim, M. H., and Park, B. J. (2015). Increased use in propofol and reported patterns of adverse events among in Korea. *Regul. Toxicol. Pharmacol.* 73, 478–483. doi: 10.1016/j.yrtph.2015.02.001

Paxinos, G., and Waston, G. (2007). *The rat brain in stereotaxic coordinates*, 6th Edn. New York: Elsevier Academic Press.

Perrin, M., Donaldson, C., Chen, R., Blount, A., Berggren, T., Bilezikjian, L., et al. (1995). Identification of a second corticotropin – releasing factor receptor gene and characterization of a cDNA expressed in heart. *Proc. Natl. Acad. Sci. U. S. A.* 92, 2969–2973. doi: 10.1073/pnas.92.7.2969

Roberto, M., Spierling, S. R., Kirson, D., and Zorrilla, E. P. (2017). Corticotropin-Releasing Factor (CRF) and Addictive Behaviors. *Int. Rev. Neurobiol.* 136, 5–51. doi: 10.1016/bs.irn.2017.06.004

Shaham, Y., Funk, D., Erb, S., Brown, T. J., Walker, C. D., and Stewart, J. (1997). Corticotropin-releasing factor, but not corticosterone, is involved in stress-induced relapse to heroin-seeking in rats. *J. Neurosci.* 17, 2605–2614. doi: 10.1523/JNEUROSCI.17-07-02605.1997

Sinha, R. (2008). Chronic stress, drug abuse, and vulnerability to addiction. *Ann. N. Y. Acad. Sci.* 1141, 105–130. doi: 10.1196/annals.1441.030

Sotomayor-Zárate, R., Abarca, J., Araya, K. A., Renard, G. M., Andrés, M. E., and Gysling, K. (2015). Exposure to repeated immobilization stress inhibits cocaine-induced increase in dopamine extracelluar levels in the rat ventral

tegmental area. *Pharmacol. Res.* 101, 116–123. doi: 10.1016/j.phrs.2015.08.015

Steger, J. S., Land, B. B., Lemos, J. C., Chavkin, C., and Phillips, P. E. M. (2020). Insidious transmission of a stress-related neuroadaptation. *Front. Behav. Neurosci.* 14:564054. doi: 10.3389/fnbeh.2020.564054

Stern, C. M., Luoma, J. I., Meitzen, J., and Mermelstein, P. G. (2011). Corticotropin releasing factor-induced CREB activation in striatal neurons occurs *via* a novel Gβγ signaling pathway. *PLoS One* 6:e18114. doi: 10.1371/journal.pone.0018114

Tan, L. A., Vaughan, J. M., Perrin, M. H., Rivier, J. E., and Sawchenko, P. E. (2017). Distribution of corticotropin-releasing factor (CRF) receptor binding in the mouse brain using a new, high-affinity radioligand, [^{125}I]-PD-Sauvagine. *J. Comp. Neurol.* 525, 3840–3864. doi: 10.1002/cne.24307

Taslimi, Z., Sarihi, A., and Haghparast, A. (2018). Glucocorticoid receptors in the basolateral amygdala mediated the restraint stress-induced reinstatement of methamphetamine-seeking behaviors in rats. *Behav. Brain Res.* 348, 150–159. doi: 10.1016/j.bbr.2018.04.022

Tzschentke, T. M., and Schmidt, W. J. (2003). Glutamatergic mechanisms in addiction. *Mol. Psychiatry* 8, 373–382. doi: 10.1038/sj.mp.4001269

Valdez, G. R., Sabino, V., and Koob, G. F. (2004). Increased anxiety-like behavior and ethanol self-administration in dependent rats: reversal *via* corticotropin-releasing factor-2 receptor activation. *Alcohol. Clin. Exp. Res.* 28, 865–872. doi: 10.1097/01.alc.0000128222.29875.40

Van Pett, K., Viau, V., Bittencourt, J. C., Chan, R. K., Li, H. Y., Arias, C., et al. (2000). Sawchenko, Distribution of mRNAs encoding CRF receptors in brain and pituitary of rat and mouse. *J. Comp. Neurol.* 428, 191–212.

Wanat, M. J., Hopf, F. W., Stuber, G. D., Phillips, P. E., and Bonci, A. (2008). Corticotropin-releasing factor increases mouse ventral tegmental area dopamine neuron firing through a protein kinase C-dependent enhancement. *J. Physiol.* 586, 2157–2170. doi: 10.1113/jphysiol.2007.150078

Wang, B., Shaham, Y., Zitzman, D., Azari, S., Wise, R. A., and You, Z. B. (2005). Cocaine experience establishes control of midbrain glutamate and dopamine by corticotropin-releasing factor: a role in stress-induced relapse to drug seeking. *J. Neurosci.* 25, 5389–5396. doi: 10.1523/JNEUROSCI.0955-05.2005

Wang, B., Yang, X., Sun, A., Xu, L., Wang, S., Lin, W., et al. (2016). Extracelluar signal-regulated kinase in nucleus accumbens mediates propofol self-administration in rats. *Neurosci. Bull.* 32, 531–537. doi: 10.1007/s12264-016-0066-1

Wischmeyer, P. E., Johnson, B. R., Wilson, J. E., Dingmann, C., Bachman, H. M., Roller, E., et al. (2007). A survey of propofol abuse in academic anesthesia programs. *Anesth. Analg.* 105, 1066–1071. doi: 10.1213/01.ane.0000270215.86253.30

Wise, R. A., and Morales, M. (2010). A ventral tegmental CRF-glutamate-dopamine interaction in addiction. *Brain Res.* 1314, 38–43. doi: 10.1016/j.brainres.2009.09.101

Wu, B., Liang, Y., Dong, Z., Chen, Z., Zhang, G., Lin, W., et al. (2016). Glucocorticoid receptor mediated the propofol self-administration by dopamine D1 receptor in nucleus accumbens. *Neuroscience* 328, 184–193.

Wu, B., Lin, W., Wang, H., Abdullah, T., Wang, B., Su, Y., et al. (2018). Glucocorticoid receptor in rat nucleus accumbens: its roles in propofol addictions. *Neurosci. Lett.* 662, 115–121. doi: 10.1016/j.neulet.2017.10.011

Yarur, H. E., Vega-Quiroga, I., González, M. P., Noches, V., Thomases, D. R., Andrés, M. E., et al. (2020). Inhibitory control of basolateral amygdalar transmission to the prefrontal cortex by local corticotropin type 2 receptor. *Int. J. Neuropsychopharmacol.* 23, 108–116. doi: 10.1093/ijnp/pyz065

Zhou, W., Liu, H., Zhang, F., Tang, S., Zhu, H., Lai, M., et al. (2007). Role of acetylcholine transmission in nucleus accumbens and ventral tegmental area in heroin-seeking induced by conditioned cues. *Neuroscience* 144, 1209–1218. doi: 10.1016/j.neuroscience.2006.11.013

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Behavioral Neuroscience

ORIGINAL RESEARCH
published: 13 January 2022
doi: 10.3389/fnbeh.2021.796502

Choice Bundling Increases Valuation of Delayed Losses More Than Gains in Cigarette Smokers

Jeffrey S. Stein[1,2], Jeremiah M. Brown[1,2], Allison N. Tegge[1], Roberta Freitas-Lemos[1], Mikhail N. Koffarnus[3], Warren K. Bickel[1] and Gregory J. Madden[4]*

[1] Fralin Biomedical Research Institute at VTC, Roanoke, VA, United States, [2] Department of Human Nutrition, Foods, and Exercise, Virginia Tech, Blacksburg, VA, United States, [3] Department of Family and Community Medicine, University of Kentucky, Lexington, KY, United States, [4] Department of Psychology, Utah State University, Logan, UT, United States

Choice bundling, in which a single choice produces a series of repeating consequences over time, increases valuation of delayed monetary and non-monetary gains. Interventions derived from this manipulation may be an effective method for mitigating the elevated delay discounting rates observed in cigarette smokers. No prior work, however, has investigated whether the effects of choice bundling generalize to reward losses. In the present study, an online panel of cigarette smokers (N = 302), recruited using survey firms Ipsos and InnovateMR, completed assessments for either monetary gains or losses (randomly assigned). In Step 1, participants completed a delay-discounting task to establish Effective Delay 50 (ED50), or the delay required for an outcome to lose half of its value. In Step 2, participants completed three conditions of an adjusting-amount task, choosing between a smaller, sooner (SS) adjusting amount and a larger, later (LL) fixed amount. The bundle size (i.e., number of consequences) was manipulated across conditions, where a single choice produced either 1 (control), 3, or 9 consequences over time (ascending/descending order counterbalanced). The delay to the first LL amount in each condition, as well as the intervals between all additional SS and LL amounts (where applicable), were set to individual participants' ED50 values from Step 1 to control for differences in discounting of gains and losses. Results from Step 1 showed significantly higher ED50 values (i.e., less discounting) for losses compared to gains ($p < 0.001$). Results from Step 2 showed that choice bundling significantly increased valuation of both LL gains and losses ($p < 0.001$), although effects were significantly greater for losses ($p < 0.01$). Sensitivity analyses replicated these conclusions. Future research should examine the potential clinical utility of choice bundling, such as development of motivational interventions that emphasize both the bundled health gains associated with smoking cessation and the health losses associated with continued smoking.

Keywords: choice bundling, sign effect, intertemporal choice, delay discounting, cigarette smoking, impulsive choice, choice bracketing

OPEN ACCESS

Edited by:
Rafal Rygula, Polish Academy of Sciences (IF PAS), Poland

Reviewed by:
David P. Jarmolowicz, University of Kansas, United States
Sally Huskinson, University of Mississippi Medical Center, United States

****Correspondence:***
Jeffrey S. Stein
jstein1@vtc.vt.edu

Specialty section:
This article was submitted to Motivation and Reward, a section of the journal Frontiers in Behavioral Neuroscience

Received: *16 October 2021*
Accepted: *21 December 2021*
Published: *13 January 2022*

Citation:
Stein JS, Brown JM, Tegge AN, Freitas-Lemos R, Koffarnus MN, Bickel WK and Madden GJ (2022) Choice Bundling Increases Valuation of Delayed Losses More Than Gains in Cigarette Smokers. Front. Behav. Neurosci. 15:796502. doi: 10.3389/fnbeh.2021.796502

INTRODUCTION

Behavioral outcomes are devalued as a function of the delay until they are experienced (for review, see Odum, 2011). This process, known as delay discounting, is reliably associated with cigarette smoking (for meta-analysis, see MacKillop et al., 2011; Amlung et al., 2016) and other tobacco use (e.g., Stein et al., 2018a; DeHart et al., 2020). For example, high discounting rates for delayed monetary gains are cross-sectionally associated with smoking status (e.g., Mitchell, 1999) and longitudinally predict both smoking initiation (Audrain-McGovern et al., 2009) and relapse following smoking cessation treatment (e.g., Yoon et al., 2007; Sheffer et al., 2014). These findings indicate that delay discounting is a potential therapeutic target in tobacco cessation (Riddle and Science of Behavior Change Working Group, 2015), in which interventions that increase valuation of delayed outcomes may also reduce cigarette smoking (e.g., Stein et al., 2016, 2018b; Chiou and Wu, 2017). Thus, understanding how delay discounting influences intertemporal choice between smaller, sooner (SS) and larger, later (LL) outcomes is critical and may lead to efficacious interventions for tobacco use.

A large and growing literature has explored the effects of various behavioral, pharmacological, and neurocognitive interventions on delay discounting. The intertemporal choices arranged in these studies involve economic gains, such as monetary and food rewards (for reviews, see Perry and Carroll, 2008; Bickel et al., 2017; Rung and Madden, 2018). However, remarkably few studies have explored the effects of these interventions on choices involving economic losses. This is concerning, as at least three sets of findings suggest that intervention effects on gains may not generalize to losses. First, losses are discounted at a lower rate than gains of an equivalent size (i.e., the "sign effect"; Thaler, 1981; Benzion et al., 1989; Murphy et al., 2001; Estle et al., 2006); thus, interventions may prove ineffective with losses due to a ceiling effect. Second, although discounting of losses is associated with cigarette smoking in a manner similar to that of gains (Odum et al., 2002; Baker et al., 2003; Johnson et al., 2007), prior research reveals mixed findings on whether discounting rates for gains and losses are correlated (Chapman, 1996; Hardisty and Weber, 2009; Mitchell and Wilson, 2010; Harris, 2012). Third, and finally, the commonly reported inverse relationship between discount rate and amount of the outcome (i.e., the "magnitude effect") appears less robust for losses than for gains (Estle et al., 2006; Mitchell and Wilson, 2010; Green et al., 2014). Collectively, these findings suggest the presence of one or more processes, secondary to discounting, that differ between valuation of delayed gains and losses. Thus, further research investigating whether valuation of delayed gains and losses are amenable to the same interventions is warranted. Knowledge gained from these studies may help guide whether clinical interventions for tobacco use should focus on enhancing sensitivity to the delayed health gains associated with smoking cessation, the delayed health losses associated with continued smoking, or both.

Delay Discounting of Gains and Losses

The extent to which the value of an outcome (gain or loss) is devalued with increasing delay is generally well-described by the following hyperbolic form (Mazur, 1987):

$$V = \frac{A}{1 + kD} \tag{1}$$

where V is the subjective value of an outcome, A is its objective amount, D is its delay, and k is a free parameter that describes the nonlinear rate of discounting. This model may be used to predict intertemporal choice between SS and LL outcomes. When the outcomes are gains, choice is allocated to the option that maximizes subjective benefit. In contrast, when the outcomes are losses, choice is allocated to the option that minimizes subjective harm.

Consider a choice between receiving either \$450 now or \$900 in 1 year. The SS gain is available immediately and, thus, is not discounted—its subjective value is equal to its nominal value (\$450). In contrast, the LL gain (\$900) is discounted according to the prevailing value of k (determined by both trait and state factors; Odum and Baumann, 2010). If $k = 0.003$, for example, the subjective value (V) from Equation 1 of the \$900 LL reward would be \$429.59. Here, preference for the SS monetary gain is predicted because it provides a larger gain (\$450) than the subjective value of the LL option (\$429.59). In contrast, if this same choice were instead between *losing* either \$450 now or \$900 in 1 year, then preference for the LL option is predicted because it minimizes subjective loss (\$429.59) compared to the SS option (\$450).

Choice Bundling of Gains and Losses

As originally noted by Ainslie (1975, 2001), a prediction unique to hyperbolic (as opposed to exponential) delay discounting is that conditions in which a single choice produces a series of repeating SS or LL outcomes (i.e., a choice bundle) can increase relative preference for the LL option compared to equivalent choices for unbundled (single) outcomes. This is due to the non-constant rate of devaluation in hyperbolic discounting in which value is lost quickly at short delays and more slowly at long delays. When a single choice produces repeating outcomes, the relatively stable subjective values of individual LL outcomes sum to a larger value than the sum of individual SS outcomes (for further discussion, see Ainslie, 2001; Ashe and Wilson, 2020; Stein and Madden, 2021).

This effect of choice bundling on delay discounting is predicted quantitatively by an additive model of hyperbolic discounting (Mazur, 1986, 1989):

$$V_{bundle} = \sum_{i=1}^{n} \left(\frac{A}{1 + kD} \right) \tag{2}$$

in which the subjective value of a bundled series of outcomes (V_{bundle}) is equal to the summed values of all rewards in the bundle (all parameters are as described for Equation 1). For example, consider again the (unbundled) choice between receiving \$450 now or \$900 in 1 year. When $k = 0.003$, choice

for the SS option is predicted because its undiscounted value ($450) exceeds the subjective value of the LL option ($429.59). In contrast, if these same amounts ($450 and $900) were distributed equally across a series of repeating rewards and the choice were instead between receiving either (a) a SS bundle of $150 now, $150 in 1 year, and $150 in 2 years or (b) a LL bundle of $300 in 1 year, $300 in 2 years, and $300 in 3 years, the summed subjective values (V_{bundle}) of the SS and LL options would now be $268.62 and $307.25, respectively. Thus, choice bundling is predicted to shift preference toward the LL over the SS gains, even though neither the absolute nor the relative differences between these amounts have changed. Likewise, if this same choice were instead between bundled losses, choice bundling is predicted to shift preference toward the SS over the LL losses.

Several studies have offered empirical support for this predicted effect of choice bundling (for review, see Ashe and Wilson, 2020), showing that bundling increases preference for LL gains (money and/or food) in both humans (Kirby and Guastello, 2001; Hofmeyr et al., 2011) and nonhumans (Ainslie and Monterosso, 2003; Stein et al., 2013). These include a recent study from our group (Stein and Madden, 2021) showing in an online sample from the general population (N = 252) that the efficacy of choice bundling is enhanced by increasing the number of rewards in the choice bundle (for a similar finding in rats, see Stein et al., 2013). Observed effects in this online study also approximated those predicted by the additive model of hyperbolic discounting (Equation 2).

Despite these encouraging results, more work remains to be done. Specifically, no prior studies have investigated if comparable effects of choice bundling can be achieved with losses. Equation 2 makes no distinction between gains and losses but, as previously noted, some degree of discordance

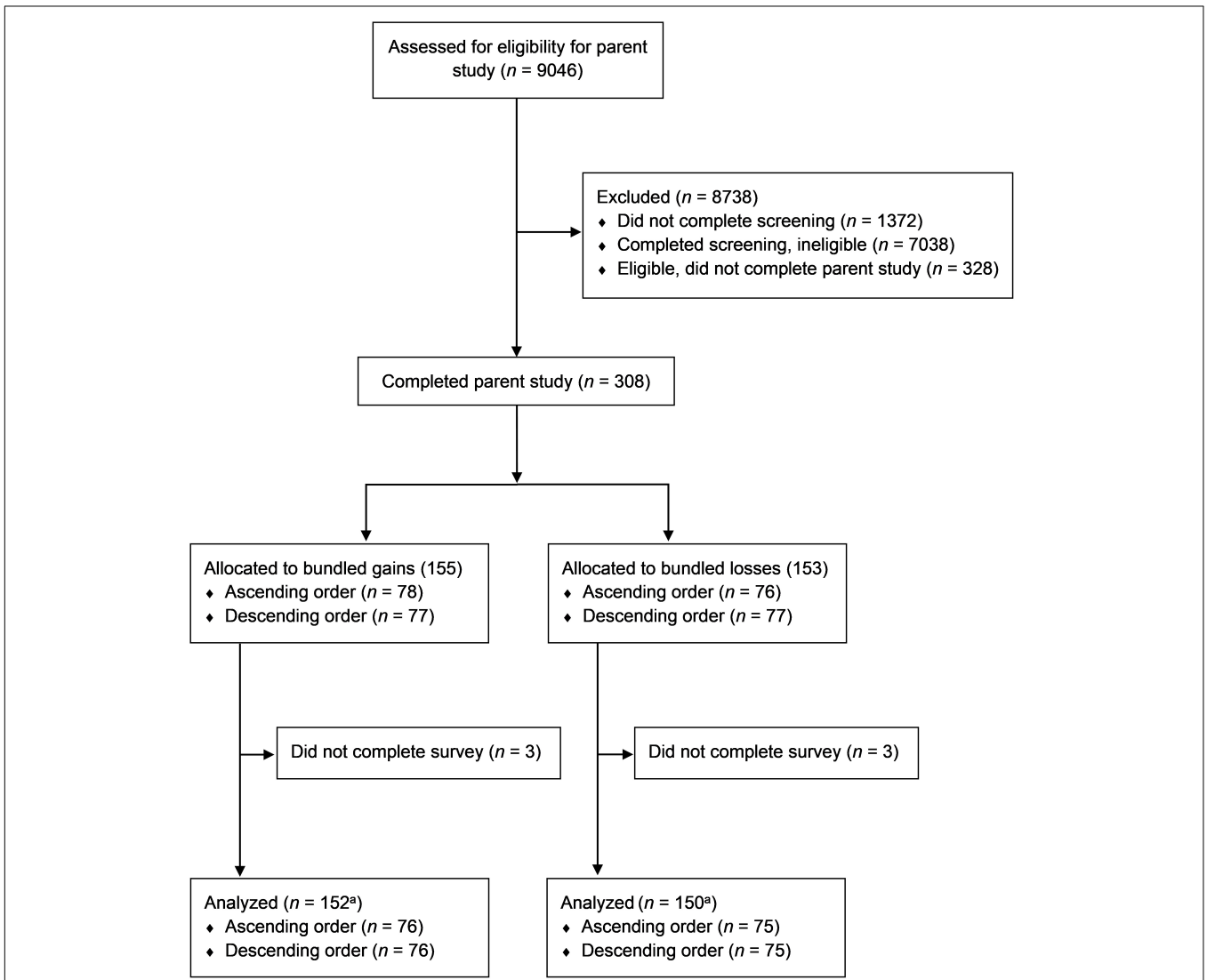


FIGURE 1 | CONSORT flow diagram showing participant flow through study screening, group allocation, and data analysis. [a]Denotes sample size in primary analysis. Subsets of this sample were used in sensitivity analyses (see text for details).

characterizes the discounting of delayed gains and losses (i.e., the "sign effect"; Thaler, 1981; Benzion et al., 1989; Murphy et al., 2001; Estle et al., 2006). In addition, only one study to our knowledge has investigated choice bundling in clinical populations (cigarette smokers; Hofmeyr et al., 2011) who may benefit from interventions to mitigate high discounting rates. Accordingly, the present study used a mixed between- and within-subjects design to examine the effects of choice bundling on valuation of delayed gains and losses in an online panel of cigarette smokers. We did so using an adaptive, two-step procedure in which we: (1) assessed delay discounting to establish individual participants' values of Effective Delay 50 (ED50), or the delay required for an outcome to lose half of its value (Yoon and Higgins, 2008), and (2) used these participant-specific ED50 values to inform the delays experienced in the choice bundling assessments in order to control for differences in discounting of gains and losses.

MATERIALS AND METHODS

A US-based panel of cigarette smokers (N = 308) were recruited by market research firms, Ipsos (iSay panel[1]) and InnovateMR,[2] for a separate parent study examining the effects of cigarette and nicotine vaping product flavor restrictions on hypothetical tobacco product purchasing. Ipsos distributed the survey to panelists in July and August 2021. Both the parent and present study were registered on www.clinicaltrials.gov (NCT05110872 and NCT05110716, respectively).Participants first completed a brief screening questionnaire in which they reported their smoking history, current smoking status, usual brand of cigarette, and age. To be eligible for both the parent and present study, participants were required to: (1) currently smoke at least 10 cigarettes per day, (2) have smoked at least 100 cigarettes in their lifetime, and (3) be 21 years of age or older. Menthol and non-menthol smokers were recruited in approximately equal numbers.

After screening, eligible participants first completed procedures for the parent study. These included multiple conditions in the Experimental Tobacco Marketplace (for review, see Bickel et al., 2018), in which they made hypothetical tobacco product purchases while the price of cigarettes and the available tobacco product flavors were varied. Following completion of these procedures, participants were randomly assigned in the present study to complete assessments for either monetary gains (n = 155) or losses (n = 153) and completed relevant procedures, described below (section "Procedures").

The numbers of participants who screened for, completed, and were analyzed for the present study are provided in **Figure 1**. Note that six participants did not complete the study (n = 3 each from gains and losses groups), leaving a final analytic sample of N = 302. Participants required a median time of 36.95 min to complete the full survey (interquartile range: 29.47–55.78) and received the equivalent of $8.57–$14.28 of monetary compensation in the form of virtual currencies (e.g., online and mobile gift cards).

[1] social.i-say.com

[2] innovatemr.com/panels/consumer-panel

Procedures

Study procedures were implemented using Qualtrics online survey software (Qualtrics, Provo, UT, United States). All procedures were reviewed and approved by the Virginia Tech Institutional Review Board. Informed consent was implied through completion of the survey.

Step 1: Assessment of Delay Discounting

Delay discounting was assessed using a version of the recently developed six-trial, adjusting-delay task (Koffarnus et al., 2021). This task was modified from the similar and commonly used five-trial, adjusting-delay task (Koffarnus and Bickel, 2014) to provide greater range and resolution in measurement of ED50 (and k). Specifically, whereas the original five-trial task provides the ability to measure only 32 possible ED50 values ranging from 1 h to 25 years, the six-trial task allows measurement of 64 possible ED50 values. In the version used in the present study, possible ED50 values ranged from 4 s to 90 years in approximately logarithmic intervals. We note, however, that these values in the original version of the six-trial task developed by Koffarnus et al. (2021) range from 5 s to 65 years.

Participants were presented with repeated, hypothetical choices between receiving or losing (depending on group) a larger amount ($900) after a delay and half of this amount ($450) immediately. The delay to the LL amount started at 1 day on the first trial and was adjusted following each trial, based on the preceding choice. Specifically, in the gains task, choices for the larger amount increased the delay, and choices for the smaller amount decreased the delay, on the next trial; in the losses task, this relationship was reversed. The adjusted value after the final trial was the delay expected to produce indifference between options and provided a measure of ED50. Higher values of ED50 reflect less discounting of the delayed outcome. Additional details regarding this task, including the task instructions, logic for trial branching, and method for scoring ED50 and k, are provided in **Supplementary Material**.

Step 2: Assessment of Choice Bundling Effects

Participants completed three conditions of an adjusting-amount task, modified from those used previously (Du et al., 2002; Athamneh et al., 2017) to allow assessment of choice bundling effects. The instructions participants read prior to the task are provided in **Supplementary Material**.

As depicted in **Figure 2**, the bundle size (i.e., number of consequences) was manipulated across conditions, where a single choice produced either 1 (control), 3, or 9 outcomes (gains or losses) over time. Participants completed these bundle-size conditions in either ascending or descending order (counterbalanced). Each condition featured six trials in which participants chose between receiving or losing (depending on group) either LL fixed amounts or adjusting SS amounts. The total amount of the LL option equaled $900. This value was divided equally among all gains/losses in the bundle (see

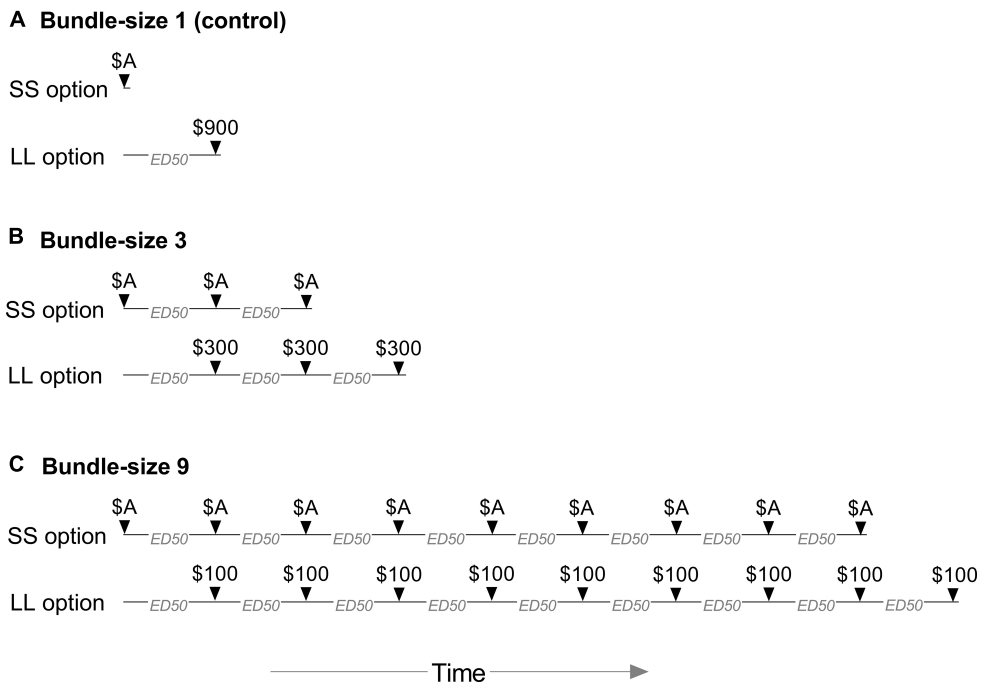


FIGURE 2 | Choices in the adjusting-amount task between the smaller, sooner (SS) and larger, later (LL) options in the bundle-size 1 (control), 3, and 9 conditions. The total monetary value (gain or loss, depending on group) of the SS adjusting amount (A) started at $450 on the first trial and was adjusted after each trial until reaching an indifference point. The delays to the first LL consequence, as well as the intervals between all SS and LL consequences, were set to individual participants' Effective Delay 50 (ED50) values from the six-trial, adjusting-delay task.

Figure 2) in order to hold the amounts constant across bundle-size conditions. This procedure controlled for the "magnitude effect" in delay discounting research, in which degree of discounting is inversely related to amount (e.g., Estle et al., 2006; for further discussion relevant to choice bundling, see Stein and Madden, 2021).

The total SS amount was also divided equally among all gains/losses in the bundle. This value started at $450 on the first trial in each condition and was adjusted following each of six trials, based on the preceding choice, according to procedures described previously (Du et al., 2002). In the gains task, choices for the LL option increased the total SS amount, and choices for the SS option decreased the total SS amount, on the next trial. In the losses task, this relationship was again reversed. The size of these adjustments (up or down) started at $225 after the first trial (half of the SS amount) and was reduced by half at each subsequent trial ($112.50 after the second trial, $56.25 after the third trial, etc.). The total adjusted amount after the final, sixth trial served as the indifference point, with higher values reflecting greater valuation of the LL option.

The delay to the first LL amount in each condition, as well as the intervals between all additional SS and LL amounts (where applicable), were set to individual participants' ED50 values from Step 1. This maximized the probability that indifference points in the bundle-size 1 control condition would be near the $450 midpoint. Moreover, in the bundle-size 3 and 9 conditions, this ensured that the intervals between all contiguous gains or losses were directly proportional to participants' baseline level of delay discounting. This was done to both control for differences in discounting of gains and losses (e.g., Green et al., 1997) and to provide approximately equal sensitivity to detect both increases and decreases in valuation of the LL option.

Data Quality

Neither the six-trial, adjusting-delay task nor the use of the adjusting-amount task in this study allowed application of standardized criteria to detect nonsystematic responding (Johnson and Bickel, 2008). To mitigate this concern, data quality in the choice bundling assessment was monitored by inclusion of three quality control questions, similar to methods used previously (Stein et al., 2018a; Stein and Madden, 2021). Specifically, after the sixth trial in each of three adjusting-amount conditions, a seventh trial asked participants to choose between $450 now and $900 now. In the bundle-size 3 and 9 conditions, these monetary amounts were framed as separate rewards, as described above for these conditions; however, all delays were removed (e.g., $300 now, $300 now, and $300 now; Stein and Madden, 2021). Choice of the smaller option in these questions was interpreted as inattention or atypical valuation of monetary rewards.

Demographic and Smoking Characteristics

At the end of the survey, participants completed a demographics questionnaire and the Heaviness of Smoking Index (Heatherton et al., 1989).

Data Analysis

All analyses were performed in SPSS version 27.0 (IBM SPSS Statistics for Windows, IBM Corp.). The final analytic sample (N = 302) provided 95% power to detect an approximately small effect size (f = 0.108) within-subjects x between-groups interaction in analysis of variance (ANOVA), assuming three repeated measures, four groups, a = 0.05, and a correlation between repeated measures of r = 0.50.

Participant Characteristics

Demographic, smoking, and other sample characteristics were compared between the four groups (gains/ascending, gains/descending, losses/ascending, and losses/descending) using two-way ANOVA, Fisher's Exact tests, or logistic regression.

Step 1: Assessment of Delay Discounting in the Six-Trial, Adjusting-Delay Task

Effective Delay 50 values were compared between the gains and losses group using one-way analysis of covariance (ANCOVA), with sign (gain, loss) as a between-subjects factor. ED50 values were nonnormally distributed and were thus log (base 10) transformed prior to analysis.

Step 2: Effects of Choice Bundling in the Adjusting-Amount Task

Indifference points in the bundle-size 1, 3, and 9 conditions were analyzed using repeated-measures ANCOVA, with bundle size as a within-subjects factor and sign (gain, loss) and order (ascending, descending) as between-subjects factors. Significant results were followed by between-group and within-subject post-hoc comparisons. Bonferroni correction was used to maintain the family-wise error rate in each post-hoc test at a = 0.05.

Sensitivity Analyses

Analysis of covariances described above were repeated in sensitivity analyses when excluding: (1) participants who failed one or more of the quality control questions and (2) participants whose ED50 values in Step 1 produced unrealistic delays to one or more bundled consequences in Step 2 (described further, below).

RESULTS

Participant Characteristics

Table 1 provides demographic characteristics for gains and losses groups, by bundle-size order (ascending and descending). On average, participants smoked 19.43 cigarettes/day (±11.78) and were 48.89 years old (±13.66). The sample was exactly 50% male and female. The majority were white (89.7%), non-Hispanic (84.8%), and reported low (i.e., <$50,000/year; 49.3%) or middle (i.e., $50,000–$150,000/year; 40.7%) incomes.

No participant characteristics differed significantly between groups ($ps > 0.05$), with the exception of ethnicity. Participants reporting Hispanic/Latino ethnicity were sampled less frequently in the losses group (10.0%) compared to the gains group (20.39%), OR = 0.261 (0.098, 0.697), p = 0.007, though likely due to chance because the groups were randomized. No significant associations were observed between ethnicity and either order or the Sign × Order interaction (in both cases, $ps > 0.05$). Ethnicity was included as a covariate in ANCOVA, described below.

Step 1: Assessment of Delay Discounting in the Six-Trial, Adjusting-Delay Task

Analysis of log transformed values revealed higher ED50s (i.e., lower discounting) for delayed losses compared to gains, $F(1, 299) = 14.008$, $p < 0.001$; $\eta_p^2 = 0.045$ (see **Figure 3**). Ethnicity was a significant covariate, $F(1, 299) = 3.940$, $p = 0.048$; $\eta_p^2 = 0.013$, with lower ED50 values (i.e., greater discounting) observed in participants reporting Hispanic/Latino ethnicity.

Step 2: Assessment of Choice Bundling Effects in the Adjusting-Amount Task

Analysis of covariance revealed significant main effects of bundle size, $F(2, 594) = 10.793$, $p < 0.001$, $\eta_p^2 = 0.035$, and sign ($F(1, 297) = 13.837$, $p < 0.001$, $\eta_p^2 = 0.045$, although significant Bundle Size × Sign, $F(2, 594) = 4.765$, $p = 0.009$, $\eta_p^2 = 0.016$, and

TABLE 1 | Demographic and smoking characteristics.

Sign	Gains		Losses	
Bundle-size order	**Ascending**	**Descending**	**Ascending**	**Descending**
n	76	76	75	75
Demographics				
Age (year; ± SD)	49.6 ± 14.5	47.2 ± 12.6	49.7 ± 13.9	49.1 ± 13.6
Gender				
% Male (*n*)	53.9 (41)	42.1 (32)	52.0 (39)	52.0 (39)
% Female (*n*)	46.1 (35)	57.9 (44)	48.0 (36)	48.0 (36)
Race				
% White (*n*)	89.5 (68)	86.8 (66)	94.7 (71)	89.2 (66)
% Asian (*n*)	3.9 (3)	0.0 (0)	0.0 (0)	1.3 (1)
% Black/African American (*n*)	5.3 (4)	10.5 (8)	5.3 (4)	1.3 (1)
% Other race or multi-racial (*n*)	1.3 (1)	2.6 (2)	0.0 (0)	8.1 (6)
% Not answered (*n*)	0.0 (0	0.0 (0	0.0 (0	1.3 (1)
Ethnicity				
% Non-Hispanic/ Latino (*n*)	73.7 (56)	85.5 (65)	90.7 (68)	89.3 (67)
% Hispanic/ Latino (*n*)	25.0 (19)	13.2 (10)	8.0 (6)	9.3 (7)
% Not answered (*n*)	1.3 (1)	1.3 (1)	1.3 (1)	1.3 (1)
Household income				46.7 (35)
% <$50k (*n*)	46.1 (35)	56.6 (43)	48.0 (36)	41.3 (31)
% $50k-$149,999 (*n*)	39.5 (30)	34.2 (26)	48.0 (36)	12.0 (9)
% ≥$150k (*n*)	14.5 (11)	9.2 (7)	4.0 (3)	
Education				
% ≤High school (*n*)	30.3 (23)	35.5 (27)	22.7 (17)	30.7 (23)
% Some college (*n*)	28.9 (22)	40.8 (31)	36.0 (27)	29.3 (22)
% ≥4-year college degree (*n*)	40.8 (31)	23.7 (18)	40.0 (30)	40.0 (30)
Smoking characteristics				
Cigarettes/day (± SD)	20.9 ± 14.6	19.5 ± 8.8	17.7 ± 7.9	19.8 ± 14.5
HSI (± SD)	3.2 ± 1.5	3.4 ± 1.3	3.0 ± 1.4	3.2 ± 1.2
Usual brand flavor				
% Menthol (*n*)	47.4 (36)	43.4 (33)	48.0 (36)	46.7 (35)

Cigarettes/day reflects daily cigarette consumption in the month preceding the survey.

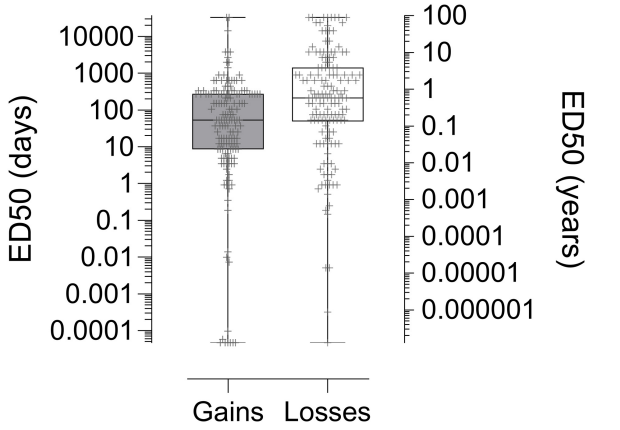


FIGURE 3 | Median Effective Delay 50 (ED50) values in the six-trial, adjusting-delay task for monetary gains (n = 152) and losses (n = 150), scaled in both days (left y axis) and corresponding years (right y axis). Higher values of ED50 reflect less discounting of the delayed gain or loss. Significantly higher ED50s were observed for losses compared to gains ($p < 0.001$).

Bundle Size × Order, $F(2, 594) = 3.304$, $p = 0.037$, $\eta_p^2 = 0.011$ interactions were also observed (see **Figure 4**). No other main effects or interactions were significant (in all cases, $Fs < 2.609$, $ps > 0.106$; see **Supplementary Material** for complete reporting of nonsignificant results). Following ANCOVA, Bonferroni-adjusted *post hoc* comparisons were conducted to further investigate the significant Bundle Size × Sign and Bundle Size × Order interactions.

Bundle Size × Sign

Analysis of within-subject comparisons revealed significantly higher indifference points in the bundle-size 3 and 9 conditions compared to the bundle-size 1 condition in both the gains and losses groups (in all cases, $ps < 0.001$). No significant differences were observed between bundle-sizes 3 and 9 in either the gains or losses groups (in both cases, $ps > 0.174$). Analysis of between-subject comparisons revealed significantly higher indifference points in the losses compared to the gains group at bundle-size 3 and 9 (in both cases, $ps < 0.001$), but not bundle-size 1 (control), $p = 0.179$.

Bundle Size × Order

Analysis of within-subject comparisons revealed significantly higher indifference points in the bundle-size 3 and 9 conditions compared to the bundle-size 1 condition in both the ascending and descending orders (in all cases, $ps < 0.001$). No significant differences were observed between bundle-sizes 3 and 9 in either the ascending or descending orders (in both cases, $ps > 0.270$). Analysis of between-subject comparisons revealed no significant differences in indifference points between ascending and descending orders at any bundle size (in all cases, $ps > 0.174$).

Sensitivity Analysis: Data Quality Checks

A total of 29 participants (9.60% of the sample) failed one or more of the three quality control questions in the choice bundling assessment (n = 7, 4, 8, and 10 in the gains/ascending, gains/descending, losses/ascending, and losses/descending groups, respectively). In logistic regression, the odds of this response type did not differ significantly between the gains and losses groups, OR = 1.177 (0.404, 3.427), $p = 0.765$, ascending and descending order groups, OR = 0.548 (0.153, 1.954), $p = 0.354$, or their interaction, OR = 2.353 (0.469, 11.796), $p = 0.298$.

In a sensitivity analysis, the ANCOVA described above was repeated when excluding these 29 participants. Briefly, all conclusions for main effects, interactions, and adjusted *post hoc* comparisons were consistent with those from the primary analysis. Full results are provided in **Supplementary Material** Section 2.2.

Sensitivity Analysis: Unrealistic Delays

Due to the use of participant-specific ED50 values as intervals between consecutive gains/losses in the adjusting-amount task, participants with high ED50 values encountered delays to one or more bundled consequences that exceeded their expected lifespan. For example, if a participant's ED50 value in the six-trial, adjusting delay task were approximately 20 years, then any delayed gain or loss beyond the third in the bundle-size 9 condition would feature a delay exceeding 60 years (e.g., 20 years × 4 = 80). We thus explored the frequency with which participants encountered these unrealistic delays and their possible influence on outcomes.

Taking a conservative approach, we identified all participants exposed to a maximum delay in the choice bundling assessment (i.e., the final gain or loss at bundle-size 9, or ED50 × 9) that exceeded their expected remaining life years, given their current age. Expected remaining life years for the United States general population were collected from data reported by the National Center for Health Statistics and the Centers for Disease Control (Arias, 2021), and ranged from 56.9 years for 20-year-olds to 9.1 years for 80-year-olds. A total of n = 57 such participants (18.87% of the sample) were identified who met this criterion (n = 6, 5, 18, and 28 in the gains/ascending, gains/descending, losses/ascending, and losses/descending groups, respectively). In logistic regression, the odds of this response type was significantly greater in the losses compared to gain groups, OR = 3.684 (1.372, 9.894), $p = 0.010$, but did not differ significantly between order groups, OR = 0.822 (0.240, 2.816), $p > 0.755$, or the Sign × Order interaction, OR = 2.296 (0.555, 9.502), $p = 0.251$.

In a sensitivity analysis, we repeated the ANCOVA described above when excluding these 57 participants. Briefly, conclusions for main effects and interactions were consistent with those from the primary analysis, with the following exception: the effect of ethnicity was significant, $F(1, 240) = 4.357$, $p = 0.038$, $\eta_p^2 = 0.018$, with lower indifference points observed for Hispanic/Latino compared to other participants; however, ethnicity did not significantly interact with bundle size, $F(2, 480) = 1.277$, $p = 0.280$, $\eta_p^2 = 0.005$. Conclusions from adjusted post-hoc comparisons were also consistent with those from the primary analysis, with the following exception. Indifference points in the losses group were significantly higher compared to the gains group

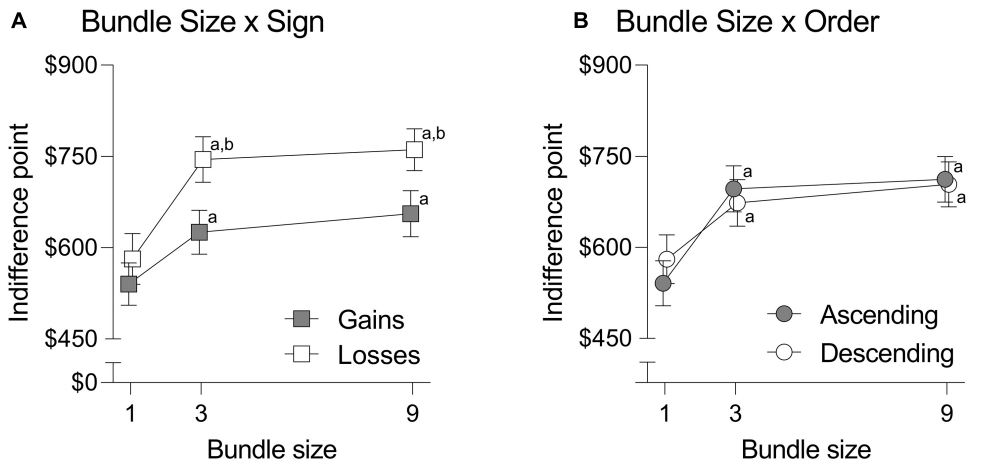


FIGURE 4 | Significant effects of the Bundle Size x Sign **(A)** and Bundle Size x Order **(B)** interactions on indifference points in the adjusting-amount task. Error bars reflect 95% confidence intervals. Higher indifference points reflect greater valuation of the LL option. [a]Significantly different from bundle-size 1 within the same sign or order group, $p < 0.001$. [b]Significantly different from the opposing sign or order group at the same bundle size, $p < 0.001$.

at bundle-size 1 ($p = 0.035$). Full results are provided in **Supplementary Material**, Section 2.3.

DISCUSSION

Data from the present study replicate prior findings in which choice bundling increases valuation of delayed gains (Kirby and Guastello, 2001; Ainslie and Monterosso, 2003; Hofmeyr et al., 2011; Stein et al., 2013; Stein and Madden, 2021), and extend these findings by showing that choice bundling produces even larger increases in valuation of delayed losses. This interaction between choice bundling and sign (gain vs. loss) was evident in the primary analysis including all data as well as in sensitivity analyses excluding participants with potentially poor quality data and unrealistic delays. Likewise, adjusted post-hoc comparisons generally revealed larger effects of choice bundling for losses compared to gains. The effects of bundle size also significantly interacted with bundle-size order (ascending vs. descending) in all analyses. Importantly, however, we observed no significant three-way interaction between bundle size, sign, and order, indicating that the differential effects of choice bundling for losses compared to gains did not depend on order.

Choice Bundling and the Sign Effect

In choices for unbundled outcomes, losses are reliably discounted at a lower rate than gains (Thaler, 1981; Benzion et al., 1989; Murphy et al., 2001; Estle et al., 2006; Tanaka et al., 2014), meaning that individuals are typically more likely to minimize losses in intertemporal choice (by preferring the SS loss) than to maximize gains (by preferring the LL gain). Indeed, this "sign effect" for unbundled outcomes was replicated in the present study in the initial assessment of discounting (see **Figure 3**). Although the mechanisms underlying this gain–loss asymmetry are not well understood, some have argued (e.g., Loewenstein and Prelec, 1992) that it may emerge from the phenomenon of loss aversion, in which losses exert greater influence on choice than equivalently sized gains (Kahneman and Tversky, 1979; Tversky and Kahneman, 1991; Rasmussen and Newland, 2008). Loss aversion may, in turn, interact with the "magnitude effect," in which larger amounts are discounted at a lower rate than smaller amounts (Thaler, 1981; Kirby and Maraković, 1995; Green et al., 1997; Mellis et al., 2017). Because losses are subjectively valued more highly than gains, the sign effect in intertemporal choice may be a special instance of the magnitude effect (e.g., Loewenstein and Prelec, 1992).

The sign effect may also be the result of feelings of dread and anticipatory anxiety experienced when waiting for losses (Berns et al., 2006; Hardisty and Weber, 2019; Molouki et al., 2019). As others have noted (e.g., Hardisty and Weber, 2020), waiting for gains is a multi-dimensional experience in which individuals may enjoy imagining the delayed, positive outcomes while also disliking having to wait for them. In contrast, waiting for losses or other aversive events is unidimensional, in which individuals dislike both the outcomes and having to wait for them, producing greater motivation to escape that aversive emotional state and "get it over with."

The present study is the first to demonstrate that the sign effect is also evident in intertemporal choice for bundled outcomes. That is, significant interactions between bundle size and sign were observed in all analyses. Interestingly, in using the present study's two-step adaptive procedures, this asymmetry in bundling effects was evident even when controlling for baseline differences in discounting of gains and losses; that is, in analyses in which indifference points in the bundle-size 1 control did not significantly differ between gains and losses (see **Figure 4** and **Supplementary Figure 1**). Only in one sensitivity analysis (see **Supplementary Figure 2**) were significant differences between losses and gains observed in the bundle-size 1 control condition, although the Bundle Size × Sign interaction nonetheless remained significant in that analysis.

Choice Bundling and the Preference Reversal Effect for Unbundled Outcomes

Choice bundling effects are related to another set of experimental findings, the "preference reversal" effect, in which adding a delay to both choice options can shift preference between unbundled SS and LL outcomes (for review, see Madden and Johnson, 2010). For example, one may prefer an immediate SS reward over a LL reward (e.g., $500 now vs. $1000 in 1 year), but switch their preference to the LL reward as the delays to *both* options increase (e.g., $500 in 1 year vs. $1,000 in 2 years).

Both the preference reversal effect for unbundled choices and choice bundling effects emerge from predictions of hyperbolic delay discounting. Specifically, in the preference reversal effect, adding an equal delay to both choice options of sufficient length (depending on individual delay discounting rate; Pope et al., 2019) allows the hyperbolic discounted value curve of the LL option to transect and exceed that of the now-discounted SS option, resulting in greater preference for LL gains (e.g., Rachlin and Green, 1972; Green et al., 1994; Pope et al., 2019) and SS losses (Holt et al., 2008). Notably, choice bundling manipulations also involve adding delays to each sequential pair of SS and LL outcomes (e.g., see **Figure 2**). For example, in the present study, the second SS and LL outcome in the bundling condition occurred at ED50 and 2*ED50, respectively; the third SS and LL outcomes occurred at 2*ED50 and 3*ED50, respectively; and so on (see **Figure 2**). Thus, the greater relative value of the LL option in each of these outcome pairs accumulates incrementally in the summed subjective value of the LL option to exceed that of the SS option. In this way, choice bundling effects leverage hyperbolic discounting to influence choice.

Potential Clinical Utility of Choice Bundling

Prior research demonstrates that high rates of delay discounting predict initiation of cigarette smoking (Audrain-McGovern et al., 2009), differentiate smokers from non-smokers and former smokers (Odum et al., 2002; Stein et al., 2018a), are associated with greater addiction severity (Johnson et al., 2007; Sweitzer et al., 2008), and predict relapse following cessation (Yoon et al., 2007; Sheffer et al., 2014). These findings establish delay discounting as a potential therapeutic target (Riddle and Science of Behavior Change Working Group, 2015), in which interventions that reduce delay discounting may also facilitate smoking cessation (e.g., by increasing the relative value of long-term good health compared to immediate nicotine reinforcement). Preliminary experimental evidence further supports this view, as an intervention that guides individuals to engage in episodic prospection (i.e., to simulate future events) reduces delay discounting, cigarette smoking, and economic valuation of cigarettes (Stein et al., 2016, 2018b; Chiou and Wu, 2017).

Given these findings, development of additional methods to mitigate the possible role of high discounting rates in smoking behavior may yield efficacious treatments for cessation. Choice bundling has been shown in several studies to increase adaptive preference for LL gains (for review, see Ashe and Wilson, 2020) and, in the present study, SS losses. However, the majority of these studies employed precise control over the timing and magnitude of behavioral consequences in order to observe these effects. In contrast, in clinical contexts, manipulation of the natural consequences of cigarette smoking is not possible. For example, a treatment provider cannot control when or how frequently a patient may experience the health losses associated with continued smoking or health gains associated with cessation. For this reason, adaptation of laboratory-based choice bundling methods is necessary before attempts at clinical application. Two prior laboratory studies (Kirby and Guastello, 2001; Hofmeyr et al., 2011) have shown that a bundling-focused framing intervention, in which experimenters suggested to participants' that their current choices were predictive of future choices (and are, therefore, bundled) increases preference for LL gains. Although this framing intervention has not been evaluated clinically to our knowledge, these studies suggest that interventions that prompt individuals to view their decisions as a temporally extended pattern of behavior producing cumulative outcomes may promote more adaptive intertemporal choice.

Importantly, most of the negative health consequences of cigarette smoking (e.g., COPD) are chronic conditions in which bundled symptoms (e.g., impaired breathing, circulation, and stamina) are experienced and escalate over time. As suggested previously (Stein and Madden, 2021), bundling-focused, motivational interventions could therefore be designed to guide individuals to repeatedly evaluate (e.g., with every urge to smoke) the cumulative value of long-term health against the momentary value of nicotine reinforcement. Toward this end, evidence from the present study that choice bundling produces larger effects for losses compared to gains may be critical. That is, gain-loss asymmetry in choice bundling suggests that attempts to develop bundling-focused clinical interventions for smoking cessation may take advantage of the sign effect by emphasizing the negative consequences of continued smoking as opposed to the positive consequences of smoking cessation. However, further research is required to determine whether the sign effect in choice bundling for monetary outcomes generalizes to other commodities, such as hypothetical health (e.g., Odum et al., 2002). Likewise, further research should examine whether the effects of choice bundling are observed during nicotine withdrawal, as prior research shows that 12 h of smoking abstinence increases delay discounting (Heckman et al., 2017) and this nicotine-deprived state may more closely approximate the clinical environment in which individuals are attempting to abstain from smoking.

Potential Limitations

A few limitations of the present study deserve note. First, use of the adjusting-amount task to generate a single indifference point may have limited resolution to detect effects of choice bundling. The adjusting-amount task is most commonly used to assess indifference points across a range of delays (e.g., 1 month to 20 years; Du et al., 2002), yielding a full discounting curve, from which high-resolution estimates of discounting may be derived. In contrast, assessment of only a single indifference point yields a less granular estimate of discounting and may

have resulted in a ceiling effect that diminished sensitivity to detect differences between bundle-sizes 3 and 9, as differences in intertemporal choice for gains between these conditions have been shown in prior studies using alternative methods (Stein et al., 2013; Stein and Madden, 2021).

Second, use of the two-step, adaptive procedure in which we assessed ED50 using the 6-trial, adjusting-delay task followed by assessment of indifferent points using the adjusting-amount task, limited the ability to examine concordance between observed effects and those predicted by individual participants' k values in the additive hyperbolic discounting model (Equation 2), as done previously (Stein et al., 2013; Stein and Madden, 2021). Specifically, if both tasks produced perfectly concordant estimates of choice, then assessment at the bundle-size 1 (control) condition should have yielded indifference points at \$450 (half of \$900). In contrast, mean indifference points in this condition were all above \$540, regardless of sign or order. This suggests that the six-trial task overestimates k (i.e., underestimates ED50) relative to the adjusting-amount task. This is consistent with prior evidence that the similar five-trial, adjusting-delay task also produces higher estimates of k than the adjusting-amount task, despite strong correlations between tasks (e.g., r = 0.67–0.86 Koffarnus and Bickel, 2014; Stein et al., 2017). In future studies, researchers should consider the use of only a single task to minimize measurement error.

Third, as a result of the method in which choice bundling was arranged, approximately 19% of the sample were exposed to one or more delays in the adjusting-amount task that likely exceeded their expected lifespan. This did not substantially impact our conclusions, as a sensitivity analysis excluding these participants revealed largely similar effects as the primary analysis. Nonetheless, in future studies, researchers may explore use of alternative delays and intervals between bundled consequences (e.g., half of ED50) in order to reduce or eliminate the probability of exposure to these unrealistic delays. Alternatively, as suggested previously (Stein et al., 2013; Stein and Madden, 2021), bundle size could be limited to no more than three gains or losses to reduce the cumulative delay period. This is unlikely to substantially limit effect sizes because observed effects of choice bundling and those predicted by Equation 2 are largest at smaller bundle sizes, with larger bundle sizes subject to diminishing marginal efficacy (for discussion, see Stein and Madden, 2021).

Fourth, although recruitment of opt-in, online panels in addiction science can provide useful and generalizable evidence in decision-making research (Strickland and Stoops, 2019; Mellis and Bickel, 2020), it often yields participant samples that are not representative of the broader population of interest. This was true in the present study, in which college-educated adults were over-represented and minorities were under-represented compared to prevalence in the United States population of smokers. As such, future research should examine the generality of the effects observed here in more diverse, nationally representative samples. Moreover, despite use of random allocation and minimal attrition, groups were not balanced on ethnicity (90.0 and 79.61% Non-Hispanic/Latino in the gains and losses groups, respectively). This imbalance contributed unwanted variability in choice estimates and may have reduced effect sizes. Nonetheless, effects of choice bundling were evident even when including this relatively minor difference in ethnicity as a covariate and, importantly, ethnicity did not significantly interact with bundle size, sign, or order to influence choice in the assessment of choice bundling.

CONCLUSION

We conclude that choice bundling increases valuation of both delayed monetary gains and losses in cigarette smokers, although effects for losses are larger compared to gains. Future research should examine whether choice bundling effects generalize to non-monetary, health outcomes and whether choice bundling can lead to efficacious interventions for smoking cessation.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: https://osf.io/63xjr/?view_only=3e8c00292e8e46ec87866bcc69443c01.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Virginia Tech Institutional Review Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

JS and GM contributed to conception and design of the study. RF-L organized recruitment of the participant sample with Ipsos. RF-L and JS created the survey instruments. JS and JB performed the statistical analyses, with input from AT. JS and JB wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

FUNDING

This research was supported by National Institutes of Health grants P01CA217806 and R21DA046339. The funding agencies had no role in study design, data collection, analysis and interpretation of the data, nor in the preparation and submission of the report, including the decision to submit.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnbeh.2021.796502/full#supplementary-material

REFERENCES

Ainslie, G. (1975). Specious reward: a behavioral theory of impulsiveness and impulse control. *Psychol. Bull.* 82, 463–496.

Ainslie, G. (2001). *Breakdown of Will*. Cambridge: Cambridge University Press.

Ainslie, G., and Monterosso, J. R. (2003). Building blocks of self-control: increased tolerance for delay with bundled rewards. *J. Exp. Anal. Behav.* 79, 37–48.

Amlung, M., Vedelago, L., Acker, J., Balodis, I., and Mackillop, J. (2016). Steep delay discounting and addictive behavior: a meta-analysis of continuous associations. *Addiction* 112, 51–62. doi: 10.1111/add.13535

Arias, E. (2021). *Provisional Life Expectancy Estimates for January Through June, 2020*. Atlanta, GA: Centersfor Disease Control and Prevention.

Ashe, M. L., and Wilson, S. J. (2020). A brief review of choice bundling: a strategy to reduce delay discounting and bolster self-control. *Addict. Behav. Rep.* 11:100262. doi: 10.1016/j.abrep.2020.100262

Athamneh, L. N., Stein, J. S., and Bickel, W. K. (2017). Will delay discounting predict intention to quit smoking? *Exp. Clin. Psychopharmacol.* 25, 273–280. doi: 10.1037/pha0000129

Audrain-McGovern, J., Rodriguez, D., Epstein, L. H., Cuevas, J., Rodgers, K., and Wileyto, E. P. (2009). Does delay discounting play an etiological role in smoking or is it a consequence of smoking? *Drug Alcoh. Depend.* 103, 99–106. doi: 10.1016/j.drugalcdep.2008.12.019

Baker, F., Johnson, M. W., and Bickel, W. K. (2003). Delay discounting in current and never-before cigarette smokers: similarities and differences across commodity, sign, and magnitude. *J. Abnorm. Psychol.* 112, 382–392.

Benzion, U., Rapoport, A., and Yagil, J. (1989). Discount rates inferred from decisions: an experimental study. *Manag. Sci.* 35, 270–284. doi: 10.1287/mnsc.35.3.270

Berns, G. S., Chappelow, J., Cekic, M., Zink, C. F., Pagnoni, G., and Martin-Skurski, M. E. (2006). Neurobiological substrates of dread. *Science* 312, 754–758. doi: 10.1126/science.1123721

Bickel, W. K., Pope, D. A., Kaplan, B. A., DeHart, W. B., Koffarnus, M. N., and Stein, J. S. (2018). Electronic cigarette substitution in the experimental tobacco marketplace: a review. *Prevent. Med.* 117, 98–106. doi: 10.1016/j.ypmed.2018.04.026

Bickel, W. K., Stein, J. S., Moody, L. N., Snider, S. E., Mellis, A. M., and Quisenberry, A. J. (2017). "Toward narrative theory: interventions for reinforcer pathology in health behavior," in *Impulsivity*, ed. J. R. Stevens (Cham: Springer), 227–267. doi: 10.1007/978-3-319-51721-6_8

Chapman, G. B. (1996). Temporal discounting and utility for health and money. *J. Exp. Psychol. Learn. Mem. Cogn.* 22, 771–791. doi: 10.1037//0278-7393.22.3.771

Chiou, W.-B., and Wu, W.-H. (2017). Episodic future thinking involving the nonsmoking self can induce lower discounting and cigarette consumption. *J. Stud. Alcoh. Drugs* 78, 106–112. doi: 10.15288/jsad.2017.78.106

DeHart, W. B., Friedel, J. E., and Berry, M. (2020). Comparison of delay discounting of different outcomes in cigarette smokers, smokeless tobacco users, e-cigarette users, and non-tobacco users. *J. Exp. Anal. Behav.* 114, 203–215.

Du, W., Green, L., and Myerson, J. (2002). Cross-cultural comparisons of discounting delayed and probabilistic rewards. *Psychol. Rec.* 52:479.

Estle, S. J., Green, L., Myerson, J., and Holt, D. D. (2006). Differential effects of amount on temporal and probability discounting of gains and losses. *Mem. Cogn.* 34, 914–928. doi: 10.3758/bf03193437

Green, L., Fristoe, N., and Myerson, J. (1994). Temporal discounting and preference reversals in choice between delayed outcomes. *Psychonom. Bull. Rev.* 1, 383–389. doi: 10.3758/BF03213979

Green, L., Myerson, J., and McFadden, E. (1997). Rate of temporal discounting decreases with amount of reward. *Mem. Cogn.* 25, 715–723.

Green, L., Myerson, J., Oliveira, L., and Chang, S. E. (2014). Discounting of delayed and probabilistic losses over a wide range of amounts. *J. Exp. Anal. Behav.* 101, 186–200. doi: 10.1002/jeab.56

Hardisty, D. J., and Weber, E. U. (2009). Discounting future green: money versus the environment. *J. Exp. Psychol.* 138, 329–340. doi: 10.1037/a0016433

Hardisty, D. J., and Weber, E. U. (2019). *Kisses vs. Shocks: Contemplation Asymmetries (Partly) Explain Why Negative Events are Discounted Less than Positive Events. In (Partly) Explain Why Negative Events are*. Amsterdam: Elsevier.

Hardisty, D. J., and Weber, E. U. (2020). Impatience and savoring vs. dread: asymmetries in anticipation explain consumer time preferences for positive vs. negative events. *J. Consum. Psychol.* 30, 598–613. doi: 10.1002/jcpy.1169

Harris, C. R. (2012). Feelings of dread and intertemporal choice. *J. Behav. Dec. Mak.* 25, 13–28. doi: 10.1002/bdm.709

Heatherton, T. F., Kozlowski, L. T., and Frecker, R. C. (1989). Measuring the heaviness of smoking: using self-reported time to the first cigarette of the day and number of cigarettes smoked per day. *Br. J. Add.* 84, 791–800.

Heckman, B. W., MacQueen, D. A., Marquinez, N. S., MacKillop, J., Bickel, W. K., and Brandon, T. H. (2017). Self-control depletion and nicotine deprivation as precipitants of smoking cessation failure: a human laboratory model. *J. Consult. Clin. Psychol.* 85, 381–396. doi: 10.1037/ccp0000197

Hofmeyr, A., Ainslie, G., Charlton, R., and Ross, D. (2011). The relationship between addiction and reward bundling: an experiment comparing smokers and non-smokers. *Addiction* 106, 402–409.

Holt, D. D., Green, L., Myerson, J., and Estle, S. J. (2008). Preference reversals with losses. *Psychonom. Bull. Rev.* 15, 89–95. doi: 10.3758/pbr.15.1.89

Johnson, M. W., and Bickel, W. K. (2008). An algorithm for identifying nonsystematic delay-discounting data. *Exp. Clin. Psychopharmacol.* 16, 264–274. doi: 10.1037/1064-1297.16.3.264

Johnson, M. W., Bickel, W. K., and Baker, F. (2007). Moderate drug use and delay discounting: a comparison of heavy, light, and never smokers. *Exp. Clin. Psychopharmacol.* 15, 187–194. doi: 10.1037/1064-1297.15.2.187

Kahneman, D., and Tversky, A. (1979). Prospect theory: an analysis of decision under risk. *Econo. J. Econo. Soc.* 47, 363–391.

Kirby, K. N., and Guastello, B. (2001). Making choices in anticipation of similar future choices can increase self-control. *J. Exp. Psychol. Appl.* 7, 154–164. doi: 10.1037//1076-898x.7.2.154

Kirby, K. N., and Maraković, N. N. (1995). Modeling myopic decisions: evidence for hyperbolic delay-discounting within subjects and amounts. *Organ. Behav. Hum. Dec. Process.* 64, 22–30. doi: 10.1006/obhd.1995.1086

Koffarnus, M. N., and Bickel, W. K. (2014). A 5-trial adjusting delay discounting task: accurate discount rates in less than one minute. *Exp. Clin. Psychopharmacol.* 22, 222–228. doi: 10.1037/a0035973

Koffarnus, M. N., Rzeszutek, M. J., and Kaplan, B. A. (2021). Additional discounting rates in less than one minute: task variants for probability and a wider range of delays. *Exp. Clin. Psychopharmacol.* 22:222. doi: 10.13140/RG.2.2.31281.92000

Loewenstein, G., and Prelec, D. (1992). Anomalies in intertemporal choice: evidence and an interpretation. *Q. J. Econ.* 107, 573–597.

MacKillop, J., Amlung, M. T., Few, L. R., Ray, L. A., Sweet, L. H., and Munafò, M. R. (2011). Delayed reward discounting and addictive behavior: a meta-analysis. *Psychopharmacology* 216, 305–321. doi: 10.1007/s00213-011-2229-0

Madden, G. J., and Johnson, P. S. (2010). "A delay-discounting primer," in *Impulsivity: The Behavioral and Neurological Science of Discounting*, eds G. J. Madden and W. K. Bickel (Washington, DC: American Psychological Association), 11–37. doi: 10.1037/12069-001

Mazur, J. E. (1986). Choice between single and multiple delayed reinforcers. *J. Exp. Anal. Behav.* 46, 67–77. doi: 10.1901/jeab.1986.46-67

Mazur, J. E. (1987). "An adjusting procedure for studying delayed reinforcement," in *The Effect of Delay and of Intervening Events on Reinforcement Value*, eds M. L. Commons, J. E. Mazur, J. A. Nevin, and H. Rachlin (Mahwah, NJ: Lawrence Erlbaum Associates, Inc), 55–73.

Mazur, J. E. (1989). Theories of probabilistic reinforcement. *J. Exp. Anal. Behav.* 51, 87–99. doi: 10.1901/jeab.1989.51-87

Mellis, A. M., and Bickel, W. K. (2020). Mechanical Turk data collection in addiction research: utility, concerns and best practices. *Addiction* 115:10. doi: 10.1111/add.15032

Mellis, A. M., Woodford, A. E., Stein, J. S., and Bickel, W. K. (2017). A second type of magnitude effect: reinforcer magnitude differentiates delay discounting between substance users and controls. *J. Exp. Anal. Behav.* 107, 151–160. doi: 10.1002/jeab.235

Mitchell, S. H. (1999). Measures of impulsivity in cigarette smokers and non-smokers. *Psychopharmacology* 146, 455–464.

Mitchell, S. H., and Wilson, V. B. (2010). The subjective value of delayed and probabilistic outcomes: outcome size matters for gains but not for losses. *Behav. Process.* 83, 36–40. doi: 10.1016/j.beproc.2009.09.003

Molouki, S., Hardisty, D. J., and Caruso, E. M. (2019). The sign effect in past and future discounting. *Psychol. Sci.* 30, 1674–1695. doi: 10.1177/0956797619876982

Murphy, J. G., Vuchinich, R. E., and Simpson, C. A. (2001). Delayed reward and cost discounting. *Psychol. Rec.* 51, 571–588.

Odum, A. L. (2011). Delay discounting: I'm a k, you're a k. *J. Exp. Anal. Behav.* 96, 427–439. doi: 10.1901/jeab.2011.96-423

Odum, A. L., and Baumann, A. A. L. (2010). "Delay discounting: state and trait variable," in *Impulsivity: The Behavioral and Neurological Science of Discounting*, Vol. 453, ed. G. J. Madden (Washington, DC: American Psychological Association), 39–65.

Odum, A. L., Madden, G. J., and Bickel, W. K. (2002). Discounting of delayed health gains and losses by current, never-and ex-smokers of cigarettes. *Nicot. Tobacco Res.* 4, 295–303.

Perry, J. L., and Carroll, M. E. (2008). The role of impulsive behavior in drug abuse. *Psychopharmacology* 200, 1–26. doi: 10.1007/s00213-008-1173-0

Pope, D. A., Poe, L., Stein, J. S., Snider, S. E., Bianco, A. G., and Bickel, W. K. (2019). Past and future preference reversals are predicted by delay discounting in smokers and non-smokers. *Exp. Clin. Psychopharmacol.* 27, 19–28. doi: 10.1037/pha0000224

Rachlin, H., and Green, L. (1972). Commitment, choice and self-control1. *J. Exp. Anal. Behav.* 17, 15–22. doi: 10.1901/jeab.1972.17-15

Rasmussen, E. B., and Newland, M. C. (2008). Asymmetry of reinforcement and punishment in human choice. *J. Exp. Anal. Behav.* 89, 157–167. doi: 10.1901/jeab.2008.89-157

Riddle, M., and Science of Behavior Change Working Group (2015). News from the NIH: using an experimental medicine approach to facilitate translational research. *Transl. Behav. Med.* 5, 486–488. doi: 10.1007/s13142-015-0333-0

Rung, J. M., and Madden, G. J. (2018). Experimental reductions of delay discounting and impulsive choice: a systematic review and meta-analysis. *J. Exp. Psychol.* 147, 1349–1381. doi: 10.1037/xge0000462

Sheffer, C. E., Christensen, D. R., Landes, R., Carter, L. P., Jackson, L., and Bickel, W. K. (2014). Delay discounting rates: a strong prognostic indicator of smoking relapse. *Addict. Behav.* 39, 1682–1689. doi: 10.1016/j.addbeh.2014.04.019

Stein, J. S., Heckman, B. W., Pope, D. A., Perry, E. S., Fong, G. T., Cummings, K. M., et al. (2018a). Delay discounting and e-cigarette use: an investigation in current, former, and never cigarette smokers. *Drug Alcoh. Depend.* 191, 165–173. doi: 10.1016/j.drugalcdep.2018.06.034

Stein, J. S., and Madden, G. J. (2021). Choice bundling, unpacked: observed and predicted effects on intertemporal choice in an additive model of hyperbolic delay discounting. *PLoS One* 16:e0259830. doi: 10.1371/journal.pone.0259830

Stein, J. S., Smits, R. R., Johnson, P. S., Liston, K. J., and Madden, G. J. (2013). Effects of reward bundling on male rats' preference for larger-later food rewards. *J. Exp. Anal. Behav.* 99, 150–158.

Stein, J. S., Sze, Y. Y., Athamneh, L., Koffarnus, M. N., Epstein, L. H., and Bickel, W. K. (2017). Think fast: rapid assessment of the effects of episodic future thinking on delay discounting in overweight/obese participants. *J. Behav. Med.* 40, 832–838. doi: 10.1007/s10865-017-9857-8

Stein, J. S., Tegge, A. N., Turner, J. K., and Bickel, W. K. (2018b). Episodic future thinking reduces delay discounting and cigarette demand: an investigation of the good-subject effect. *J. Behav. Med.* 41, 269–276. doi: 10.1007/s10865-017-9908-1

Stein, J. S., Wilson, A. G., Koffarnus, M. N., Daniel, T. O., Epstein, L. H., and Bickel, W. K. (2016). Unstuck in time: episodic future thinking reduces delay discounting and cigarette smoking. *Psychopharmacology* 233, 3771–3778. doi: 10.1007/s00213-016-4410-y

Strickland, J. C., and Stoops, W. W. (2019). The use of crowdsourcing in addiction science research: amazon mechanical turk. *Exp. Clin. Psychopharmacol.* 27, 1–18. doi: 10.1037/pha0000235

Sweitzer, M. M., Donny, E. C., Dierker, L. C., Flory, J. D., and Manuck, S. B. (2008). Delay discounting and smoking: association with the Fagerström test for nicotine dependence but not cigarettes smoked per day. *Nicot. Tobacco Res.* 10, 1571–1575. doi: 10.1080/14622200802323274

Tanaka, S. C., Yamada, K., Yoneda, H., and Ohtake, F. (2014). Neural mechanisms of gain–loss asymmetry in temporal discounting. *J. Neurosci.* 34, 5595–5602. doi: 10.1523/JNEUROSCI.5169-12.2014

Thaler, R. (1981). Some empirical evidence on dynamic inconsistency. *Econ. Lett.* 8, 201–207. doi: 10.1016/0165-1765(81)90067-7

Tversky, A., and Kahneman, D. (1991). 37Loss aversion in riskless choice: a reference-dependent model. *Q. J. Econ.* 106, 1039–1061.

Yoon, J. H., and Higgins, S. T. (2008). Turning k on its head: comments on use of an ED50 in delay discounting research. *Drug Alcoh. Depend.* 95, 169–172. doi: 10.1016/j.drugalcdep.2007.12.011

Yoon, J. H., Higgins, S. T., Heil, S. H., Sugarbaker, R. J., Thomas, C. S., and Badger, G. J. (2007). Delay discounting predicts postpartum relapse to cigarette smoking among pregnant women. *Exp. Clin. Psychopharmacol.* 15, 176–186. doi: 10.1037/1064-1297.15.2.186

Conflict of Interest: Although the following activities/relationships do not create a conflict of interest pertaining to this manuscript, in the interest of full disclosure, the authors would like to report the following: WB is a principal of HealthSim, LLC; BEAM Diagnostics, Inc.; and Red 5 Group, LLC. In addition, he serves on the scientific advisory board for Sober Grid, Inc.; and Ria Health; serves as a consultant for Boehringer Ingelheim International; and works on a project supported by Indivior, Inc. JS has received funding from the National Institutes of Health through a subcontract awarded to BEAM Diagnostics, Inc.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Behavioral Neuroscience

ORIGINAL RESEARCH
published: 24 January 2022
doi: 10.3389/fnbeh.2021.782991

Are You Sure: Preference and Ambivalence in Delay Discounting

Sergej Grunevski†, Aaron P. Smith† and Richard Yi†*

Cofrin Logan Center for Addiction Research and Treatment, University of Kansas, Lawrence, KS, United States

Delay discounting (DD) research has become ubiquitous due to its robust associations with clinical outcomes. Typical DD tasks involve multiple trials in which participants indicate preference between smaller, sooner and larger, later rewards. Scoring of these binary choice tasks has not considered trial-level ambivalence as a possible decision-making construct. The present study explored the extent to which trial-level ambivalence varied within-individual using an established assessment of DD (the Monetary Choice Questionnaire). Results indicate that degree of ambivalence peaks around the trials associated with the DD rate. Moreover, ambivalence is associated with a diminished impact of reward delay differences on choice, where greater delay differences decrease the odds of choosing the larger, later rewards. Taken together, we believe ambivalence to be a relevant construct for research on intertemporal decision making, and it may be particularly useful in the study of manipulations on individual rates of DD.

Keywords: ambivalence, choice, preference, delay discounting, Monetary Choice Questionnaire

OPEN ACCESS

Edited by:
Gregory J. Madden,
Utah State University, United States

Reviewed by:
Suzanne Mitchell,
Oregon Health and Science University, United States
Jillian Rung,
University of Florida, United States

***Correspondence:**
Richard Yi
ryi1@ku.edu

†***ORCID:***
Sergej Grunevski
orcid.org/0000-0002-2355-0502
Aaron P. Smith
orcid.org/0000-0002-5417-014X
Richard Yi
orcid.org/0000-0002-1873-7874

Specialty section:
This article was submitted to Motivation and Reward, a section of the journal Frontiers in Behavioral Neuroscience

Received: *25 September 2021*
Accepted: *08 December 2021*
Published: *24 January 2022*

Citation:
Grunevski S, Smith AP and Yi R (2022) Are You Sure: Preference and Ambivalence in Delay Discounting. Front. Behav. Neurosci. 15:782991. doi: 10.3389/fnbeh.2021.782991

INTRODUCTION

Delay discounting (DD) refers to the reduction in the subjective value of an outcome when its delivery is delayed (Odum, 2011), and a substantial body of literature has linked rates of DD to behaviors where immediate rewards have delayed consequences. For instance, higher rates of DD, indicating steeper reductions in subjective value across increasing delays to reward receipt, are associated with substance misuse (Yi et al., 2010; MacKillop et al., 2011) and poor treatment outcomes (MacKillop and Kahler, 2009; Sheffer et al., 2012; Stanger et al., 2013), risky sexual behavior (Chesson et al., 2006), overeating (Kekic et al., 2020), and other behaviors associated with similar intertemporal trade-offs.

Common procedures for assessing DD are multi-trial binary choice tasks where the individual indicates preference between smaller, sooner rewards (SSs; usually money) and larger, later rewards (LLs; also money). Though the manner of determining the index of DD (i.e., scoring) varies by task, most variations of these binary choice tasks summarize the pattern of choices across all trials to determine a *rate* of DD, e.g., the k value per Mazur's (1987) hyperbolic discounting equation. For instance, the Monetary Choice Questionnaire (MCQ; Kirby et al., 1999) is a 27-trial binary choice task where participants are presented fixed pairs of immediate/delayed outcomes and asked to indicate the preferred outcome in each trial (e.g., "Would you prefer $15 today, or $35 in 13 days?"). A DD rate obtained from the MCQ reflects the approximate point of switching from preferring the SSs to LLs when trials are placed in rank order of associated DD rate (i.e., the discount rate at which

the SS and LL are of equal value). However, an implicit assumption not explicitly stated in scoring these tasks is that an individual has a constant degree of certainty (conversely, ambivalence) in their preference across trials. That is, it is assumed that a participant who prefers *$34 today* rather than *$35 in 186 days* is equally certain in their preference for *$15 today* rather than *$35 in 13 days*. We hypothesize that this assumption is likely incorrect. That is, as the immediate/delayed outcomes approach values of subjective equivalence at an individual level, the decisions become more difficult and increase the degree of ambivalence about the participant's preference.

Previous efforts have sought to examine this possibility using behavioral proxies for the ambivalence construct. As it is intuitive for a greater degree of deliberation to occur as the subjective values of two options approach equivalence, one might expect that the deliberation period increases as the outcomes become subjectively equivalent at the individual level. Multiple studies examining choice reaction times (RTs) in DD tasks as the indirect measure of ambivalence have found that RTs tend to be longest on trials around the point of subjective equivalence (Robles and Vargas, 2007, 2008; Rodriguez et al., 2014). Moreover, a study examining mouse cursor trajectories in similar tasks discovered that trials around the point of subjective equivalence (termed *indifference point* in other DD assessments; Mazur, 1987) were associated with significantly greater mouse curvatures and, by implication, deliberation (Dshemuchadse et al., 2013). As these studies examined behavioral proxies for ambivalence, the current study sought to explore decision making as it relates to choice difficulty *via* degree of participant-reported ambivalence on each trial of a binary choice DD task. Defining *ambivalence* as the state of indecision toward an attitude (in this case, preference), we proposed to evaluate within-individual variability in degree of self-reported ambivalence across trials in the MCQ. We used previous research on ambivalence as a starting point (Priester and Petty, 1996, 2001) to develop four different assessment strategies. Within the MCQ, and individual's *k* value represents the approximate point where they switch from preferring SSs to LLs. Stated differently, along the continuum of MCQ trials, the *k* value ostensibly denotes the point of equivalence between SSs and LLs of the surrounding trials; as such, degree of ambivalence should steadily increase toward and peak around this "switch point." Our overall hypothesis was that ambivalence would vary across MCQ trials and, specifically, that the (H1) within-individual variability in ambivalence would track switches in preference (i.e., ambivalence peaks around switch point).

In addition to discount rates, another means of analyzing discounting data is *via* how "sensitive" a participant is to the relative differences in reward delays and magnitudes of both choice options (Wileyto et al., 2004; Young, 2018). Within this paradigm, the reward magnitude and delay sensitivities individually predict trial-level preference: high sensitivity to when choice options would be received is associated with choosing SSs more frequently due to their immediacy, whereas high sensitivity to how much money each choice option would deliver is associated with choosing LLs more frequently due to their magnitude. If a participant's ambivalence across trials is relatively high, however, their ability to discriminate between choice options would likely be reduced. Therefore, we further hypothesized that individuals experiencing ambivalence between the choice options would show reduced sensitivities to the options' reward delay and magnitude differences. Specifically, as ambivalence increases, it was hypothesized (H2) that the relative impact of the reward magnitude and delay sensitivities on trial-level choices would diminish (i.e., trend toward 0).

MATERIALS AND METHODS

Participants

Participants (N = 370; 79.9% White, 37.5% women, M_{age} = 35.12 years, age range: 19–65 years) who self-reported to be 18 years or older and located in the United States were recruited from the Amazon Mechanical Turk (MTurk) worker pool. To qualify, MTurk workers had to have completed at least 100 MTurk "jobs," i.e., Human Intelligence Tasks (HITs), and to have at least a 95% HIT approval rate. Participants with these characteristics have been shown to provide higher quality data without the use of attention check questions (Peer et al., 2014).

Measures

Delay Discounting Assessment

The standard 27-item MCQ (Kirby et al., 1999) presents participants with choices between SS/LL monetary rewards. SS magnitudes range from $11 to $78 and LL magnitudes range from $25 to $85; the delays for the LLs range from 7 to 186 days. Each trial is classified into a magnitude condition based on the amount of the LL, and we only used the small ($25–$35) and large ($75–$85) magnitude items, resulting in 18 trials used per participant. Each magnitude condition consists of nine trials, each of which has an associated discount rate, i.e., *k* of Mazur (1987), and can be rank ordered from 1 (lowest associated *k* value) to 9 (highest associated *k* value). See **Table 1** for listing of MCQ trials used.

Ambivalence Measurement Conditions

Monetary Choice Questionnaire trials were adapted with four possible strategies to assess ambivalence (i.e., ambivalence measurement conditions): A1, A2, A3, and A4. Inclusion of these four conditions was exploratory, as we are aware of no previous efforts to assess trial-level ambivalence for preferences in binary choice DD tasks.

In the A1, A2, or A3 conditions, each MCQ trial was followed with a question asking the participant to indicate degree of *certainty* (A1), *unhappiness if receiving the choice they didn't select* (A2), or *indecision* (A3; adapted from Priester and Petty, 2001). Participants in the A1, A2, and A3 conditions responded using an 11-point Likert scale ranging from 0 (*not at all certain*, *not at all unhappy, feel no indecision at all*, respectively) to 10 (*completely certain*, *completely unhappy, feel maximum indecision,* respectively). In condition A4, the binary choice trials were replaced with a 100-point continuous slider to indicate degree of relative preference between strongest preference for the SS at the far left (0th point) and strongest preference for the LL at the far right (100th point).

TABLE 1 | Abbreviated Monetary Choice Questionnaire.

SS	LL	Delay in days	*k* at indiff.	*k* rank
$34	$35	186	0.00016	1
$78	$80	162	0.00016	1
$28	$30	179	0.00040	2
$80	$85	157	0.00040	2
$22	$25	136	0.0010	3
$67	$75	119	0.0010	3
$25	$30	80	0.0025	4
$69	$85	91	0.0025	4
$19	$25	53	0.0060	5
$55	$75	61	0.0060	5
$24	$35	29	0.016	6
$54	$80	30	0.016	6
$14	$25	19	0.041	7
$41	$75	20	0.041	7
$15	$35	13	0.10	8
$33	$80	14	0.10	8
$11	$30	7	0.25	9
$31	$85	7	0.25	9

Note: k at indiff. = the value of the discount rate at which the immediate and delayed rewards are of equal value; k rank = trials with the same values of k grouped in ascending rank order; SS = smaller, sooner rewards; LL = larger, later rewards. Table adapted from Kirby et al. (1999).

Procedure

The study was administered using Qualtrics. Magnitude conditions and ambivalence measurement conditions were paired and counterbalanced such that all participants were exposed to each magnitude condition of the MCQ (small and large) *via* a different ambivalence measurement condition, termed magnitude-ambivalence pairings. Specifically, initial data collection only included the A1 and A2 conditions, whereas subsequent participants (latter half of the sample) were exposed only to the A3 and A4 conditions. This resulted in four possible magnitude-ambivalence pairings in A1/A2 (Small-A1 and Large-A2; Small-A2 and Large-A1; Large-A1 and Small-A2; Large-A2 and Small-A1) and four possible magnitude-ambivalence pairings in A3/A4 (Small-A3 and Large-A4; Large-A4 and Small-A3; Large-A3 and Small-A4; Small-A4 and Large-A3). Trials within magnitude conditions were blocked and randomized within that block. Upon completion of the study, which was estimated to take no longer than 5 min, participants were compensated the recommended pay rate requested by MTurk workers, i.e., $0.10 per minute for a total of $0.50 (Chandler and Shapiro, 2016). Participants read over an information statement before deciding to participate, and all procedures were approved by the Institutional Review Board (Human Research Protection Program) at the University of Kansas-Lawrence campus.

Data Analysis

All data preparations and plotting were conducted using the *tidyverse* framework (Wickham et al., 2019) in the R 3.6.3 statistical environment (R Core Team, 2019). Mixed model analyses were conducted using the *lme4* package (Bates et al., 2015), and subsequent contrasts and interactions were probed using the *emmeans* package (Lenth, 2021). We report *b*, the unstandardized coefficients of our regression models.

Data Preparation

Ambivalence and Choice Scoring

Due to differences in question phrasing and scale ranges, equivalent numerical scores between the ambivalence measurement conditions did not necessarily correspond to identical degrees of ambivalence. For instance, degree of certainty (A1) refers to the exact opposite of degree of indecision (A3); moreover, a 10-point Likert scale denoting degree of certainty (A1) produces qualitatively different scores compared to a 100-point slider scale (A4) that indicates relative preference between the SS and LL. Therefore, ambivalence scores were adjusted such that the minimum possible score represents *least ambivalence*, and the maximum possible score represents *most ambivalence*. For A1 and A2, scores were flipped about the midpoint such that 0 represents least ambivalence, and 10 represents most ambivalence. For A3, the original scaling was preserved (i.e., 0 represents least ambivalence, and 10 represents most ambivalence). For A4, the raw 0–100 scale provides the relative preference of the LL to the SS (0-completely prefer SS; 100-completely prefer LL); therefore, to calculate ambivalence *via* the distance from the midpoint, each score was subtracted by 50, made an absolute value, subtracted again by 50, made again an absolute value (so that 0 represents least ambivalence, and 50 represents most ambivalence), and lastly divided by 5 to match the scale range (0–10) of the other ambivalence conditions.

Maximum Ambivalence and Switch Trial Computation

Within a magnitude condition for each participant, the maximum ambivalence trial was denoted as the trial with the highest ambivalence score. Trial numbers were averaged if multiple trials had the same maximum ambivalence score. To designate the trial for the switch point, we denoted the second trial around the switch in preference as the switch trial (i.e., the first trial where an LL is preferred when trials are ordered by ascending *k* rank) for participants who switched preference once across trials. For participants with multiple switch points, *k* values were computed as the discount rate most consistent with the response pattern or as the geometric mean of discount rates that were equally consistent (Gray et al., 2016). Then, the switch trial was denoted as the trial with the *k* value of the next highest *k* rank. For instance, if a response pattern yielded a 0.0019 *k* value, the switch trial would be marked as 4 according to its *k* rank (in **Table 1**).

H1: Within-Individual Ambivalence Tracks Preference Switches

Prior to any H1 analyses, trial numbers were centered within individuals such that 0 represents the switch trial. Although the location of switch trials varied between individuals and magnitude conditions, preference switches occurred most often

within two trials around MCQ trial 6 by *k* rank. Thus, switch-centered trials farthest away from the 0-point had relatively few data points and high standard errors. To address this, switch-centered trials with cell counts totaling less than 20% of the participant count within each magnitude-ambivalence pairing were removed prior to H1 analyses. Moreover, if a participant never switched preference for a given magnitude condition, then that trial set was excluded from analyses because switch trials cannot be readily estimated from such response patterns (their data are shown in the **Supplementary Material**). For reference, 15.1 and 16.5% of our response patterns in small and large magnitude conditions, respectively, did not show a preference switch, whereas by ambivalence measurement condition, response patterns without preference switches were: A1 (16.8%), A2 (14.6%), A3 (14.1%), and A4 (17.8%).

As previously stated, it was expected that ambivalence would peak around the switch point. Initially, we attempted to fit non-linear curves (i.e., Gaussian and Cauchy) to the ambivalence scores *via* the *nlme* package in R (Pinheiro et al., 2021) due to the apparent non-linear form of the data. However, the non-linear models had convergence issues potentially due to a subset of individuals not showing the apparent non-linear form. Thus, instead of a non-linear approach, we used a dual-slopes mixed model with two linear slopes for before and after the switch trial and set the intercept on the switch trial; this intercept was chosen *via* model comparisons showing that the point of maximum ambivalence for most individuals was indeed at the switch trial (see **Supplementary Material** for more information on this approach).

The two slope terms were then quantified to determine (1) if ambivalence scores do indeed increase prior to the switch trial, (2) if, after a switch trial, ambivalence scores decrease again, and 3) whether there is asymmetry between slopes before versus after the switch trial. All nominal factors (magnitude condition, ambivalence measurement condition) within the model were effects coded. Random effects included both slope terms and random intercepts that were nested within individuals.

H2: Trial-Level Ambivalence Covaries With Diminished Sensitivities to Reward Delay and Magnitude

The goal of H2 analyses was to investigate whether greater degree of ambivalence is associated with diminished sensitivity to reward magnitude and delay differences as it relates to trial-level choice. We compared logistic mixed models following previous examples (Wileyto et al., 2004; Young, 2018) to determine if adding ambivalence variables (measurement conditions and scores) provided incremental predictive validity according to Akaike Information Criterion (AIC; Akaike, 1974). When interpreting AIC values, lower values indicate preferred models with a minimum difference of 4 required to prefer one model over another (Burnham et al., 2011). Three models were compared: (1) a "Base" model with only reward magnitude and delay sensitivity predictors (natural log-transformed LL/SS ratios) as done previously (Wileyto et al., 2004; Young, 2018), (2) a "BaseAmbMag" model with the reward sensitivities and magnitude-ambivalence pairings, and (3) an "AmbMag" model with reward sensitivities, magnitude-ambivalence pairings, and ambivalence scores. The interaction terms between the reward sensitivities and ambivalence scores would directly test H2, assuming that AmbMag is found to be the preferred model according to AIC differences. For all models, reward sensitivities were included as continuous, random effects in addition to their fixed effects. Any model terms that did not include the reward sensitivities, either as first-order terms or interactions, were removed as done previously (Young, 2018).

RESULTS AND DISCUSSION

Participant Attention and Data Quality

We used the detection of the magnitude effect (Thaler, 1981; Benzion et al., 1989; Myerson and Green, 1995; Green et al., 1997; Grace and McLean, 2005), the well-established phenomenon where smaller rewards are discounted more steeply than larger rewards, as our group-level attention check. A paired samples *t*-test contrasted within-individual differences in natural log-transformed *k* values between small and large magnitude conditions, and detected a significant difference, $t(369) = 26.35$, $p < 0.001$, Cohen's $d = 0.32$, with small magnitude rewards being discounted more steeply than large magnitude ones, $M_{Difference} = 0.66$, $SD = 0.48$. Although this study is limited in the lack of response validity indicators to gauge participants' attentiveness and engagement, our replication of the well-established magnitude effect serves as our group-level attention check and provides some assurance that participants were paying attention to the survey. Moreover, only MTurk workers that had completed at least 100 HITs with at least a 95% HIT approval were eligible for this study, which has been shown to provide higher quality data (Peer et al., 2014) and has been recommended as an alternative to using attention checks (Chandler and Shapiro, 2016). Additionally, when averaging consistency estimates between magnitude conditions, 79.2% of our participants had perfect consistency (one switch point per magnitude condition). Some researchers have suggested consistency scores serve as a proxy for attentiveness (Gray et al., 2016), so we believe the majority of our participants paid attention to and understood the task. Finally, there have been reports of "poorer data quality" in MTurk studies because of the presence of non-United States participants who may be hiding their IP address and subsequent geolocation (for a discussion, refer to Kennedy et al., 2020). Our data suggest that 2.9% of our sample consisted of participants with IP addresses outside the United States, whereas 7.3% of our sample used a virtual private network (VPN) to mask their geolocation. We elected not to remove these participants because (1) we believed the proportion of non-US participants was sufficiently small and unlikely to impact our results and (2) it is not uncommon for many United States participants to use a VPN service (Security.org Team, 2021). Moreover, even amongst the literature suggesting that a higher proportion of data from individuals using VPN is "poorer quality" (e.g.,

Kennedy et al., 2020), the absolute rate of "poorer quality" data remains low.

H1: Within-Individual Ambivalence Tracks Preference Switches

Figures 1, **2** show mean ambivalence scores centered on switch trials across magnitude-ambivalence pairings overlaid with dual-slopes mixed model predictions. Visual inspection of the figures suggests qualitative support for H1. That is, when centered on participants' respective switch trials, ambivalence peaks around and steadily declines away from the switch trial. However, while the aggregate data took on an apparent non-linear form, many participants also showed constant ambivalence across trials (8.7–29.9% of individuals depending on the magnitude-ambivalence pairing; see **Supplementary Figure 3** in the **Supplementary Material** for exemplar ambivalence score patterns). This between-subject variability may have led to the non-linear models described in section "Materials and Methods" failing to converge. As such, a dual-slopes linear mixed model quantified the apparent trends utilizing slope terms for ambivalence scores both before and after the switch trial.

The results from the dual-slopes linear mixed model overall supported the H1 hypothesis (see **Table 2**). Across magnitude-ambivalence pairings, ambivalence scores increased prior to the switch trial (b = 0.37, 95% CI = [0.32, 0.42], SEM = 0.02, $p < 0.001$) and decreased after the switch trial (b = −0.53, 95% CI = [−0.60, −0.46], SEM = 0.04, $p < 0.001$). The decreases in ambivalence scores following the switch trial were also sharper than the increases preceding it (ps < 0.001); however, post-switch slopes were likely steeper due to the right side of the switch trial on the X-axis containing more trials across pairings (see **Figures 1**, **2**). All slope values between pairings were significantly different from 0 (positive before switch, negative after switch; ps < 0.001), meaning each ambivalence measurement condition seemed to adequately characterize degree of ambivalence across the switch-centered MCQ trials. Given the multiple ambivalence measurement conditions, a secondary question of interest was concerned with identifying the condition that characterized ambivalence with highest sensitivity. However, the data showed minimal differences between conditions: the only significant comparison was A4 having a more negative slope after switch compared to A3 ($p < 0.01$). In that regard, ambivalence measurement conditions showed relatively consistent sensitivity in characterizing ambivalence scores for switch-centered trials. Additionally, ambivalence score means for switch-centered trials (**Figures 1**, **2**) were relatively low and close to score means for trial sets where participants did not switch preference (**Supplementary Figures 1**, **2**). Although this observation is important to note, we believe the lack of within-individual variation in participants who did not switch preference provides further support for H1 and that the relevant comparison is the constant versus variable ambivalence for trial sets without a switch trial and those with one, respectively.

Overall, H1 was supported in that ambivalence scores tended to vary across trials and track switches in preferences. Our study shows that participant-reported ambivalence scores peak at the switch trial and steadily decrease away from it with minimal differences between magnitude-ambivalence pairings, which to the authors' knowledge is the first study to validate this within an assessment of DD. These findings parallel those of studies using mouse cursor trajectories (Dshemuchadse et al., 2013) and response times (Robles and Vargas, 2007, 2008; Rodriguez et al., 2014) to explore decision making around the point of subjective value equivalence, which show correlates of greater choice deliberation. While these convergent findings are interesting, it is presently unclear whether cursor trajectories or RTs merely covary with ambivalence scores or directly map onto the ambivalence construct. Regardless, the demonstrated variability in ambivalence scores and relation to trials associated with the discount rate allowed us to investigate how ambivalence factors in trial-level decision making in H2.

TABLE 2 | Parameter estimates of the dual-slopes linear mixed model of ambivalence scores.

	Fixed effects				
Parameter	***b***	**95% CI**	**SE**	***z/t***	***p***
(Intercept)	**3.60**	**[3.36, 3.84]**	**0.12**	**29.57**	**<0.001**
SmallMag	−0.02	[−0.12, 0.09]	0.05	− 0.30	0.76
A1	**−0.65**	**[−0.93, −0.37]**	**0.14**	**−4.52**	**<0.001**
A2	**1.98**	**[1.70, 2.26]**	**0.14**	**13.78**	**<0.001**
A3	**−0.40**	**[−0.68, −0.12]**	**0.14**	**−2.78**	**0.01**
Pre-Switch	**0.37**	**[0.32, 0.42]**	**0.02**	**14.77**	**<0.001**
Post-Switch	**−0.53**	**[−0.60, −0.46]**	**0.04**	**−14.76**	**<0.001**
SmallMag × A1	−0.12	[−0.47, 0.23]	0.18	−0.67	0.50
SmallMag × A2	0.05	[−0.30, 0.40]	0.18	0.28	0.78
SmallMag × A3	−0.02	[−0.38, 0.33]	0.18	−0.14	0.89
SmallMag × Pre-Switch	−0.002	[−0.03, 0.04]	0.02	0.07	0.95
SmallMag × Post-Switch	0.01	[−0.04, 0.07]	0.03	0.51	0.61
A1 × Pre-Switch	−0.06	[−0.13, 0.01]	0.04	−1.68	0.09
A1 × Post-Switch	−0.02	[−0.13, 0.08]	0.05	−0.46	0.65
A2 × Pre-Switch	−0.03	[−0.10, 0.04]	0.04	−0.83	0.40
A2 × Post-Switch	0.07	[−0.04, 0.18]	0.05	1.28	0.20
A3 × Pre-Switch	−0.001	[−0.07, 0.07]	0.04	−0.06	0.95
A3 × Post-Switch	**0.12**	**[0.02, 0.22]**	**0.05**	**2.38**	**0.02**
SmallMag × A1 × Pre-Switch	0.04	[−0.03, 0.12]	0.04	1.13	0.26
SmallMag × A2 × Pre-Switch	0.02	[−0.05, 0.10]	0.04	0.59	0.55
SmallMag × A3 × Pre-Switch	**−0.11**	**[−0.19, −0.03]**	**0.04**	**−2.82**	**0.05**
SmallMag × A1 × Post-Switch	−0.02	[−0.13, 0.10]	0.06	−0.31	0.76
SmallMag × A2 × Post-Switch	−0.04	[−0.16, 0.07]	0.06	−0.71	0.48
SmallMag × A3 × Post-Switch	**0.17**	**[0.06, 0.28]**	**0.06**	**3.11**	**0.002**

SmallMag, small magnitude condition; Pre-Switch, slope term before switch point (i.e., before switch); Post-Switch, slope term after switch point (i.e., after switch); A1, Ambivalence measurement condition 1; A2, Ambivalence measurement condition 2; A3, Ambivalence measurement condition 3; 95% CI reflect Wald confidence intervals. Significant effects in bold.

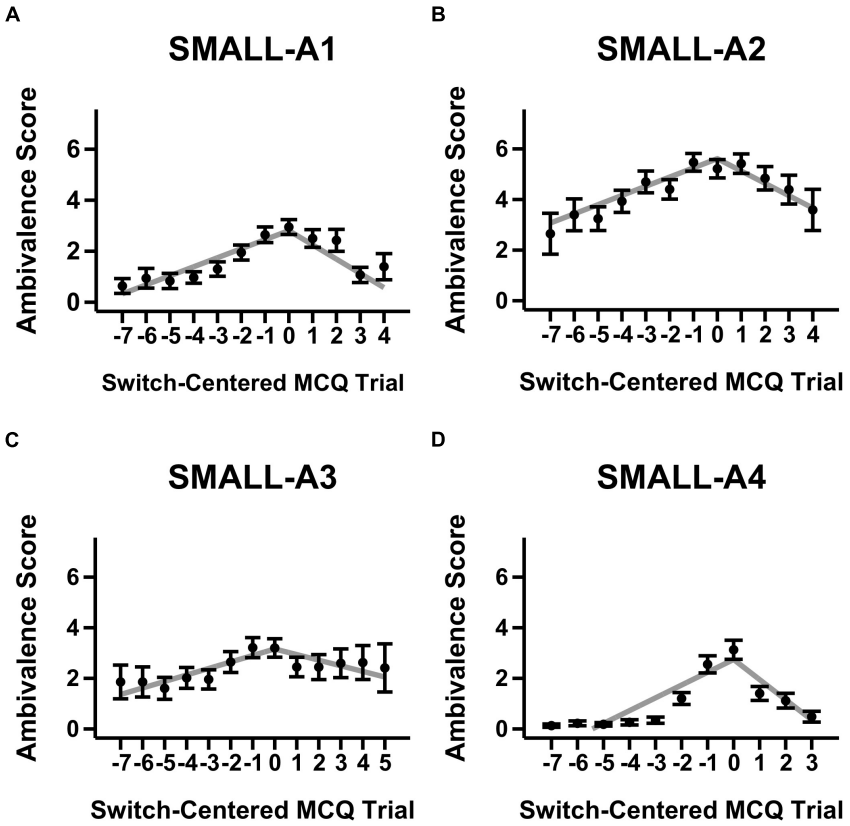


FIGURE 1 | Mean ambivalence scores and dual-slopes mixed model predictions for small magnitude trials split by ambivalence measurement condition. X-axis denotes the MCQ trial number centered by switch trial, Y-axis denotes the degree of ambivalence, and the panels denote the specific magnitude-ambivalence pairing: **(A)** Small-A1; **(B)** Small-A2; **(C)** Small-A3; **(D)** Small-A4. Black points indicate the trial-level means in self-reported ambivalence scores with standard error bars. Gray lines indicate the predicted ambivalence scores from the dual-slopes mixed model.

H2: Trial-Level Ambivalence Covaries With Diminished Sensitivities to Reward Delay and Magnitude

H1 revealed that within-individual ambivalence tracked switches in preference across DD trials. H2 sought to extend H1 by testing associations between trial-level ambivalence and sensitivities to reward magnitudes and delays. We first compared predictive utility based on AIC scores of an omnibus model including reward sensitivities, magnitude-ambivalence pairings, and ambivalence scores (AmbMag) to a model with only the reward sensitivities and magnitude-ambivalence pairings (BaseAmbMag) as well as a model with only the reward sensitivities (Base). Overall, the AmbMag model (omnibus; AIC = 4112.0) had substantially improved predictive utility compared to the BaseAmbMag model (AIC = 4159.0, ΔAIC = 47 versus AmbMag), which itself evinced substantially improved predictive utility compared to the Base model (AIC = 4306.1, ΔAIC = 147.1 versus BaseAmbMag). The results therefore warrant that adding ambivalence estimates to models predicting DD choices improves model accuracies.

The omnibus AmbMag model estimates are shown in **Table 3**. The effects of reward magnitude (OR = 420836.64, b = 12.95, 95% CI = [11.01, 14.90], SEM = 0.99, $p < 0.001$) and delay (OR = 0.29, b = −1.25, 95% CI = [−1.38, −1.12], SEM = 0.07, $p < 0.001$) both significantly modulated DD choices as shown previously (Young, 2018). Specifically, as the magnitude differences between choice options increasingly favored the LL option, so too did trial choices. Conversely, as the LL became increasingly delayed relative to the SS, choice allocations favored the SS. Moreover, the reward delay sensitivity was found to depend on the magnitude condition (OR = 0.90, b = −0.11, 95% CI = [−0.16, −0.06], SEM = 0.03, $p < 0.001$), such that participants were more sensitive to the reward delay differences in the small magnitude condition compared to the large magnitude one ($p < 0.001$). This interaction reflects what is commonly referred to as the "magnitude effect" within DD research (Thaler, 1981; Benzion et al., 1989; Myerson and Green, 1995; Green et al., 1997; Grace and McLean, 2005), and serves as further evidence that reward magnitude is a key dimension in DD decision making.

Across magnitude-ambivalence pairings, the effect of reward delay sensitivity (OR = 1.03, b = 0.03, 95% CI = [0.01, 0.04], SEM = 0.01, $p < 0.001$) on trial-level choice decreased as ambivalence scores increased (i.e., increasing ambivalence trended delay sensitivity values toward 0). In other words, the delay to the LL seemed to weigh less in participants' decision

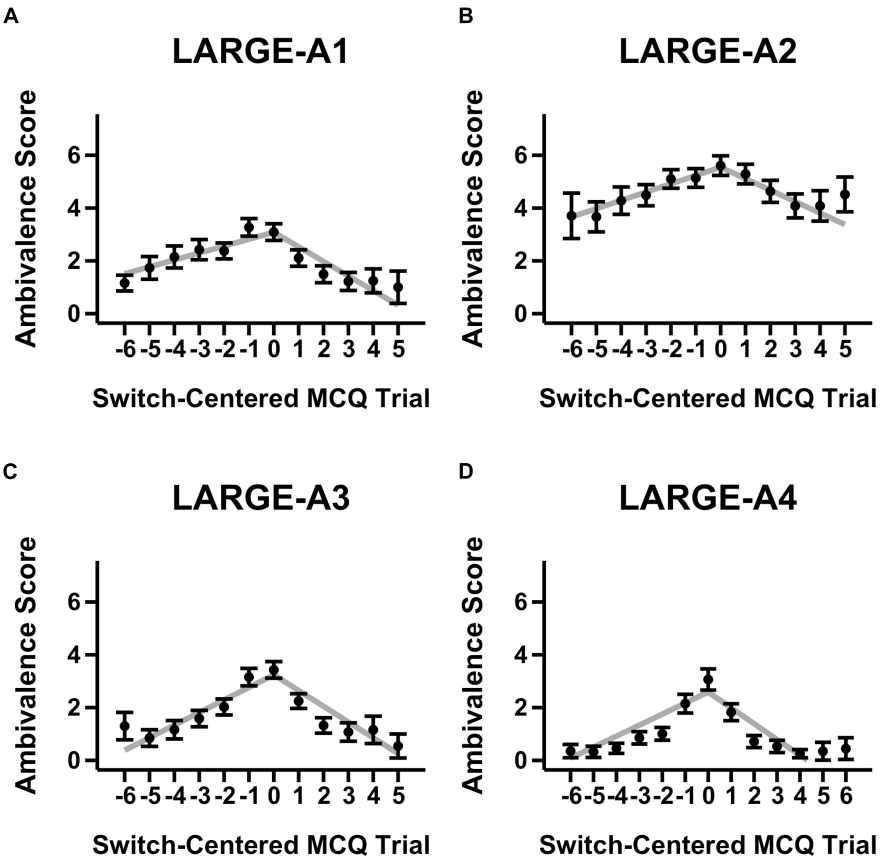


FIGURE 2 | Mean ambivalence scores and dual-slopes mixed model predictions for large magnitude trials split by ambivalence measurement condition. X-axis denotes the MCQ trial number centered by switch trial, Y-axis denotes the degree of ambivalence, and the panels denote the specific magnitude-ambivalence pairing: **(A)** Large-A1; **(B)** Large-A2; **(C)** Large-A3; **(D)** Large-A4. Black points indicate the trial-level means in self-reported ambivalence scores with standard error bars. Gray lines indicate the predicted ambivalence scores from the dual-slopes mixed model.

making when they were less certain about their preference. While we observed significant interactions between reward delay sensitivity, ambivalence scores, magnitude condition, and ambivalence measurement condition (see **Table 3**), we choose not to interpret these effects as (1) H1 analyses showed all magnitude-ambivalence pairings to consistently characterize trends in ambivalence scores and (2) we had no *a priori* hypotheses regarding differences between the ambivalence measurement conditions.

That ambivalence scores covary with reduced sensitivities to delays between choice options demonstrates a novel finding in DD research. Nonetheless, H2 is partially supported in that participants' sensitivity to reward magnitude differences does not seem to vary even as their choice ambivalence increases, and they may also look to features other than the delays between choice options when making their decision. However, what features may become more prominent during states of ambivalence is left to future research.

Limitations and Future Directions

It is necessary to acknowledge that the primary limitation of our study is the use of hypothetical outcomes for our DD assessment. However, prior research has shown statistically equivalent effects when using real versus hypothetical rewards for these assessments (Matusiewicz et al., 2013). A broader limitation of our study is the use of the MCQ as our chosen DD assessment. Although it is a popular task for assessing DD, some have criticized its fixed-choice structure as lacking in adequate sampling of the possible parameter space of reward magnitudes and delays (Young, 2018). For instance, while the range of magnitude differences is $1–$54 (translates to 0–1 in natural log transformed magnitude ratio between LL/SS), the range of delays to LL receipt is 7–186 days (translates to 2–6 in natural log transformed delay ratio between LL/SS). Hence, it is unclear how ambivalence may track participants' choice patterns given an alternative DD assessment. Future research may consider alternative assessments and models of DD to study choice ambivalence, including ones that incorporate each trial-level decision to model discounting behavior (Dai and Busemeyer, 2014; Rodriguez et al., 2014; Dai et al., 2016; Molloy et al., 2020; Kvam et al., 2021).

Furthermore, the present study is limited in the lack of response validity indicators to gauge attentiveness at the level of individual participants (for a discussion on response validity

TABLE 3 | Parameter estimates of the logistic mixed model of ambivalence and sensitivities to delay and magnitude ratio.

	Fixed Effects					
Parameter	***OR***	***b***	**95% CI**	**SE**	***z/t***	***p***
AmbMag Model						
MagRatio	**420836.64**	**12.95**	**[11.01,14.90]**	**0.99**	**13.05**	**<0.001**
DelayRatio	**0.29**	**−1.25**	**[−1.38, −1.12]**	**0.07**	**−18.42**	**<0.001**
MagRatio × SmallMag	0.65	−0.43	[−0.89,0.03]	0.23	−1.84	0.065
DelayRatio × SmallMag	**0.90**	**−0.11**	**[−0.16, −0.06]**	**0.03**	**−4.01**	**<0.001**
MagRatio × A1	0.84	−0.18	[−2.67,2.31]	1.27	−0.14	0.89
MagRatio × A2	0.31	−1.16	[−3.73,1.40]	1.31	−0.89	0.37
MagRatio × A3	1.40	0.34	[−0.92,1.61]	0.65	0.53	0.59
DelayRatio × A1	0.94	−0.06	[−0.19,0.07]	0.07	−0.92	0.36
DelayRatio × A2	1.02	0.02	[−0.12,0.15]	0.07	0.22	0.82
DelayRatio × A3	1.05	0.05	[−0.08,0.18]	0.07	0.78	0.44
MagRatio × AmbScore	0.90	−0.10	[−0.24,0.03]	0.07	−1.49	0.14
DelayRatio × AmbScore	**1.03**	**0.03**	**[0.01,0.04]**	**0.01**	**3.81**	**<0.001**
MagRatio × SmallMag x A1	1.16	0.15	[−1.60,1.90]	0.89	0.17	0.87
MagRatio × SmallMag x A2	0.55	−0.60	[−2.41,1.20]	0.92	−0.65	0.51
MagRatio × SmallMag x A3	1.08	0.08	[−1.63,1.79]	0.87	0.10	0.92
DelayRatio × SmallMag x A1	1.00	0	[−0.16,0.17]	0.08	0.05	0.95
DelayRatio × SmallMag x A2	1.13	0.12	[−0.05,0.30]	0.09	1.41	0.16
DelayRatio × SmallMag x A3	1.16	0.15	[−0.01,0.31]	0.08	1.81	0.07
MagRatio × SmallMag × AmbScore	0.98	−0.02	[−0.13,0.09]	0.06	−0.36	0.72
DelayRatio × SmallMag × AmbScore	1.01	0.01	[−0.01,0.02]	0.01	1.09	0.27
MagRatio × AmbScore × A1	**0.78**	**−0.25**	**[−0.47, −0.03]**	**0.11**	**−2.20**	**0.03**
MagRatio × AmbScore × A2	1.12	0.11	[−0.08,0.31]	0.10	1.15	0.25
MagRatio × AmbScore × A3	1.03	0.03	[−0.16,0.23]	0.10	0.33	0.74
DelayRatio × AmbScore × A1	1.00	0	[−0.02,0.02]	0.01	−0.04	0.97
DelayRatio × AmbScore × A2	0.99	−0.01	[−0.03,0.01]	0.01	−1.33	0.18
DelayRatio × AmbScore × A3	**0.97**	**−0.03**	**[−0.05, −0.01]**	**0.01**	**−3.02**	**0.002**
MagRatio × SmallMag × A1 × AmbScore	0.91	−0.09	[−0.34,0.15]	0.13	−0.75	0.45
MagRatio × SmallMag × A2 × AmbScore	1.06	0.06	[−0.16,0.28]	0.11	0.53	0.59
MagRatio × SmallMag × A3 × AmbScore	1.21	0.19	[−0.004,0.39]	0.01	1.92	0.054
DelayRatio × SmallMag × A1 × AmbScore	1.02	0.02	[−0.001,0.05]	0.01	1.98	0.057
DelayRatio × SmallMag × A2 × AmbScore	**0.96**	**−0.04**	**[−0.06, −0.01]**	**0.01**	**−3.14**	**0.002**
DelayRatio × SmallMag × A3 × AmbScore	0.99	−0.01	[−0.03,0.01]	0.01	−1.08	0.28

MagRatio, sensitivity to magnitude differences; DelayRatio, sensitivity to delay differences; A1, Ambivalence condition 1; A2, Ambivalence condition 2; A3, Ambivalence condition 3; OR, odds ratio. 95% CI reflect Wald confidence intervals. Significant effects in bold.

indicators, see Chmielewski and Kucker, 2020). While we believe participants demonstrated sufficient attentiveness on a group level, we cannot rule out the possibility that the potential inclusion of participants that might have otherwise failed response validity indicators impacted our model estimates. Participants who used a VPN or had a non-United States IP address may have been more likely to fail such indicators and bias our estimates further. This project also did not include a comparator condition to assess whether inquiries about ambivalence impacted rate of DD, nor did it include potentially less reactive measures of ambivalence, such as trial-level RT as in previous work (Robles and Vargas, 2007, 2008; Rodriguez et al., 2014).

A direction for future research would be to directly assess the convergence between non-reactive (e.g., response time) and reactive (e.g., mouse cursor trajectory, self-reported ambivalence scores) measures relevant to choice difficulty. One idea that we propose might be particularly worthwhile is a construct we call the *window of ambivalence*. Ambivalence is relatively high for several trials around the switch trial when observing **Figures 1**, **2**. This range of relatively high ambivalence scores may be termed the "window of ambivalence," which has not been identified in previous research. We attempted to index this window by assessing the spread parameters from non-linear distribution curve fits to ambivalence data across trials. However, similar to our previous non-linear modeling attempts, the models had convergence issues that deemed the analysis plan untenable (see **Supplementary Material** for more information on this approach). Future research may wish to expand upon this work through assessing the true functional form of the window of ambivalence. Then, researchers could include manipulations of DD (e.g., Radu et al., 2011) to

see whether the ambivalence window tracks the change in discounting rate along the trial continuum (such as in the MCQ) and whether the window expands or shrinks following the manipulation.

In conclusion, we used largely novel assessment strategies to characterize trial-level ambivalence in a DD task. On a group-level, our results showed that: (1) ambivalence tracks preference switches across trials; and (2) ambivalence is associated with a reduced ability to discriminate between reward delays when it comes to trial-level choice. We believe that ambivalence may be an interesting construct to explore further in research on DD choice and manipulations of individual rates of DD.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants have been reviewed and approved by the Institutional Review Board (Human Research Protection Program) at the University of Kansas-Lawrence campus.

AUTHOR CONTRIBUTIONS

RY and SG contributed to the conception and designed of the study. SG organized the database and wrote the first draft of the manuscript. SG and AS performed the statistical analyses. All authors contributed to manuscript revision, read, and approved the submitted version.

FUNDING

The present research was partially supported by funding from the National Center for Advancing Translational Sciences 5TL1TR002368 (AS).

ACKNOWLEDGMENTS

The authors would like to acknowledge Michael Young for his statistical guidance and assistance. The first author dedicates this work to his grandfather, Jovan Jurukovski, who inspired him to pursue a career in academic research.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnbeh.2021.782991/full#supplementary-material

REFERENCES

Akaike, H. (1974). A new look at the statistical model identification. *IEEE Trans. Autom. Control* 19, 716–723. doi: 10.1109/TAC.1974.1100705

Bates, D., Maechler, M., Bolker, B., and Walker, S. (2015). Fitting linear mixed-effects models using lme4. *J. Stat. Softw.* 67, 1–48. doi: 10.18637/jss.v067.i01

Benzion, U., Rapoport, A., and Yagil, J. (1989). Discount rates inferred from decisions: an experimental study. *Manag. Sci.* 39:270.

Burnham, K. P., Anderson, D. R., and Huyvaert, K. P. (2011). AIC model selection and multimodel inference in behavioral ecology: some background, observations, and comparisons. *Behav. Ecol. Sociobiol.* 65, 23–35. doi: 10.1007/s00265-010-1029-6

Chandler, J., and Shapiro, D. (2016). Conducting clinical research using crowdsourced convenience samples. *Annu. Rev. Clin. Psychol.* 12, 53–81. doi: 10.1146/annurev-clinpsy-021815-093623

Chesson, H. W., Leichliter, J. S., Zimet, G. D., Rosenthal, S. L., Bernstein, D. I., and Fife, K. H. (2006). Discount rates and risky sexual behaviors among teenagers and young adults. *J. Risk Uncertain.* 32, 217–230. doi: 10.1007/s11166-006-9520-1

Chmielewski, M., and Kucker, S. C. (2020). An MTurk crisis? Shifts in data quality and the impact on study results. *Soc. Psychol. Personal. Sci.* 11, 464–473. doi: 10.1177/1948550619875149

Dai, J., and Busemeyer, J. R. (2014). A probabilistic, dynamic, and attribute-wise model of intertemporal choice. *J. Exp. Psychol. Gen.* 143, 1489–1514. doi: 10.1037/a0035976

Dai, J., Gunn, R. L., Gerst, K. R., Busemeyer, J. R., and Finn, P. R. (2016). A random utility model of delay discounting and its application to people with externalizing psychopathology. *Psychol. Assess.* 28, 1198–1206. doi: 10.1037/pas0000248

Dshemuchadse, M., Scherbaum, S., and Goschke, T. (2013). How decisions emerge: action dynamics in intertemporal decision making. *J. Exp. Psychol. Gen.* 142, 93–100. doi: 10.1037/a0028499

Grace, R. C., and McLean, A. P. (2005). Integrated versus segregated accounting and the magnitude effect in temporal discounting. *Psychon. Bull. Rev.* 12, 732–739. doi: 10.3758/BF03196765

Gray, J. C., Amlung, M. T., Palmer, A. A., and MacKillop, J. (2016). Syntax for calculation of discounting indices from the monetary choice questionnaire and probability discounting questionnaire: syntax for MCQ and PDQ. *J. Exp. Anal. Behav.* 106, 156–163. doi: 10.1002/jeab.221

Green, L., Myerson, J., and Mcfadden, E. (1997). Rate of temporal discounting decreases with amount of reward. *Mem. Cogn.* 25, 715–723. doi: 10.3758/BF03211314

Kekic, M., McClelland, J., Bartholdy, S., Chamali, R., Campbell, I. C., and Schmidt, U. (2020). Bad things come to those who do not wait: temporal discounting is associated with compulsive overeating, eating disorder psychopathology and food addiction. *Front. Psychiatry* 10:978. doi: 10.3389/fpsyt.2019.00978

Kennedy, R., Clifford, S., Burleigh, T., Waggoner, P. D., Jewell, R., and Winter, N. J. G. (2020). The shape of and solutions to the MTurk quality crisis. *Polit. Sci. Res. Methods* 8, 614–629. doi: 10.1017/psrm.2020.6

Kirby, K. N., Petry, N. M., and Bickel, W. K. (1999). Heroin addicts have higher discount rates for delayed rewards than non-drug-using controls. *J. Exp. Psychol. Gen.* 128, 78–87.

Kvam, P. D., Romeu, R. J., Turner, B. M., Vassileva, J., and Busemeyer, J. R. (2021). Testing the factor structure underlying behavior using joint cognitive models: impulsivity in delay discounting and Cambridge gambling tasks. *Psychol. Methods* 26, 18–37. doi: 10.1037/met0000264

Lenth, R. V. (2021). *emmeans: Estimated Marginal Means, aka Least-Squares Means*. Available online at: https://CRAN.R-project.org/package=emmeans (accessed October 15, 2021).

MacKillop, J., Amlung, M. T., Few, L. R., Ray, L. A., Sweet, L. H., and Munafò, M. R. (2011). Delayed reward discounting and addictive behavior: a meta-analysis. *Psychopharmacology* 216, 305–321. doi: 10.1007/s00213-011-2229-0

MacKillop, J., and Kahler, C. W. (2009). Delayed reward discounting predicts treatment response for heavy drinkers receiving smoking cessation treatment. *Drug Alcohol Depend* 104, 197–203. doi: 10.1016/j.drugalcdep.2009.04.020

Matusiewicz, A. K., Carter, A. E., Landes, R. D., and Yi, R. (2013). Statistical equivalence and test-retest reliability of delay and probability discounting using real and hypothetical rewards. *Behav. Process.* 100, 116–122. doi: 10.1016/j.beproc.2013.07.019

Mazur, J. E. (1987). "An adjusting procedure for studying delayed reinforcement," in *The Effect of Delay and of Intervening Events on Reinforcement Value Quantitative Analyses of Behavior*, Vol. 5, eds M. L. Commons, J. E. Mazur, J. A. Nevin, and H. Rachlin (Hillsdale, NJ: Lawrence Erlbaum Associates, Inc), 55–73.

Molloy, M. F., Romeu, R. J., Kvam, P. D., Finn, P. R., Busemeyer, J., and Turner, B. M. (2020). Hierarchies improve individual assessment of temporal discounting behavior. *Decision* 7, 212–224. doi: 10.1037/dec0000121

Myerson, J., and Green, L. (1995). Discounting of delayed rewards: models of individual choice. *J. Exp. Anal. Behav.* 64, 263–276. doi: 10.1901/jeab.1995.64-263

Odum, A. L. (2011). Delay discounting: I'm a k, You're a k. *J. Exp. Anal. Behav.* 96, 427–439. doi: 10.1901/jeab.2011.96-423

Peer, E., Vosgerau, J., and Acquisti, A. (2014). Reputation as a sufficient condition for data quality on Amazon mechanical turk. *Behav. Res. Methods* 46, 1023–1031. doi: 10.3758/s13428-013-0434-y

Pinheiro, J., Bates, D., DebRoy, S., Sarkar, D., and R Core Team (2021). *nlme: Linear and Nonlinear Mixed Effects Models*. Available online at: https://cran.r-project.org/package=nlme (accessed October 15, 2021).

Priester, J. R., and Petty, R. E. (1996). The gradual threshold model of ambivalence: relating the positive and negative bases of attitudes to subjective ambivalence. *J. Pers. Soc. Psychol.* 71, 431–449.

Priester, J. R., and Petty, R. E. (2001). Extending the bases of subjective attitudinal ambivalence: interpersonal and intrapersonal antecedents of evaluative tension. *J. Pers. Soc. Psychol.* 80, 19–34.

R Core Team (2019). *R: A Language and Environment for Statistical Computing*. Vienna: R Foundation For Statistical Computing.

Radu, P. T., Yi, R., Bickel, W. K., Gross, J. J., and McClure, S. M. (2011). A mechanism for reducing delay discounting by altering temporal attention. *J. Exp. Anal. Behav.* 96, 363–385. doi: 10.1901/jeab.2011.96-363

Robles, E., and Vargas, P. A. (2007). Functional parameters of delay discounting assessment tasks: order of presentation. *Behav. Processes* 75, 237–241. doi: 10.1016/j.beproc.2007.02.014

Robles, E., and Vargas, P. A. (2008). Parameters of delay discounting assessment: number of trials, effort, and sequential effects. *Behav. Process.* 78, 285–290. doi: 10.1016/j.beproc.2007.10.012

Rodriguez, C. A., Turner, B. M., and McClure, S. M. (2014). Intertemporal choice as discounted value accumulation. *PLoS One* 9:e90138. doi: 10.1371/journal.pone.0090138

Security.org Team (2021). *VPN Consumer Usage, Adoption, and Shopping Study: 2021*. Available online at: https://www.security.org/resources/vpn-consumer-report-annual/ (accessed December 5, 2021).

Sheffer, C., Mackillop, J., McGeary, J., Landes, R., Carter, L., Yi, R., et al. (2012). Delay discounting, locus of control, and cognitive impulsiveness independently predict tobacco dependence treatment outcomes in a highly dependent, lower socioeconomic group of smokers. *Am. J. Addict.* 21, 221–232. doi: 10.1111/j.1521-0391.2012.00224.x

Stanger, C., Budney, A. J., and Bickel, W. K. (2013). A developmental perspective on neuroeconomic mechanisms of contingency management. *Psychol. Addict. Behav. J. Soc. Psychol. Addict. Behav.* 27, 403–415. doi: 10.1037/a0028748

Thaler, R. (1981). Some empirical evidence on dynamic inconsistency. *Econ. Lett.* 8, 201–207. doi: 10.1016/0165-1765(81)90067-7

Wickham, H., Averick, M., Bryan, J., Chang, W., McGowan, L., François, R., et al. (2019). Welcome to the tidyverse. *J. Open Source Softw.* 4:1686. doi: 10.21105/joss.01686

Wileyto, E. P., Audrain-Mcgovern, J., Epstein, L. H., and Lerman, C. (2004). Using logistic regression to estimate delay-discounting functions. *Behav. Res. Methods Instrum. Comput.* 36, 41–51. doi: 10.3758/BF03195548

Yi, R., Mitchell, S., and Bickel, W. K. (2010). "Delay discounting and substance abuse-dependence," in *Impulsivity: The Behavioral and Neurological Science of Discounting*, eds G. Madden, W. K. Bickel, and T. Critchfield (Washington, D.C: American Psychological Association), 191–211.

Young, M. E. (2018). Discounting: a practical guide to multilevel analysis of choice data. *J. Exp. Anal. Behav.* 109, 293–312. doi: 10.1002/jeab.316

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Behavioral Neuroscience

SYSTEMATIC REVIEW
published: 10 February 2022
doi: 10.3389/fnbeh.2022.787322

Deprivation Has Inconsistent Effects on Delay Discounting: A Review

Haylee Downey[1,2], *Jeremy M. Haynes*[1], *Hannah M. Johnson*[1] *and Amy L. Odum*[1]*

[1] Odum Laboratory, Department of Psychology, Utah State University, Logan, UT, United States, [2] Translational Biology Medicine and Health Graduate Program, Virginia Tech, Blacksburg, VA, United States

Delay discounting, the tendency for outcomes to be devalued as they are more temporally remote, has implications as a target for behavioral interventions. Because of these implications, it is important to understand how different states individuals may face, such as deprivation, influence the degree of delay discounting. Both dual systems models and state-trait views of delay discounting assume that deprivation may result in steeper delay discounting. Despite early inconsistencies and mixed results, researchers have sometimes asserted that deprivation increases delay discounting, with few qualifications. The aim of this review was to determine what empirical effect, if any, deprivation has on delay discounting. We considered many kinds of deprivation, such as deprivation from sleep, drugs, and food in humans and non-human animals. For 23 studies, we analyzed the effect of deprivation on delay discounting by computing effect sizes for the difference between delay discounting in a control, or baseline, condition and delay discounting in a deprived state. We discuss these 23 studies and other relevant studies found in our search in a narrative review. Overall, we found mixed effects of deprivation on delay discounting. The effect may depend on what type of deprivation participants faced. Effect sizes for deprivation types ranged from small for sleep deprivation (Hedge's *g*s between −0.21 and 0.07) to large for opiate deprivation (Hedge's *g*s between 0.42 and 1.72). We discuss possible reasons why the effect of deprivation on delay discounting may depend on deprivation type, including the use of imagined manipulations and deprivation intensity. The inconsistency in results across studies, even when comparing within the same type of deprivation, indicates that more experiments are needed to reach a consensus on the effects of deprivation on delay discounting. A basic understanding of how states affect delay discounting may inform translational efforts.

Keywords: delay discounting, review, state, deprivation, withdrawal

OPEN ACCESS

Edited by:
Marco Bortolato,
The University of Utah, United States

Reviewed by:
Serge H. Ahmed,
Centre National de la Recherche Scientifique (CNRS), France
Marta Malesza,
Jagiellonian University, Poland

***Correspondence:**
Amy L. Odum
amy.odum@usu.edu

Specialty section:
This article was submitted to Motivation and Reward, a section of the journal Frontiers in Behavioral Neuroscience

Received: *30 September 2021*
Accepted: *11 January 2022*
Published: *10 February 2022*

Citation:
Downey H, Haynes JM, Johnson HM and Odum AL (2022) Deprivation Has Inconsistent Effects on Delay Discounting: A Review. Front. Behav. Neurosci. 16:787322. doi: 10.3389/fnbeh.2022.787322

INTRODUCTION

Delay discounting refers to the tendency for outcomes to be devalued as they occur more remotely in the future (Mazur, 1987; Odum, 2011a). Delay discounting is used as a measure of sensitivity to delayed consequences, where greater delay discounting indicates less sensitivity to delayed consequences (Strickland and Johnson, 2021). Greater degree of delay discounting has been associated with a variety of poor health behaviors, including smoking (e.g., Bickel et al., 1999; Mitchell, 1999), substance use (e.g., Reynolds, 2006; MacKillop et al., 2011), more energy-dense food purchasing choices (e.g., Appelhans et al., 2019), risky sexual behaviors (e.g., Johnson and Bruner, 2012; Sweeny et al., 2020), problematic gambling (e.g., Alessi and Petry, 2003), and lower

exercise frequency (e.g., Daugherty and Brase, 2010; Sweeney and Culcea, 2017). In addition, a meta-analysis indicated that individuals diagnosed with schizophrenia, bipolar disorder, and major depressive disorder may tend to have steeper delay discounting than controls (Amlung et al., 2019). Delay discounting also predicts success in substance use treatment programs for adolescents using marijuana (Stanger et al., 2012) and for mothers who smoke tobacco cigarettes (Yoon et al., 2007). Because of associations with numerous health behaviors and psychiatric illnesses (Amlung et al., 2019; Levitt et al., 2020), delay discounting has been called a trans-disease process (Bickel et al., 2019; Felton et al., 2020; although see Bailey et al., 2021).

As a trans-disease process, delay discounting may be so steep or so shallow that it is considered maladaptive. For instance, individuals with substance use disorders may show excessive delay discounting (i.e., less sensitivity to delayed rewards) whereas individuals with anorexia nervosa may show especially low delay discounting (i.e., less sensitivity to immediate rewards; Levitt al., 2020). Several behavioral interventions have been developed that seek to reduce steep discounting, and thus patterns of maladaptive behavior (Rung and Madden, 2018). For instance, episodic future thinking (EFT; prospective imagining) has been shown to reduce delay discounting of money and number of self-administered cigarette puffs in the laboratory (Stein et al., 2016). To help individuals make optimal choices (i.e., choices that decrease risk of morbidity and mortality; Fields et al., 2014), it is important to consider the state that a person is in while making a choice. Delay discounting may change due to changes in state (Odum and Baumann, 2010). Deprivation is a state that may influence sensitivity to rewards. One might reasonably predict that individuals are more sensitive to immediate rewards when they are hungry, tired, thirsty, or more broadly, when they are deprived of something they need.

Deprivation is generally regarded as a fundamental determinant of reinforcer effectiveness, especially for behavior analysts (e.g., Michael, 1982; Miller, 2006). For instance, food may be more valuable when an individual is hungry and less so when sated. Furthermore, non-human animals are generally food restricted in behavioral research when food serves as a reinforcer (e.g., Hurwitz and Davis, 1983). Evolutionarily, it may be *adaptive* for immediate outcomes to be more valuable when deprived (Logue, 1988). Withdrawal, or deprivation from a drug, may increase valuation for immediate rewards specifically when the reward may be used to reduce negative affect brought on by withdrawal (Baker et al., 2004). Deprivation clearly has implications for the valuation of an outcome; after being deprived, something one needs immediately to survive may have a much higher value than other things (see Loewenstein, 1996).

The relationship between deprivation and valuation was studied as early as the 1980s in the self-control paradigm (e.g., Christensen-Szalanski et al., 1980). In the self-control and the delay discounting paradigms, participants make a series of choices between smaller sooner and larger later outcomes. In the delay discounting paradigm, tasks aim to find amounts participants are indifferent to receiving now or at a range of delays (Odum, 2011a). Indifference points are then plotted to create a delay discounting curve and mathematical models can be fit to the indifference points (see, e.g., Mazur, 1987; Green and Myerson, 2004). The dependent measures often used in delay discounting, the parameter k and the Area Under the Curve (AUC), are determined by the shape of the whole curve. In delay discounting, a greater number of smaller sooner choices results in a steeper delay discounting curve. In contrast, there are no indifference point curves in the self-control paradigm. Rather, the frequency of larger later choices may be determined for a number of delays or sometimes only one delay (Evenden and Ryan, 1996). A greater number of choices for larger later outcomes indicates more self-control and less impulsivity (De Wit, 2009). In humans and non-human animals, number of choices for larger later outcomes has been found to found to increase, decrease, and not change as a result of food deprivation (Logue and Peña-Correal, 1985; Logue et al., 1988; Kirk and Logue, 1997), contrary to assumptions. Other frameworks that predict an increase in sensitivity to immediate consequences due to deprivation include dual systems approaches (e.g., Van den Bos and McClure, 2012).

Delay discounting has long been theorized to involve the interplay between two (dual) systems (e.g., Schneider and Shiffrin, 1977; Thaler and Shefrin, 1981; Schelling, 1984). Some researchers conceptualize impulsivity as transitioning from cold to hot states (Logue, 1988; Metcalfe and Mischel, 1999; Frederick et al., 2002) while others refer to a myopic "doer" and a farsighted "planner" (Thaler and Shefrin, 1981). More recently, researchers have investigated how several different neurological systems may interact to determine delay discounting choices (Frost and McNaughton, 2017; Noda et al., 2020; Loganathan et al., 2021). These models all include a valuation system and a cognitive control system. The valuation system consists of at least the ventral striatum, ventromedial prefrontal cortex, and medial orbitofrontal cortex and *determines* the present value of the two choice alternatives (smaller sooner and larger later, e.g., Noda et al., 2020; Loganathan et al., 2021; Stanger et al., 2013).The cognitive control system, including the lateral prefrontal cortex and dorsal anterior cingulate cortex, *compares* the present value of the two choices (Bickel et al., 2018; Noda et al., 2020; Loganathan et al., 2021).

In the competing neurobehavioral decision systems (CNDS) dual-systems model, dysregulation of the cognitive control system and the valuation system leads to maladaptive behavior (Bickel et al., 2012, 2016, 2019). Greater activation of the valuation system relative to the control system is associated with more choices for smaller sooner outcomes in delay discounting tasks (Frost and McNaughton, 2017). For example, a smaller Area Under the Curve (AUC; Myerson et al., 2001) is associated with greater activation in the valuation system, specifically the ventral striatum, and less activation in the executive system, specifically the ventromedial prefrontal cortex (Frost and McNaughton, 2017). Dysregulation of the executive and valuation systems is thought to be caused by factors such as stress and substance use (e.g., cocaine, Bickel et al., 2016). For instance, stress may reduce cognitive resources, leading to a hypoactive control system (Bickel et al., 2014, 2016). Accordingly, the CNDS model predicts that deprivation may result in hyperactivity in the valuation system or hypoactivity in the control system, leading to a greater number of choices for smaller sooner outcomes in a

delay discounting task, seemingly resulting in greater sensitivity to immediate outcomes (Loewenstein, 1996; Bickel et al., 2012; Van den Bos and McClure, 2012).

Because delay discounting may be both state-like and trait-like (Odum, 2011b; Odum et al., 2020; Haynes et al., 2021), one may also predict that deprivation can modulate delay discounting. Trait influences on delay discounting are evidenced by the fact that delay discounting measurements for individuals tend to be relatively stable over time and relatively similar in different situations (Odum and Baumann, 2010; Felton et al., 2020). State effects occur when delay discounting differs across repeated measurements due to changes in the environment or organism. For example, in one experiment, 20 individuals with problematic gambling completed delay discounting tasks in a gambling setting (i.e., a betting facility with a bar) or at a non-gambling setting (e.g., a coffee shop; Dixon et al., 2006). Individuals tended to have a lower AUC (steeper delay discounting) when they completed the task in the gambling setting compared to the non-gambling setting, demonstrating that context may play a role in determining degree of delay discounting. Drug administration (De Wit and Mitchell, 2010), emotion (Wilson and Daly, 2004), stress (Fields et al., 2014), blood glucose level (Wang and Dvorak, 2010; Wang and Huangfu, 2017), and context (Dixon et al., 2006) have all been investigated as states that may influence delay discounting. Because several state manipulations have been shown to modulate delay discounting, it is reasonable to predict that delay discounting may change due to deprivation manipulations as well.

In sum, deprivation has generally been thought to result in increased impulsivity, an assumption with arguably high face validity. However, it is not clear exactly *how* deprivation (and other experimental manipulations) may result in changes in delay discounting (Bailey et al., 2021). Although it seems clear that valuation of outcomes may change due to deprivation, there may not necessarily be a direct impact on the process of delay discounting itself. It may be that deprivation changes subjective valuation, which may systematically influence choices on a delay discounting task (and thus *k*-values), but the underlying *process* of discounting delayed rewards and sensitivity to delayed outcomes may remain the same.

In addition to underdeveloped theoretical explanations, results of early experiments on the effect of deprivation on delay discounting are mixed (e.g., Richards et al., 1997; Giordano et al., 2002; Mitchell, 2004). Researchers have often concluded that deprivation magnifies impulsivity, generally citing two experiments that reported large increases in delay discounting (i.e., Giordano et al., 2002; Field et al., 2006; see, e.g., Berns et al., 2007; De Wit, 2009; Van den Bos and McClure, 2012; Ashare and Kable, 2015; see however Bickel et al., 2015). Because studies that have shown little to no change in delay discounting due to deprivation may not have been cited as frequently as those that report large changes, the effects of deprivation may not be as clear as is commonly represented. Therefore, we conducted a review of experiments that measured delay discounting and manipulated deprivation level in human and non-human animals. For studies with available data, we computed and compared effect sizes. We discuss other relevant studies in a narrative review.

METHOD

Literature Search and Screening

We searched PubMed and EBSCOhost to identify studies that assessed the effect of withdrawal or deprivation on delay discounting. The original search was conducted in September 2019 using the terms ("delay discounting" or "temporal discounting" or "intertemporal choice") and ("deprivation" or "withdrawal" or "satiation." Additional searches were conducted in June 2021 to include any more recently published articles. The searches resulted in a total of 109 unique articles. Abstracts were screened to ensure studies were relevant, empirical, and measured delay discounting. A total of 50 articles passed abstract screening. We included two additional articles that were not found in the literature search; these articles were found during manuscript preparation or in the references of articles that passed screening and were relevant to the review. Additional criteria were imposed to compute and compare effect sizes. Some articles did not clearly measure delay discounting during a deprivation state and a control state or baseline state and were thus excluded ($n = 10$). Studies that did not experimentally manipulate deprivation were also excluded ($n = 9$; e.g., studies that used self-reported deprivation as a covariate). Non-human animal rearing experiments (e.g., rats reared in social isolation; $n = 2$) were excluded because these studies were studying phenomena that are arguably different from the purpose of the review, which was to examine short-term state changes in deprivation state A total of 31 studies met inclusion criteria (see **Figure 1**).

Data Collection

Three authors extracted data from articles that met inclusion criteria. To compute effect sizes, we collected the sample size of each experimental group and measures of central tendency and variability for delay discounting for each study. If measures of central tendency and variability were not available, we used the result of a *t*-test or Cohen's *d*. We did not compute effect sizes for studies that solely reported an *F*-statistic because effect sizes may be inflated when calculated from *F*-statistics (Hullett and Levine, 2003). The data we collected were listed in the text or Supplementary Material, represented in a figure, or provided by an author. If data were in a figure, a graphical data extraction tool was used to estimate the measure (Rohatgi, 2018). If the data were not present in the article and the study was published in the last 10 years, the corresponding author was contacted via email, once initially and once a month later to follow up if necessary. We contacted (or attempted to contact) authors of 6 articles. We were able to compute 54 effect sizes from 23 studies. Studies that used *k* as a dependent measure were reverse coded to aid in interpretation; AUC and *k* are inversely related, so reverse coding *k* results in similar interpretation for the two measures. For studies without available effect size data, we discussed the study in a narrative review if the study conducted an experiment on the effect of deprivation on delay discounting and at least discussed the result of the manipulation.

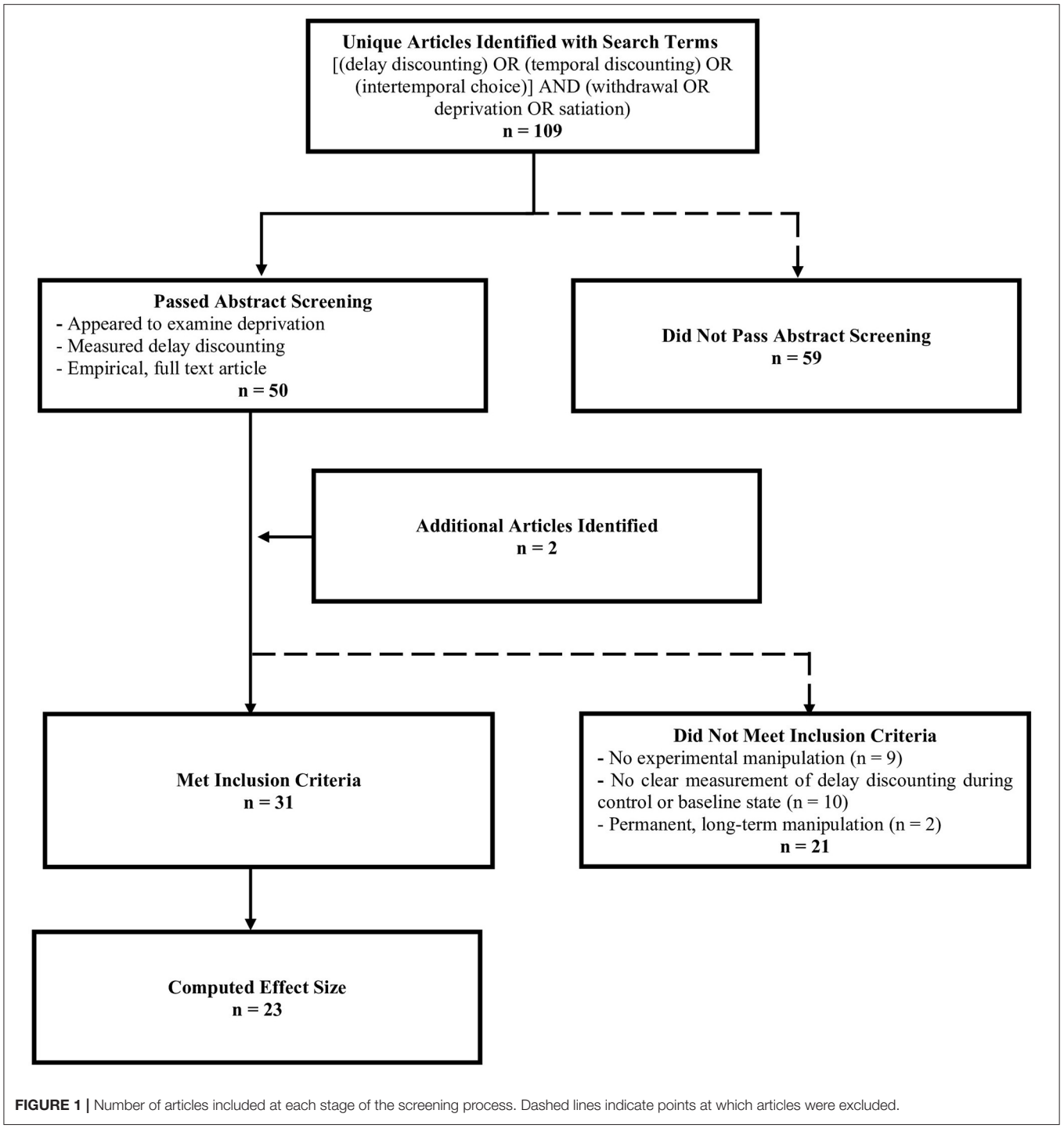


FIGURE 1 | Number of articles included at each stage of the screening process. Dashed lines indicate points at which articles were excluded.

Computation of Effect Sizes

To estimate the effect of deprivation on delay discounting, we calculated Hedge's *g* for each study with data available and that met our inclusion criteria. Hedge's *g* is a measure of effect size, calculated from Cohen's *d*, that corrects for an upward bias in effect size among small samples ($N < 20$; Goulet-Pelletier and Cousineau, 2018). One study reported only Cohen's *d* and no descriptive statistics (Skrynka and Vincent, 2019); however, for all other studies, we calculated Cohen's *d* from descriptive statistics reported in the text or obtained from the authors, and from *t*-statistics. For studies that reported descriptive statistics, we calculated Cohen's *d* using Equation (1),

$$Cohen's\ d = \frac{M_{Non-Deprived} - M_{Deprived}}{Pooled\ SD} \quad (1)$$

where $M_{Non-Deprived}$ and $M_{Deprived}$ are the mean estimates of delay discounting (e.g., AUC) obtained from the non-deprived and deprived groups, respectively, and pooled *SD* is the pooled standard deviation of the estimates of delay discounting. For between-subject designs, the pooled *SD* was calculated using Equation (2),

$$Pooled\ SD_{Between} = \sqrt{\frac{(n_1 - 1)\,SD_1^2 + (n_2 - 1)\,SD_2^2}{n_1 + n_2 - 2}} \quad (2)$$

where $n_{\text{Non-Deprived}}$ and n_{Deprived} are the sample sizes for the non-deprived and deprived groups, respectively, and $SD_{\text{Non-Deprived}}$ and SD_{Deprived} are the standard deviations for the non-deprived and deprived groups, respectively. For within-subject designs, the pooled *SD* was calculated using Equation (3),

$$Pooled\ SD_{Within} = \sqrt{\frac{SD_1^2 + SD_2^2}{2}} \quad (3)$$

where $SD_{\text{Non-Deprived}}$ and SD_{Deprived} are the standard deviations from the non-deprived and deprived states, respectively. A small subset of studies reported standard errors only; therefore, we calculated standard deviations for these studies by multiplying the standard error by $\sqrt{n}$. For studies that did not report descriptive statistics, we calculated Cohen's *d* from paired-samples *t*-statistics using Equation (4),

$$Cohen's\ d = \frac{t}{\sqrt{n}} \quad (4)$$

After obtaining Cohen's *d* for each study, we calculated Hedge's *g* with Equation (5),

$$Hedge's\ g = Cohen's\ d \times J \quad (5)$$

where *J* is a correction applied to Cohen's *d* to correct for an upward bias in *d* (Borenstein et al., 2009). The correction *J* was calculated with Equation (6),

$$J = \left(1 - \frac{3}{4df - 1}\right) \quad (6)$$

where *df* are the degrees of freedom, given by *N* – 2 for between-subject designs and N_{Pairss} – 1 for within-subject designs. Finally, we calculated 95% confidence intervals around each Hedge's *g*. To do this, we first calculated the variance of Cohen's *d* for between-subject designs with Equation (7),

$$V_d = \frac{n_1 + n_2}{n_1 n_2} + \frac{d^2}{2\,(n_1 + n_2)} \quad (7)$$

and for within-subject designs with Equation (8),

$$V_d = \left(\frac{1}{n} + \frac{d^2}{2n}\right) 2\,(1 - r) \quad (8)$$

where *r* is correlation between observations in a pair. As in Rung and Madden (2018), we assumed an $r = 0.5$ for all studies. Next, we calculated the variance of Hedge's *g* with Equation (9),

$$V_g = J^2 \times V_d \quad (9)$$

From the variance of Hedge's *g*, we calculated the standard error (*SE*) with Equation (10),

$$SE_g = \sqrt{V_g} \quad (10)$$

and confidence intervals with Equation (11),

$$95\%\ C.I. = Hedge's\ g \pm \left(1.96 \times SE_g\right) \quad (11)$$

Figures 2–7 show effect sizes for each study for each outcome type of which subjects were deprived. Both Hedge's *g* and Cohen's *d* are computed using standardized mean differences, and thus interpretation of the two are similar (Ferguson, 2009). The midline represents an effect size of 0, which indicates delay discounting does not differ during deprivation and control conditions. Accordingly, effect sizes farther from the midline are larger. Effect sizes to the left of the midline are negative, and indicate that delay discounting was lower (i.e., less impulsivity) in the deprivation condition than in the control condition (the opposite of the predicted effect). Effect sizes to the right of the midline are positive, and indicate that delay discounting was higher (i.e., more impulsivity) in the deprivation condition than in the control condition (the predicted effect).

RESULTS AND DISCUSSION

Overall, we found inconsistent effects of deprivation on delay discounting. The effect sizes we computed range from Hedge's $g = -1.98$ to 1.81. To try to better understand why the range of effect sizes is so large, we grouped the findings with respect to the outcome of which subjects were deprived. We found that most studies could be classified into the broader deprivation categories of Food and Water Deprivation, Nicotine Deprivation, Opioid Deprivation, Deprivation of Other Drugs, Sleep Deprivation, and Financial Deprivation. For each deprivation type, we also discuss physiological, affective, or cognitive changes that subjects may experience as a result of the deprivation manipulation. We first discuss studies with human and non-human animal subjects, then we discuss studies with only human participants.

Food and Water Deprivation

Surprisingly, unlike other deprivation manipulations, moderate food and water deprivation have few effects on cognition and behavior. Benau et al. (2014) concluded that short-term fasting in humans has inconsistent or no effects on cognition (e.g., Zajac et al., 2021), but does affect motor performance (reducing reaction times) and increases negative affect. Food restriction in rats may lead to increased operant responding for drugs and to increased levels of corticosterone (i.e., stress; Carroll, 1985; Nowland et al., 2011), but this effect is generally studied as a long-term manipulation rather than a short-term state manipulation.

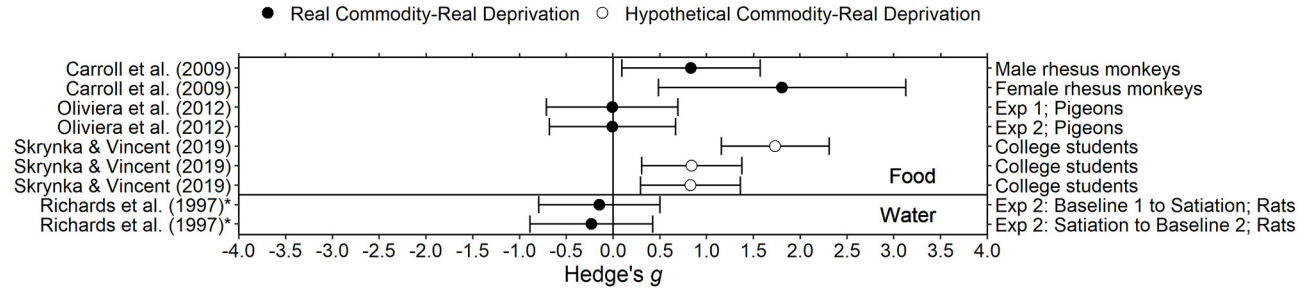


FIGURE 2 | Effect sizes for food and water deprivation experiments. Effect size is Hedge's *g*. Points closer to 0 indicate smaller effect sizes. Points to the right of the line indicate increases in delay discounting due to deprivation, the predicted effect. Solid circles indicate that the delay discounting task used real outcomes and subjects experienced real deprivation. Unfilled circles indicate that the delay discounting task used hypothetical outcomes and subjects experienced real deprivation. *Indicates the effect size was calculated using non-transformed *k*-values and thus may be biased.

Moderate water deprivation in humans similarly has, in general, no consistent effects on cognition, but does increase negative affect and decrease alertness (e.g., Neave et al., 2001; see Masento et al., 2014, for review). One study with human participants and three studies with non-human animal subjects in the present review examined the effect of deprivation of food or water on delay discounting.

Human Participants

Skrynka and Vincent (2019) examined delay discounting of hypothetical money, food, and music in 50 college students. For one session, participants were instructed to eat in the 2 h before coming to the laboratory, and in the other session, participants were instructed to fast for 10 h prior to the session. Manipulation compliance was verified by assessing blood glucose levels and subjective craving in each session. Blood glucose was within normal fasting levels for the majority of participants and subjective craving was significantly higher during the 10 h fast condition compared to the control condition. For the adjusting amount delay discounting task, delays ranged from 1 h to 1 year and the larger later amounts were equivalent to £20. Delay discounting was higher in the deprivation condition compared to the control condition for all commodities. Interestingly, the increase in delay discounting for food (Hedge's $g = 1.73$), an in-domain commodity, was larger than the increase in delay discounting for music downloads and money (Hedge's *g*s = 0.83 and 0.84, respectively), out-domain commodities.

Non-human Animal Subjects

In Richards et al. (1997), eight Sprague-Dawley rats discounted 100 μl water while deprived of water and while partially satiated in an ABA design. In the water deprivation condition (A), rats had 20 min of access to water per day, available immediately after a delay discounting session. The satiation condition (B) consisted of an additional 20 min of water available 4 h prior to the delay discounting session. Deprivation resulted in small *decreases* in delay discounting (Hedges *g*s = −0.23, −0.14; the opposite of the predicted direction). Richards et al. (1997) concluded that there is no effect of deprivation of water on delay discounting. Providing support for this conclusion, Richards et al. (1997) suggested that the manipulation was effective in manipulating water deprivation because weight and latency (time to respond in the task) increased with greater access to water.

In Carroll et al. (2009), 8 male and 5 female rhesus monkeys discounted self-administered phencyclidine (PCP) during food restriction and food satiation. Food restriction (i.e., deprivation) was defined as 85% free feeding weight and satiation was defined as being fed double the amount required to maintain 85% of free feeding weight. In the satiation condition, the amount of food was adjusted so that monkeys left at least 100 g of food uneaten. On average, delay discounting was greater during the restriction condition than in the satiation condition for both sexes (Hedge's *g*s = 0.83 for males, 1.81 for females). In a similar experiment (Carroll et al., 2009), male rhesus monkeys (*n* unspecified) also discounted PCP but were deprived of a saccharin solution. In the satiation (non-deprived) condition, saccharin (1,900 mL daily) was available for at least 14 days. In the deprivation condition, water replaced saccharin. Water intake during the saccharin deprivation period was much lower than was saccharin intake during the satiation condition. However, delay discounting was similar during the saccharin deprivation and satiation conditions.

Oliveira et al. (2013) examined the effect of food deprivation on delay discounting in pigeons using two different deprivation procedures. In the first experiment, deprivation was controlled by modulating percentage of free feeding weight: during the deprivation condition 5 female pigeons were maintained at 75–80% free feeding weight, and during the control (i.e., satiation) condition the same pigeons were maintained at 90–95% free feeding weight. In the second experiment, deprivation was controlled by modulating time since the last feeding. In the deprivation condition, six male pigeons were deprived of food for 23 h prior to the delay discounting sessions. In the control condition, the same pigeons were deprived of food for 1 h prior to sessions. In both conditions, pigeons were maintained at 80–85% free feeding weight. For both deprivation procedures, delay discounting during the deprivation condition was not significantly different from delay discounting in the control condition (Hedge's *g*s = −0.01 for Exp. 1, −0.007 for Exp. 2).

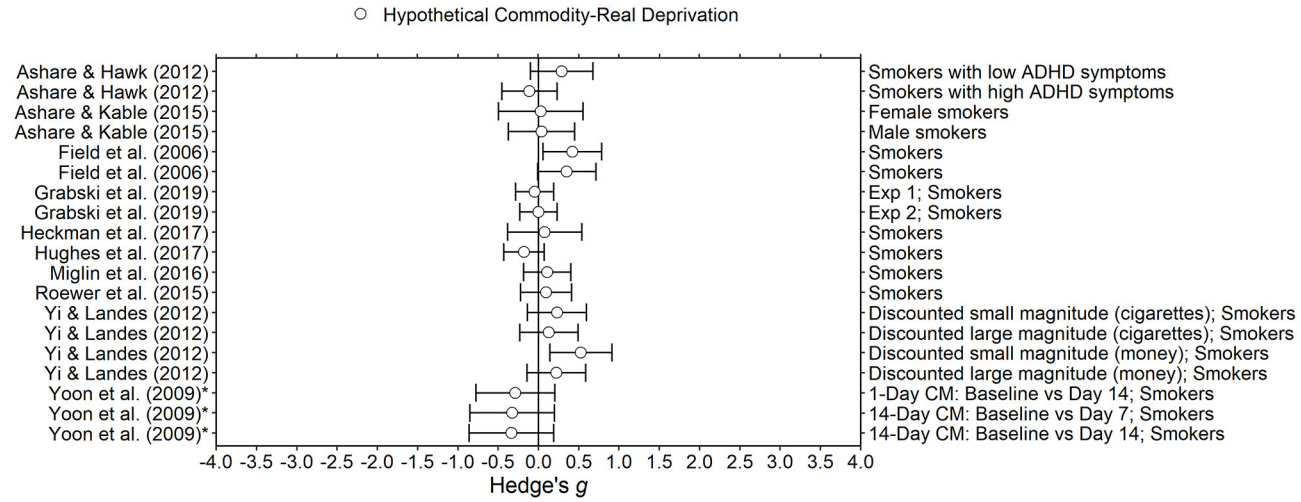


FIGURE 3 | Effect sizes for nicotine deprivation experiments. Effect size is Hedge's *g*. Points closer to 0 indicate smaller effect sizes. Points to the right of the line indicate increases in delay discounting due to deprivation, the predicted effect. Subjects discounted hypothetical outcomes and experienced real deprivation. *Indicates the effect size was calculated using non-transformed k-values and thus may be biased.

Only measures for delay discounting were reported; it was not stated whether other behavior changed due to the manipulation.

Conclusion

Overall, the effects of deprivation of food and water on delay discounting are inconsistent. One possible limitation in this area is the relatively small sample sizes used; five out of six of the experiments described above used a sample size <15. According to a power analysis, for a two-tailed paired samples *t*-test, a sample size of 90 is required to detect a medium effect size (Cohen's $d = 0.3$) when power is set to 0.8 and the significance level is set to 0.05 (Faul et al., 2007). However, in two studies, the effect size was negative, indicating increased deprivation may have decreased delay discounting, which is in the opposite direction than predicted.

As noted in Skrynka and Vincent (2019), studying deprivation state and measuring delay discounting of different commodities, specifically in- and out-of-domain commodities, may help to demonstrate the extent to which delay discounting is state-like or trait-like. If delay discounting is purely state-like, delay discounting of all outcomes should increase similarly due to a state manipulation, regardless of whether the state manipulation is relevant to the commodity discounted. If delay discounting is somewhere between a state and a trait, then the commodity discounted would play a larger role in determining degree of delay discounting for each commodity (see Figure 1 in Skrynka and Vincent, 2019). This point has implications for manipulations that seek to reduce delay discounting; effective interventions would influence behavior in all domains (i.e., financial, health, social) instead of just one.

Nicotine Deprivation

Nicotine withdrawal symptoms in humans are somatic, affective, and cognitive. Symptoms include irritability, increased appetite, difficulty paying attention, and impaired working memory (Heishman et al., 2010; McLaughlin et al., 2015). Withdrawal is thought to begin within 3–4 h of abstinence and may last up to 4 weeks (Hughes, 2007; McLaughlin et al., 2015). Impatience and impulsivity have been investigated as symptoms of nicotine withdrawal (Hughes, 2007; Hughes et al., 2014). Although smoking cessation treatments have been developed (Jorenby et al., 2006; Dallery and Raiff, 2011), many smokers trying to quit relapse within about a week (Hughes et al., 2004). Because withdrawal symptoms may play a role in relapse (Robinson et al., 2019), it is important to understand any withdrawal-related changes in cognitive processes, such as delay discounting, that occur during this time (Ashare and McKee, 2012; Ashare et al., 2014). If changes in delay discounting during withdrawal lead to more or less successful quit attempts, modulating delay discounting may help to improve quit outcomes (see Miglin et al., 2017; Rung and Madden, 2018). A total of 13 articles in the present review conducted experiments to determine the effects of nicotine abstinence on delay discounting. Effect sizes ranged from close to 0 (i.e., no change in delay discounting; Hedge's $g = -0.04$) to large and positive (Hedge's $g = 0.64$; see **Figure 4**). Several factors may explain differences between results including the samples, the deprivation length, and delay discounting tasks. Of the 13 nicotine deprivation articles, 11 used human participants.

Human Participants

In all 11 human experiments, deprivation from nicotine was verified biochemically and with subjective assessments. Biochemical abstinence was verified in all studies by analyzing expired carbon monoxide (CO) breath content. The maximum ppm allowed for abstinence varied from 4 to 11 ppm. Although analyzing CO breath content does provide indication of acute abstinence, it may not be able to verify complete abstinence

over the entire 24 h deprivation periods that many studies used (Jatlow et al., 2008). Three studies analyzed cotinine content from urinalyses, which allows for detection of all nicotine consumption, rather than just inhaled, over a longer period (Haufroid and Lison, 1998; Jatlow et al., 2008). The two studies with the longest deprivation periods used urine cotinine analysis, providing confidence that participants did indeed maintain abstinence for weeks. Both studies (Yoon et al., 2009; Hughes et al., 2017) found no change in delay discounting during nicotine abstinence. The deprivation manipulations were also verified with cravings and withdrawal symptom assessments, the most common ones being the Questionnaire on Smoking Urges (QSU; Tiffany and Drobes, 1991) and the Minnesota Nicotine Withdrawal Scale (MNWS; Hughes and Hatsukami, 1986). All 11 studies included some form of either the QSU or MNWS. Expired CO was lower, and cravings and withdrawal symptoms were higher, in nicotine deprivation sessions compared to satiated sessions for all studies that made this comparison. Finally, many studies included a battery of tasks in addition to delay discounting tasks. Changes in other tasks (e.g., cross-commodity discounting, time reproduction task, response time) were observed during deprivation for all studies that found no change in delay discounting during deprivation. For example, Ashare and Kable (2015) found no effect of nicotine deprivation on delay discounting but did find that accuracy in a time discrimination task was lower during deprived sessions compared to satiated sessions. This combined evidence suggests that overall, deprivation manipulations were effective and produced changes in deprivation state, providing increased confidence in the results.

Overall, experimental design was relatively similar across studies. All but one study (Heckman et al., 2017) made within-subject comparisons. Participants completed delay discounting tasks about 1 week apart except in one study, Roewer et al. (2015), in which the time between sessions was 24 h. Three studies were contingency management studies; participants were paid for biochemically verified abstinence (Yoon et al., 2009; Hughes et al., 2017; Miglin et al., 2017). In Yoon et al. (2009) and Hughes et al. (2017), participants completed delay discounting tasks more than two times and remained in the study for at least 2 weeks. In both studies, delay discounting remained relatively stable over time. Recall that withdrawal symptoms may last up to 4 weeks (Hughes, 2007; McLaughlin et al., 2015). Both studies were measuring delay discounting during times nicotine withdrawal symptoms have been observed previously. Although both of the longer contingency management studies (Yoon et al., 2009; Hughes et al., 2017) showed no increase in delay discounting over time, there was no consistent pattern for shorter deprivation lengths. Field et al. (2006) and Heckman et al. (2017) used similar lengths of at least 12 and 13 h, respectively, and reported increased delay discounting, whereas Ashare and McKee (2012) and Grabski et al. (2020) also used shorter deprivation lengths (<24 h) but found no effect of deprivation. The most common deprivation length was 24 h ($n = 5$). All but one study, Yi and Landes (2012), found no effect of 24 h of deprivation on delay discounting. Future research could examine whether delay discounting fluctuates systematically during the first few days of abstinence.

Studies on the effect of nicotine deprivation on delay discounting used markedly different samples (see **Table 1**). Mean age varied from 20 to 45 years across studies; some samples were college students, and some were community members. Because mean age differed by more than 20 years across studies, maximum length of nicotine dependence necessarily differed. Mean score on the Fagerstrom Test for Nicotine Dependence (FTND; Heatherton et al., 1991) ranged from 3.57 to 7.24 out of a maximum of 10, indicating large differences between level of nicotine dependence. Study requirements for number of cigarettes smoked per day also varied from 5 (Grabski et al., 2020) to 25 (Roewer et al., 2015). Mean number of cigarettes smoked ranged from 11 to more than 25 per day. Sample size ranged from 11 to 67 for within-subject comparisons, indicating that power to detect differences between conditions also varied greatly. Two studies required participants to be trying to quit and seven studies specifically excluded smokers trying to quit. We found no clear relationship between studies with larger effect sizes and participant age, dependence, or daily cigarettes smoked.

Older and younger smokers, more and less dependent smokers, and smokers trying or not trying to quit may differ in important ways that make comparisons between studies difficult or even inappropriate. Some studies were also published over a decade apart; a sample of smokers in 2004 may be different in important ways from a sample of smokers in 2020 (Hughes, 2011; Drope et al., 2018; Grant et al., 2020). However, because studies examined many types of smokers and made similar conclusions for different types of smokers, the findings are more general.

Variations in delay discounting tasks may also have contributed to the discrepancy between results (see **Table 1**). Delay discounting has been shown to be generally similar regardless of real or hypothetical outcomes (Johnson and Bickel, 2002; Madden et al., 2003). Interestingly, all studies that included a potentially real outcome task found no change in delay discounting of potentially real money due to deprivation (Mitchell, 2004; Yi and Landes, 2012; Roewer et al., 2015). Some authors have suggested that tasks with experienced delays and outcomes may be required to see the effect of state manipulations (e.g., Reynolds and Schiffbauer, 2004; Dallery and Raiff, 2007), but the effect sizes computed in the current review for other deprivation types may indicate otherwise. However, all potentially real outcomes in these studies were necessarily small amounts of money, which means that comparisons between results for real and hypothetical outcomes may be confounded by the amount of the outcome.

Although we did not compute effect sizes for cross commodity tasks, during deprived states, Mitchell (2004) found *increased* preference for immediate cigarettes over delayed money whereas Yoon et al. (2009) found *decreased* preference for immediate cigarettes. Both Mitchell (2004) and Yoon et al. (2009) suggest that the change in the reinforcing value of the outcome, rather than changes in sensitivity to delay, may play a role in the changed cross-commodity discounting. In Mitchell (2004), participants were required to stay in the laboratory for several hours after their 24 h deprivation period and could smoke only

TABLE 1 | Comparison of participant characteristics and delay discounting tasks in nicotine deprivation experiments.

				Participant characteristics					Delay discounting task		
References	**Deprivation length**	**Effect size**	**Author conclusion**	***n***	**Age**	**FTND**	**Cig. per day**	**Quit status**	**Longest delay**	**Outcome**	**Magnitude**
Mitchell (2004)	24 h	—	No effect	11	20.2	5[a]	18.9	—	365 days	Potentially real money	LL $10
Field et al. (2006)	≥13 h	0.42	Increase	30	23.3	3.6	15	Not trying to quit	25 years	Hypothetical money	LL 500 £
"	"	0.35	"	"	"	"	"	"	"	Hypothetical cigarettes	LL 500 £ worth of cigarettes
Ashare and Hawk (2012)	Overnight	0.29	Increase (Low ADHD group)	25	44	5.2	20	Not trying to quit	180 days	Hypothetical money	LL $100
"	"	−0.11	No effect (High ADHD group)	31	37	5.3	17	Not trying to quit	"	"	"
Ashare and McKee (2012)	≥18 h	—	No effect	58	35.9	5.6	18.7	Not trying to quit	179 days	Hypothetical money	$25–$85
Yi and Landes (2012)	24 h	0.64	Increase	28	40	6.4[a]	21	Not trying to quit	10 years	Hypothetical money	LL $50 and $1,000
"	"	0.22	No effect	"	"	"	"	"	10 years	Hypothetical cigarettes	LL $50 and $1,000 worth of cigarettes
"	"	—	No effect	"	"	"	"	"	6 months	Potentially real money	LL $50
Roewer et al. (2015)	24 h	0.09	No effect	37	33	7.2	≥ 25	—	190 days	Hypothetical money	SS $10
Ashare and Kable (2015)	24 h	0.07	No effect (Male)	21	37.1	4.6	18.6	Not trying to quit	months	Hypothetical money	—
"	"	0	No effect (Female)	12	40.2	4.8	14.3	"	"	"	"
Heckman et al. (2017)	12 h	0.09	Increase	128	37	6	20	Not trying to quit	179 days	Hypothetical money	$25–$85
Miglin et al. (2017)	24 h	0.11	No effect	43	45	4.9	13.7	Trying to quit	174 days	Hypothetical money	$15–$85
Grabski et al. (2020)	≥8 h	−0.05	No effect	67	21.8	4.4	11	Not trying to quit	365 days	Hypothetical money	LL 100 £
Hughes et al. (2017)	4 weeks[b]	−0.18	Decrease	61	40	5	19	Trying to quit	5 years	Hypothetical money	LL $1,000
Yoon et al. (2009)	<24 h	−0.29	No effect	15	28.1	5.3	18.2	Not trying to quit	25 years	Hypothetical money	LL $1,000
"	7 days	−0.33	"	13	29.1	6.2	21.7	"	"	"	"
"	14 days	−0.34	"	"	"	"	"	"	"	"	"

Effect size is Hedge's g. FTND, Fagerstrom Test for Nicotine Dependence. Means are listed for age, FTND score and cigarettes per day. —Indicates information was not specified. "Indicates the cell contains the same information as the cell above. Author conclusion refers to conclusion made about the effect of nicotine deprivation on delay discounting by authors of the original study, not our conclusion. LL refers to the larger later amount used in the delay discounting task.

[a]*Fagerstrom Tolerance Questionnaire.*

[b]*Delay discounting was measured 8 times over 4 weeks. This effect size compares average delay discounting at baseline to average delay discounting over 4 weeks of abstinence.*

cigarettes earned in the potentially real commodity discounting task, which may have increased immediate desire for cigarettes. The possibility of immediate relief from withdrawal in Mitchell (2004) may have increased the value of cigarettes. In contrast, smokers in Yoon et al. (2009) were paid for several days of abstinence and the value of immediate cigarettes may have decreased due to an increased motivation to quit smoking.

Out of these 11 human-subject studies, only four concluded that nicotine deprivation increased delay discounting (Ashare and Hawk, 2012, in one group only; Field et al., 2006; Heckman et al., 2017; Yi and Landes, 2012, in monetary task only). Field et al. (2006) and Yi and Landes (2012) both

[1]While Heckman et al. (2017) concluded nicotine deprivation increased delay discounting (Cohen's d = 0.36), we found the effect to be small based on our calculations from the descriptive statistics reported (Cohen's d = 0.06; Hedge's g = 0.08). We believe this finding is because effect sizes computed from F-statistics may be upwardly biased (Hullett and Levine, 2003).

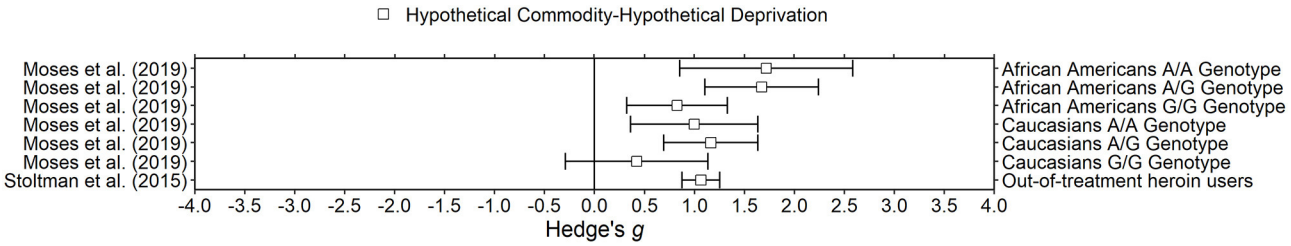


FIGURE 4 | Effect sizes for opioid deprivation experiments. Effect size is Hedge's *g*. Points closer to 0 indicate smaller effect sizes. Points to the right of the line indicate increases in delay discounting due to deprivation, the predicted effect. Subjects discounted hypothetical outcomes and experienced hypothetical deprivation.

found medium to large increases in hypothetical monetary delay discounting (Hedge's *g*s = 0.64 and 0.42, respectively). Ashare and Hawk (2012) found increases in delay discounting in participants with fewer ADHD symptoms, but not in participants with more ADHD symptoms (Hedge's $g = 0.29$). Mean participant age and nicotine dependence, and deprivation duration varied across the studies.). The six studies that found small or no effect of deprivation on delay discounting all had participant *N*'s as large or larger than those with large effect sizes (i.e., Field et al., 2006; Ashare and Hawk, 2012; Yi and Landes, 2012). Additionally, out of the 17 effect sizes we computed for experiments that examined nicotine deprivation, all but two have confidence intervals that overlap with 0 (see **Figure 4**). For these reasons, we conclude that the effect of acute nicotine deprivation on delay discounting in humans is probably small at most. This conclusion is valid only supposing that delay discounting tasks are indeed sensitive enough to detect pharmacological state changes (Odum and Baumann, 2010; Odum et al., 2020; see, however, De Wit and Mitchell, 2010) and accepting the previously discussed evidence that deprivation actually induced withdrawal in participants.

Non-human Animal Subjects

Two articles in the present review examined the effect of nicotine deprivation on impulsive choice in rats. Nicotine withdrawal in rats includes somatic signs such as head and body shakes, teeth chattering, ptosis, and yawns; and may include cognitive changes such as deficits in attention and working memory (Malin et al., 1992; Shoaib and Bizarro, 2005; Ashare et al., 2014). In Kayir et al. (2014), 22 male Wistar rats received 6.32 mg/kg/day of nicotine via an osmotic mini-pump for 13 days. In Kolokotroni et al. (2014), 29 male Lister hooded rats received 3.16 mg/kg/day of nicotine via a mini-pump for 7 days. Rats were food deprived during the duration of both experiments. Impulsive choice tasks were based on Evenden and Ryan (1996); rats were offered 1 pellet immediately and 4 or 5 pellets after delays ranging from 0 to 60 s. Rats were placed into high and low impulsive groups determined by baseline level of impulsivity. Both studies concluded that in low impulsive rats, nicotine deprivation leads to increased choice for smaller sooner food. In high impulsive rats, Kolokotroni et al. (2014) found decreases in choice for smaller sooner food and Kayir et al. (2014) found no change in choice for smaller sooner food. When considering all rats in the study, Kayir et al. (2014) found no change in choice for smaller sooner food during nicotine withdrawal. Important to note, Kayir et al. considered measurements of choice during the first 48 h after pump removal and Kolokotroni et al. (2014) measured choice for weeks after pump removal and found effects of withdrawal only during the first week. The results for the high impulsive rats could be explained by a ceiling effect; number of choices for smaller sooner food could have been so high at baseline that there would be less room to increase during deprivation. Or, perhaps, rate dependency may help to explain the difference between high and low impulsive groups (Quisenberry et al., 2016). It could also be that there is in fact a difference in the effects of withdrawal between low and high impulsive rats. In humans, Ashare and Hawk (2012) found a similar effect; those with low ADHD symptoms had greater increases in delay discounting after nicotine abstinence compared to those with high ADHD symptoms. Individual differences in response to nicotine deprivation conditions may help to explain why many other human experiments report no effect of deprivation on delay discounting. It could be that only certain individuals discount differently due to nicotine deprivation; by aggregating data, the effect of deprivation could be averaged away, resulting in apparently no change in delay discounting. Nonetheless, it may be valuable to analyze individual responses to deprivation and other state manipulations, rather than the differences in means across conditions.

Opioid Deprivation

In people who have opioid dependency, opioid deprivation can lead to pronounced opioid withdrawal symptoms. The severity and onset of opioid withdrawal symptoms depends on the severity of opioid dependence as well as if the opioids last used were short or long-acting (Wesson and Ling, 2003; Kosten and Baxter, 2019). Deprivation of short-acting opioids, including heroin and oxycodone, results in opioid withdrawal symptoms after ∼12 h. Symptoms may peak in severity around 36–72 h and then tend to end after 4–7 days (Kosten and Baxter, 2019). In contrast, opioid withdrawal symptoms for long-acting opioids, including methadone and buprenorphine, may last for 2 weeks (Kosten and Baxter, 2019). Symptom severity is greater for those that are more dependent (Wesson and Ling, 2003), but the same symptoms are seen in users of long- and short- acting

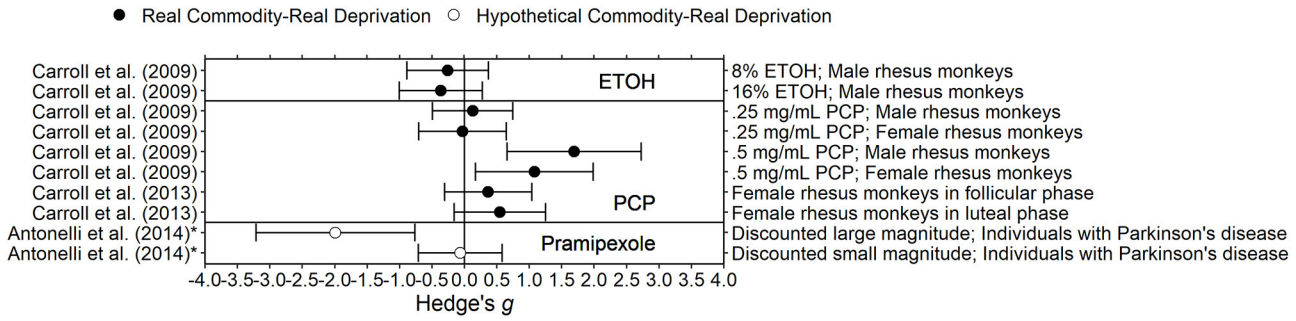


FIGURE 5 | Effect sizes for other drug deprivation experiments. Effect size is Hedge's *g*. Points closer to 0 indicate smaller effect sizes. Points to the right of the line indicate increases in delay discounting due to deprivation, the predicted effect. Solid circles indicate that the delay discounting task used real outcomes and subjects experienced real deprivation. Unfilled circles indicate that the delay discounting task used hypothetical outcomes and subjects experienced real deprivation.

opioids (Kosten and Baxter, 2019). Opioid withdrawal symptoms may include anxiety, insomnia, irritability, and cold and flu-like symptoms (i.e., hot and cold flashes, aches, nausea, vomiting, runny nose; Wesson and Ling, 2003; Kosten and Baxter, 2019). Both chronic and acute opioid use are known to produce a range of cognitive impairments (Ersek et al., 2004; Baldacchino et al., 2012). For instance, there is evidence that opioid users tend to discount delayed rewards more steeply than controls (MacKillop et al., 2011). Less is known, however, about specific cognitive changes during acute opioid withdrawal in humans. In the present review, three studies with human participants and one with non-human animal subjects examined the effect of opioid deprivation on delay discounting.

Human Participants

In Giordano et al. (2002), 13 participants in outpatient treatment for opioid dependence completed delay discounting tasks 2 h after buprenorphine administration (satiation) and 5 days after buprenorphine administration, when the maintenance dose had worn off (withdrawal). Each condition was repeated 4 times over a period of 8 weeks. Participants were on average 37.5 years old, used 5 bags of heroin daily, and were dependent for 11.9 years. Abstinence from all opioids was verified with urinalysis two to three times per week. Two positive tests for opioids over the course of the 8 week study resulted in discontinuation. An additional 13 participants started the study but did not continue due to failure to provide negative urine samples or failure to return after intake. Withdrawal was assessed with pupil radius measures and with subjective assessments. Subjective assessments of withdrawal and pupil radiuses were significantly higher during withdrawal compared to satiated conditions. Adjusting amount delay discounting tasks used outcomes of money and number of bags of heroin at magnitudes of $100, 3,000, and 10,000 (equivalent worth for bags of heroin). For the 13 participants that completed the study, *k*-values were significantly higher for deprived conditions compared to sated conditions for all commodity and magnitude combinations. Giordano et al. (2002) results demonstrated that among opiate-dependent individuals, opioid deprivation may substantially increase delay discounting. It should be noted, however, that the sample size was small, and the experiment had a high attrition rate. Thus, the results should be considered with caution. Two experiments that employed hypothetical opioid deprivation may help to provide additional evidence of an increase in delay discounting during opioid deprivation.

Stoltman et al. (2015) and Moses et al. (2019) developed a hypothetical opioid deprivation model and found that delay discounting was steeper during deprived states than during satiated states. In the hypothetical withdrawal condition, participants were instructed to answer as if they were going through opioid withdrawal. In the satiation condition, participants were instructed to answer as if they had just taken heroin. For both conditions, a few symptoms or feelings associated with the state were given in the oral instructions. The satiated and withdrawal conditions were completed back-to-back and were counterbalanced across participants. The delay discounting task was developed to be more ecologically relevant to decisions heroin users might regularly face; the delays ranged from 3 to 96 h and the larger later amount was 30 bags of $10 worth of heroin. Both studies used relatively large samples (>100) of out of treatment heroin users and required a positive urinalysis to participate. Although both Stoltman et al. (2015) and Moses et al. (2019) found increases in delay discounting, imagined withdrawal is arguably different from experienced withdrawal. It is also unclear if the increase in discounting found in Stoltman et al. (2015) and Moses et al. (2019) would generalize to more traditional delay discounting tasks with larger amounts of money and longer delays. That is, the large effect found due to hypothetical opioid withdrawal may only be large because the task involved heroin. One would predict that delay discounting for opioids and money would be related (Odum et al., 2020) but it is possible that there is an interaction between the deprivation state and the commodity discounted that does not follow the trait-like pattern (i.e., opioid deprivation may produce larger changes in delay discounting of opioids than in delay discounting of money). Nevertheless, all three human studies report increases in delay discounting due to opioid deprivation.

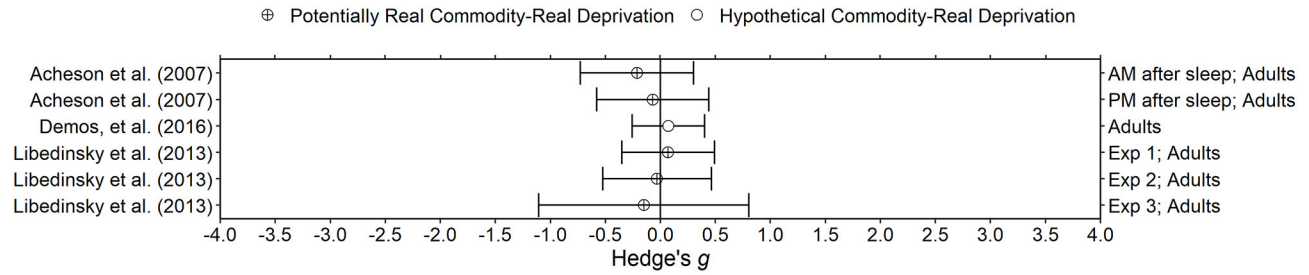


FIGURE 6 | Effect sizes for sleep deprivation experiments. Effect size is Hedge's *g*. Points closer to 0 indicate smaller effect sizes. Points to the right of the line indicate increases in delay discounting due to deprivation, the predicted effect. Circles with a cross indicate that the delay discounting task used potentially real outcomes and subjects experienced real deprivation. Unfilled circles indicate that the delay discounting task used hypothetical outcomes and subjects experienced real deprivation.

Non-human Animal Subjects

In Eppolito et al. (2013), six unsexed pigeons completed impulsive choice tasks with food during daily morphine administration and after morphine discontinuation. For four pigeons, trial omissions increased sharply after discontinuation, limiting the authors' ability to construct delay discounting curves. Interestingly, the number of choices for the larger later amount increased after discontinuation compared to during daily morphine treatment. Despite 8 weeks of, at its highest, 2 daily 100 mg/kg doses of morphine, not all pigeons showed withdrawal signs during saline probes.

In Harvey-Lewis et al. (2015), male Long-Evans rats maintained on subcutaneously injected 30 mg/kg daily morphine doses completed impulsive choice tasks with sucrose during a baseline, satiated condition and 1 h after naloxone-precipitated withdrawal. Naloxone is an opioid antagonist that has been shown to induce withdrawal in rats. Preference for smaller sooner sucrose increased after naloxone administration only for short delays (i.e., 5 and 9 s). The change in number of choices for smaller sooner sucrose depended on the naloxone dose administered, with the larger dose producing greater increases in number of choices for smaller sooner sucrose compared to the smaller dose. Although different doses of naloxone produced significantly different number of choices for smaller sooner sucrose at some delays, the authors did not report a statistical result for the comparison between baseline impulsive choice and impulsive choice after naloxone administration. The authors did, however, conclude that for short delays, naloxone-precipitated withdrawal increased the number of smaller sooner choices.

Conclusion

Although four of the five studies reported increases in delay discounting due to opioid deprivation, each had some limitations. Future studies could attempt to further validate and generalize the hypothetical deprivation condition described in Stoltman et al. (2015) and Moses et al. (2019). Once validated, the hypothetical deprivation model could be a preferable alternative to asking participants to voluntarily go through actual opioid withdrawal.

Deprivation of Other Drugs

Researchers have also examined the effects of deprivation of amphetamine, caffeine, ethanol, PCP, and pramipexole on delay discounting. Due to the limited number of studies in each drug category, we do not draw any general conclusions.

Pramipexole

In Antonelli et al. (2014), 7 Parkinson's disease patients completed a delay discounting task (Kirby et al., 1999) after 12–18 h of being deprived of their usual antiparkinsonian medication and then after 1 mg of pramipexole was administered (i.e., satiation). These sessions occurred during the same day and in the same order for each participant. It was not clear if withdrawal signs and symptoms were measured. Delay discounting was significantly higher after pramipexole administration than after deprivation only for the large magnitude task (600–1,000 CAD; Hedge's $gs = -1.99$ for large magnitude, -0.07 for small magnitude).

Stimulants

In Gipson and Bardo (2009), 24 male Sprague-Dawley rats self-administered amphetamine (0.03 or 0.1 mg/kg/infusion) for 1 h or 6 h for 36 days. Sucrose delay discounting tasks occurred during a baseline condition, during self-administration, and during 7 days after discontinuation. Compared to baseline, delay discounting increased (i.e., got steeper) during self-administration for rats in the 6 h access group and decreased for rats in the 1 h access group. Over the 7 days after amphetamine discontinuation, delay discounting decreased for rats in the 6 h access group and increased for rats in the 1 h access group, thus resulting in both groups returning to baseline levels of delay discounting. It is not clear if the difference in delay discounting between the first few days of withdrawal were significantly different from the 3 days of the baseline condition.

In Diller et al. (2008), seven male Sprague-Dawley rats received 30 mg/kg per day of caffeine via intraperitoneal injection for at least 15 days. Delay discounting sessions occurred during a control condition, during chronic caffeine administration (i.e., satiation), and during chronic saline administration (i.e., deprivation). AUC was significantly higher (i.e., discounting was less steep) during chronic caffeine administration compared to chronic saline administration. The length of the chronic saline

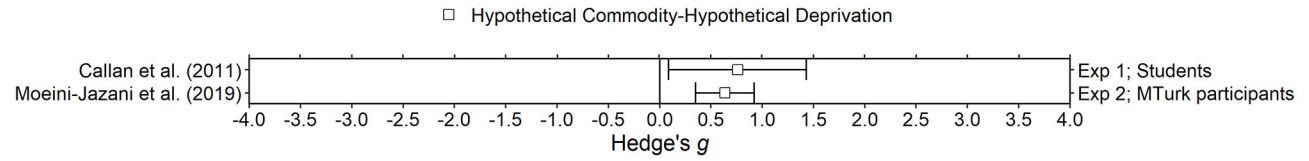


FIGURE 7 | Effect sizes for financial deprivation experiments. Effect size is Hedge's *g*. Points closer to 0 indicate smaller effect sizes. Points to the right of the line indicate increases in delay discounting due to deprivation, the predicted effect. Subjects discounted hypothetical outcomes and experienced hypothetical deprivation.

condition was not the same for all rats (mean = 16.2 days). It is not clear if all sessions or a particular subset of sessions was used to determine average delay discounting during saline administration for each rat. There may be an underestimation of the effect if all sessions were used; the effect of deprivation may be different on the first day after withdrawal than the effects of deprivation on day 15 after withdrawal.

PCP

In Carroll et al. (2009, 2013) rhesus monkeys self-administered 0.25 or 0.5 mg/mL of PCP for 2 h per day for at least 10 days and discounted saccharin during a baseline condition, self-administration of PCP, and for 6 days after withdrawal of PCP. Carroll et al. (2009) found that for eight males and six females, for both doses, delay discounting of saccharin was steeper during PCP withdrawal compared to baseline (before PCP administration). Only the comparison for males at the 0.5 mg/mL dose was significantly different from baseline, although all dose and gender combinations were in the same direction. Carroll et al. (2013) found that for seven females, for both doses of PCP, delay discounting was steeper during PCP withdrawal compared to baseline, although the magnitude of the effect may have depended on phase of the menstrual cycle.

Ethanol

In Carroll et al. (2009), eight male rhesus monkeys self-administered ethanol (8 or 16% wt/vol) for 10 days and discounted saccharin during a baseline condition, self-administration of ethanol, and for 6 days after withdrawal of ethanol. For both doses, delay discounting was not significantly different during ethanol withdrawal compared to baseline.

Sleep Deprivation

Acute sleep loss has been associated with a variety of physiological and affective changes including decreased positive mood states, increased food intake, and increased blood glucose levels (Landolt et al., 2014). Sleep deprivation may also impair cognitive function, including working memory, attention, and psychomotor tasks (Killgore, 2010; Landolt et al., 2014).

Three studies in the present review examine the effects of sleep deprivation on delay discounting in human participants. Acheson et al. (2007) and Libedinsky et al. (2013) both examined the effect of 24 h of sleep deprivation on delay discounting of potentially real money. In both studies, the 30 or less participants were on average in their early 20 s. Demos et al. (2016) examined the effect of partial sleep deprivation, defined as four nights of 6 h of sleep, using a hypothetical monetary delay discounting task (i.e., Kirby et al., 1999). Demos et al. (2016) used a slightly larger ($n = 34$) and older sample (mean age = 37 years). In all three studies, participants were only included if they had good sleeping habits. All studies used a within-subjects design with 1 week in between sessions, except for Experiment 3 in Libedinsky et al. (2013), which used a between-subjects design. Libedinsky et al. (2013) and Demos et al. (2016) used activity monitors to verify compliance with the sleep manipulations, whereas the sleep deprivation occurred entirely in the laboratory in Acheson et al. (2007). All studies used other measures besides delay discounting and found some differences due to sleep deprivation (e.g., decreases in positive mood, more errors in the Go/No-Go task, increased effort discounting), providing evidence of the effectiveness of the deprivation manipulation. All three studies (six deprived/non-deprived comparisons total) found no effect of sleep deprivation on delay discounting (Hedge's *g*s between −0.21 and 0.07). Although the results of the included studies are consistent, it is possible that a longer sleep deprivation period may induce changes in delay discounting (Libedinsky et al., 2013). Interestingly, the results of the studies in the present review are not consistent with Reynolds and Schiffbauer (2004). They developed an experiential discounting task (EDT), which includes choices involving both delay and probability, and found increases in impulsive choice after participants experienced 21 h without sleep. It may be that the probabilistic aspect of outcomes in the EDT contributed to the increase in impulsive choice; other research has demonstrated increases in risky choices due to sleep deprivation (Killgore, 2010).

Financial Deprivation

Personal relative deprivation, or more broadly, financial deprivation, can be described as feelings of having fewer monetary resources, especially when compared to others (Moeini-Jazani et al., 2019). People who have been made to feel as if they have fewer financial resources have been shown to consume more calorie-dense food (Briers and Laporte, 2013), purchase more lottery tickets (Haisley et al., 2008), and save less, all arguably present-oriented behaviors (Shah et al., 2012). Lower income is associated with greater risk aversion and elevated delay discounting (Green et al., 1996; Haushofer and Fehr, 2014). It may be that people in financial deprivation states, either actual or experimentally induced, shift their attention to the present, thereby increasing delay discounting (Shah et al., 2012; Moeini-Jazani et al., 2019). An alternative view is that individuals with less money should value monetary outcomes more so than wealthy individuals, thereby leading to a magnitude effect in which

wealthy individuals discount more steeply than lower-income individuals because money is less valuable to those with high income (Oliveira et al., 2013).

Three studies in the present review manipulated feelings of financial status in between-subjects designs. Though the three studies use different terminology, they all arguably manipulate the same thing. In Callan et al. (2011; Study 1) participants were told that their discretionary income was about the same or much lower than others (i.e., false feedback) to invoke feelings of relative deprivation. Van den Bergh et al. (2008; Study 3, control group only[1]) manipulated the scale in which participants reported their income and Moeini-Jazani et al. (2019; Study 2, control group only[2]) used versions of both methods with each participant. The scale manipulation method has been established as an effective way to induce feelings of financial deprivation and has been shown to affect performance in other tasks (e.g., Haisley et al., 2008; Briers and Laporte, 2013). Moeini-Jazani et al. (2019) also conducted a pretest to validate their manipulation. Participants in Van den Bergh et al. (2008) and Callan et al. (2011) were students, with a mean age of around 19 years, while participants in Moeini-Jazani et al. (2019) were older (mean age = 36 years) and recruited online via MTurk. Also important to note, the sample size in Moeini-Jazani et al. (2019) was much larger ($n > 100$ for each group) than in Van den Bergh et al. (2008) and Callan et al. (2011; N's ∼30–35 for each group). Van den Bergh et al. (2008) and Moeini-Jazani et al. (2019) used fill in the blank delay discounting tasks (e.g., $65 now is worth ____ in x months) with a relatively short set of delays (maximum delays were 18 months and 1 month, respectively) and relatively small magnitudes of larger later amounts ($65 and €15, respectively). Callan et al. (2011) used an adjusting amount task with a fixed larger later outcome of $1,000 and a slightly longer maximum delay of 2 years.

For delay discounting of money, all studies found higher levels of delay discounting for those in the deprivation group compared to the non-deprivation group. The effect was large and statistically significant in Callan et al. (2011; Hedge's $g = 0.76$) and Moeini-Jazani et al. (2019; Hedge's $g = 0.64$), but Van den Bergh et al. (2008) did not report any statistical test results for this comparison. Van den Bergh et al. (2008) also examined delay discounting of bars of candy and cans of soda. Mean AUC for the deprived group was similar to the non-deprived group for delay discounting of both candy and soda. Because of the consistency in the data overall, we conclude that delay discounting of money tends to increase after monetary deprivation manipulations. It is unclear how long the effect of the manipulation lasts; the delay discounting task occurred soon after the manipulation in all studies. It is also unclear if the effect would generalize to delay discounting of other commodities, but it is potentially important that participants were discounting a commodity that was in-domain relative to the manipulation (i.e., deprived of money and discounted money).

[2]Van den Bergh et al. (2008) and Moeini-Jazani et al. (2019) both had other manipulations hypothesized to interact with monetary deprivation to increase or decrease delay discounting; we look at only the control condition to more clearly understand only the effects of the deprivation manipulation.

CONCLUSION

We were not able to make conclusions for each deprivation category, but it does appear that the effect of deprivation on delay discounting may depend on the type of deprivation subjects faced. In humans, nicotine and sleep deprivation tend to have little to no effect on delay discounting, whereas opioid deprivation and feelings of financial deprivation tend to increase delay discounting. The effect of deprivation of food and water on delay discounting is less clear. It is interesting that even though theoretical frameworks (e.g., CNDS model) predict increases in delay discounting, we do not see consistent effects for all types of deprivation.

Previous research indicates that delay discounting is both state-like and trait-like (Odum et al., 2020). The inconsistent effects of deprivation on delay discounting may provide additional evidence that delay discounting is not entirely a trait. If delay discounting was purely trait-like, delay discounting would not change due to any deprivation manipulation (see Skrynka and Vincent, 2019). Yet, in the present review, deprivation resulted in increased, decreased, and no change in delay discounting. Although these findings do provide additional evidence that modulation of delay discounting due to state is possible, it is puzzling that not all types of deprivation manipulations resulted in changes in delay discounting.

One interesting pattern we found was that manipulations that were imagined (i.e., imagined opioid withdrawal, financial deprivation) tended to increase delay discounting, whereas manipulations that were more physiological in nature (i.e., sleep and nicotine deprivation) produced little to no change in delay discounting. This result may suggest that the cognitive appraisal of states could propel modulations in delay discounting. That is, intentional acknowledgment of deprivation symptoms may be important in increasing delay discounting. Related, it may also be that the instructions given in imagined state manipulations specifically highlighted a present experience, perhaps thereby shifting attention to the present, similar to how EFT may shift attention to the future (Lin and Epstein, 2014). To test this suggestion, one could examine the effect of imagined sleep deprivation, for example, on delay discounting. All experiments in the present review concluded that actual sleep deprivation had no effect on delay discounting. If imagined sleep deprivation did increase delay discounting, then something about the imagined state, rather than experiencing tiredness, may be causing the change in delay discounting.

Another possible reason we did not see consistent effects of deprivation is that there may be an effect of domain matching. Specifically, manipulations may have a greater impact on delay discounting if the commodity discounted is relevant to the manipulation (see Skrynka and Vincent, 2019). In many of the opioid deprivation and financial deprivation experiments, participants discounted opioids and money, respectively, and we concluded that deprivation tends to increase delay discounting for these deprivation types. We do not consistently see this pattern, however, for other types of deprivation. For instance, of the two studies in which participants discounted cigarettes and were deprived of nicotine, one found increased delay

discounting of cigarettes and one found no change in delay discounting of cigarettes (Field et al., 2006; Yi and Landes, 2012). More experiments are needed to examine the potential interaction between domain matching and manipulations; the generalizability of manipulations has implications for behavioral interventions that aim to change delay discounting. It is important to know if changing delay discounting of food will also influence delay discounting of money, for example, and thus if a range of behaviors or just a class of behaviors can be changed by a single intervention.

In dual-systems models, "visceral influences" like hunger and cravings should increase impulsivity (see e.g., Loewenstein, 1996). The types of deprivation we examined all tend to result in some sort of negative cognitive, emotional, or physiologic change, although the severity of deprivation "symptoms" varies. For instance, opioid withdrawal results in flu-like symptoms and nicotine withdrawal may result in irritability and anxiety. Despite all deprivation manipulations resulting in arguably "visceral" states, we do not see consistent effects of deprivation manipulations on delay discounting. It may be that there is a threshold of discomfort or arousal that must be surpassed in order for a visceral influence to result in significant dysregulation of the control and valuation systems, and thus in heightened delay discounting. Nicotine deprivation may certainly be unpleasant, but arguably not as much as opioid deprivation may be.

It may be instead, rather than visceral influences requiring a threshold, that the effect of visceral influences on delay discounting is more nuanced than previously thought. In Richards et al. (1997) and Oliveira et al. (2013), the effects of water and food deprivation were studied in non-human animals; there was little to no effect of deprivation on delay discounting in these studies (although see Carroll et al., 2009). Non-human animals provide arguably more experimental control (e.g., one can be more certain that a non-human animal subject followed the deprivation protocol). If there is little effect of food and water deprivation on delay discounting in non-human animal models, then perhaps our idea of what constitutes a visceral influence should change. However, the non-human animal literature on delay discounting and deprivation must be reconciled with the human literature, as we found some discrepancies in results between species.

The effects of deprivation, and other states, on delay discounting may provide the impetus for the design of behavioral interventions. In the present review, we found that opioid deprivation tends to result in increased delay discounting; it may be that increased delay discounting during abstinence leads to greater relapse vulnerability. By knowing if people tend to discount future outcomes more so while going through withdrawal, contingency management treatments, for instance, could be designed with shorter delays to incentives to leverage preference for sooner outcomes (Miglin et al., 2017). Similarly, EFT has been shown to reduce self-administered cigarette puffs in the laboratory (Stein et al., 2016); perhaps EFT cues could be administered strategically during deprivation states like abstinence to compensate for maladaptive increases in delay discounting.

The present review is the first to examine the effect of experimental manipulations of deprivation on delay discounting. We found more types of deprivation manipulations than we anticipated, and therefore our search terms may have been limited. Despite this limitation, our review provides the advantage of examining the deprivation literature broadly. As more data emerge, it may be fruitful to examine each deprivation type individually with search terms more relevant to specific manipulations (e.g., Hughes et al., 2014).

Deprivation does not always increase delay discounting, contrary to the predictions of theoretical frameworks. Delay discounting may be a trans-disease process and has been used as target for behavioral interventions (Bickel et al., 2019). Thus, a basic understanding of how delay discounting is affected by various states, including deprivation, will be needed for future translational research.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: https://osf.io/vjb6e/?view_only=96119bfc0dc04bccbd0698808f59621a.

AUTHOR CONTRIBUTIONS

All authors were involved in conceptualization and design. HJ, JH, and HD collected the data. JH conducted the data analysis and created figures. HJ designed a figure. HD wrote the manuscript with support from AO and JH. All authors reviewed the results and approved the final version of the manuscript.

ACKNOWLEDGMENTS

The authors would like to thank Caroline Towse, D. Perez, and Kailey Morrissey for assistance in the early stages of manuscript preparation. We confirm that no part of this manuscript has been disseminated elsewhere or in any other format. The authors would like to thank the Virginia Tech Open Access Subvention Fund and the Utah State University Open Access Funding Initiative for providing funding for the article processing fee associated with the publication of this manuscript.

REFERENCES

*Acheson, A., Richards, J. B., and de Wit, H. (2007). Effects of sleep deprivation on impulsive behaviors in men and women. *Physiol. Behav.* 91, 579–587. doi: 10.1016/j.physbeh.2007.03.020

Alessi, S. M., and Petry, N. M. (2003). Pathological gambling severity is associated with impulsivity in a delay discounting procedure. *Behav. Process.* 64, 345–354. doi: 10.1016/S0376-6357(03)00150-5

Amlung, M., Marsden, E., Holshausen, K., Morris, V., Patel, H., Vedelago, L., et al. (2019). Delay discounting as a transdiagnostic process in

psychiatric disorders: a meta-analysis. *JAMA Psychiatry* 76, 1176–1186. doi: 10.1001/jamapsychiatry.2019.2102

*Antonelli, F., Ko, J. H., Miyasaki, J., Lang, A. E., Houle, S., Valzania, F., et al. (2014). Dopamine-agonists and impulsivity in Parkinson's disease: impulsive choices vs. impulsive actions. *Hum. Brain Mapp.* 35, 2499–2506. doi: 10.1002/hbm.22344

Appelhans, B. M., Tangney, C. C., French, S. A., Crane, M. M., and Wang, Y. (2019). Delay discounting and household food purchasing decisions: the SHoPPER study. *Health Psychol.* 38, 334–342. doi: 10.1037/hea0000727

Ashare, R. L., Falcone, M., and Lerman, C. (2014). Cognitive function during nicotine withdrawal: implications for nicotine dependence treatment. *Neuropharmacology* 76, 581–591. doi: 10.1016/j.neuropharm.2013.04.034

Ashare, R. L., and Hawk, L. W. (2012). Effects of smoking abstinence on impulsive behavior among smokers high and low in ADHD-like symptoms. *Psychopharmacol.* 219, 537–547. doi: 10.1007/s00213-011-2324-2

*Ashare, R. L., and Kable, J. W. (2015). Sex differences in time perception during smoking abstinence. *Nicot. Tobacco Res.* 17, 449–454. doi: 10.1093/ntr/ntu260

Ashare, R. L., and McKee, S. A. (2012). Effects of varenicline and bupropion on cognitive processes among nicotine-deprived smokers. *Exp. Clin. Psychopharmacol.* 20:63. doi: 10.1037/a0025594

Bailey, A. J., Romeu, R. J., and Finn, P. R. (2021). The problems with delay discounting: a critical review of current practices and clinical applications. *Psychol. Med.* 51, 1799–1806. doi: 10.1017/S0033291721002282

Baker, T. B., Piper, M. E., McCarthy, D. E., Majeskie, M. R., and Fiore, M. C. (2004). Addiction motivation reformulated: an affective processing model of negative reinforcement. *Psychol. Rev.* 111:33. doi: 10.1037/0033-295X.111.1.33

Baldacchino, A., Balfour, D. J. K., Passetti, F., Humphris, G., and Matthews, K. (2012). Neuropsychological consequences of chronic opioid use: a quantitative review and meta-analysis. *Neurosci. Biobehav. Rev.* 36, 2056–2068. doi: 10.1016/j.neubiorev.2012.06.006

Benau, E. M., Orloff, N. C., Janke, E. A., Serpell, L., and Timko, C. A. (2014). A systematic review of the effects of experimental fasting on cognition. *Appetite* 77, 52–61. doi: 10.1016/j.appet.2014.02.014

Berns, G. S., Laibson, D., and Loewenstein, G. (2007). Intertemporal choice-toward an integrative framework. *Trends Cogn. Sci.* 11, 482–488. doi: 10.1016/j.tics.2007.08.011

Bickel, W. K., Athamneh, L. N., Basso, J. C., Mellis, A. M., DeHart, W. B., Craft, W. H., et al. (2019). Excessive discounting of delayed reinforcers as a trans-disease process: update on the state of the science. *Curr. Opin. Psychol.* 30, 59–64. doi: 10.1016/j.copsyc.2019.01.005

Bickel, W. K., Jarmolowicz, D. P., Mueller, E. T., Koffarnus, M. N., and Gatchalian, K. M. (2012). Excessive discounting of delayed reinforcers as a trans-disease process contributing to addiction and other disease-related vulnerabilities: emerging evidence. *Pharmacol. Therap.* 134, 287–297. doi: 10.1016/j.pharmthera.2012.02.004

Bickel, W. K., MacKillop, J., Madden, G. J., Odum, A. L., and Yi, R. (2015). Experimental manipulations of delay discounting and related processes: an introduction to the special issue. *J. Exp. Anal. Behav.* 103:133. doi: 10.1002/jeab.133

Bickel, W. K., Mellis, A. M., Snider, S. E., Athamneh, L. N., Stein, J. S., and Pope, D. A. (2018). 21st century neurobehavioral theories of decision making in addiction: review and evaluation. *Pharmacol. Biochem. Behav.* 164, 4–21. doi: 10.1016/j.pbb.2017.09.009

Bickel, W. K., Moody, L., Quisenberry, A. J., Ramey, C. T., and Sheffer, C. E. (2014). A competing neurobehavioral decision systems model of SES-related health and behavioral disparities. *Prevent. Med.* 68, 37–43. doi: 10.1016/j.ypmed.2014.06.032

Bickel, W. K., Odum, A. L., and Madden, G. J. (1999). Impulsivity and cigarette smoking: delay discounting in current, never, and ex-smokers. *Psychopharmacology* 146, 447–454. doi: 10.1007/PL00005490

Bickel, W. K., Snider, S. E., Quisenberry, A. J., Stein, J. S., and Hanlon, C. A. (2016). Competing neurobehavioral decision systems theory of cocaine addiction: from mechanisms to therapeutic opportunities. *Prog. Brain Res.* 223, 269–293. doi: 10.1016/bs.pbr.2015.07.009

Borenstein, M., Hedges, L. V., Higgins, J. P., and Rothstein, H. R. (2009). *Introduction to Meta-Analysis, 1st Edn.* New York, NY: Russell Sage Foundation. doi: 10.1002/9780470743386

Briers, B., and Laporte, S. (2013). A wallet full of calories: the effect of financial dissatisfaction on the desire for food energy. *J. Market. Res.* 50, 767–781. doi: 10.1509/jmr.10.0513

*Callan, M. J., Shead, N. W., and Olson, J. M. (2011). Personal relative deprivation, delay discounting, and gambling. *J. Pers. Soc. Psychol.* 101, 955–973. doi: 10.1037/a0024778

Carroll, M. E. (1985). The role of food deprivation in the maintenance and reinstatement of cocaine-seeking behavior in rats. *Drug. Alcohol Depend.* 16, 95–109. doi: 10.1016/0376-8716(85)90109-7

*Carroll, M. E., Kohl, E. A., Johnson, K. M., and LaNasa, R. M. (2013). Increased impulsive choice for saccharin during PCP withdrawal in female monkeys: influence of menstrual cycle phase. *Psychopharmacology* 227, 413–424. doi: 10.1007/s00213-012-2963-y

*Carroll, M. E., Mach, J. L., La Nasa, R. M., and Newman, J. L. (2009). Impulsivity as a behavioral measure of withdrawal of orally delivered PCP and nondrug rewards in male and female monkeys. *Psychopharmacology* 207, 85–98. doi: 10.1007/s00213-009-1636-y

Christensen-Szalanski, J. J., Goldberg, A. D., Anderson, M. E., and Mitchell, T. R. (1980). Deprivation, delay of reinforcement, and the selection of behavioural strategies. *Anim. Behav.* 28, 341–346. doi: 10.1016/S0003-3472(80)80042-X

Dallery, J., and Raiff, B. R. (2007). Delay discounting predicts cigarette smoking in a laboratory model of abstinence reinforcement. *Psychopharmacology* 190, 485–496. doi: 10.1007/s00213-006-0627-5

Dallery, J., and Raiff, B. R. (2011). Contingency management in the 21st century: technological innovations to promote smoking cessation. *Substan. Use Misuse* 46, 10–22. doi: 10.3109/10826084.2011.521067

Daugherty, J. R., and Brase, G. L. (2010). Taking time to be healthy: predicting health behaviors with delay discounting and time perspective. *Pers. Individ. Dif.* 48, 202–207. doi: 10.1016/j.paid.2009.10.007

De Wit, H. (2009). Impulsivity as a determinant and consequence of drug use: a review of underlying processes. *Addict. Biol.* 14, 22–31. doi: 10.1111/j.1369-1600.2008.00129.x

De Wit, H., and Mitchell, S. H. (2010). "Drug effects on delay discounting," in *Impulsivity: The Behavioral and Neurological Science of Discounting,* eds G. J. Madden and W. K. Bickel (Washington, DC: American Psychological Association), 213–241. doi: 10.1037/12069-008

*Demos, K. E., Hart, C. N., Sweet, L. H., Mailloux, K. A., Trautvetter, J., Williams, S. E., et al. (2016). Partial sleep deprivation impacts impulsive action but not impulsive decision-making. *Physiol. Behav.* 164, 214–219. doi: 10.1016/j.physbeh.2016.06.003

Diller, J. W., Saunders, B. T., and Anderson, K. G. (2008). Effects of acute and repeated administration of caffeine on temporal discounting in rats. *Pharmacol. Biochem. Behav.* 89, 546–555. doi: 10.1016/j.pbb.2008.02.008

Dixon, M. R., Jacobs, E. A., and Sanders, S. (2006). Contextual control of delay discounting by pathological gamblers. *J. Appl. Behav. Anal.* 39. 413–422. doi: 10.1901/jaba.2006.173-05

Drope, J., Liber, A. C., Cahn, Z., Stoklosa, M., Kennedy, R., Douglas, C. E., et al. (2018). Who's still smoking? Disparities in adult cigarette smoking prevalence in the United States. *J. Clin.* 68, 106–115. doi: 10.3322/caac.21444

Eppolito, A. K., France, C. P., and Gerak, L. R. (2013). Effects of acute and chronic morphine on delay discounting in pigeons. *J. Exp. Anal. Behav.* 99, 277–289. doi: 10.1002/jeab.25

Ersek, M., Cherrier, M. M., Overman, S. S., and Irving, G. A. (2004). The cognitive effects of opioids. *Pain Manage. Nurs.* 5, 75–93. doi: 10.1016/j.pmn.2003.11.002

Evenden, J. L., and Ryan, C. N. (1996). The pharmacology of impulsive behaviour in rats: the effects of drugs on response choice with varying delays of reinforcement. *Psychopharmacology* 128, 161–170. doi: 10.1007/s002130050121

Faul, F., Erdfelder, E., Lang, A. G., Bucher, A. (2007). G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav. Res. Methods* 39, 175–191. doi: 10.3758/BF03193146

Felton, J. W., Collado, A., Ingram, K., Lejuez, C. W., and Yi, R. (2020). Changes in delay discounting, substance use, and weight status across adolescence. *Health Psychol.* 39:413. doi: 10.1037/hea0000833

Ferguson, C. J. (2009). An effect size primer: A guide for clinicians and researchers. *Prof. Psychol. Res. Pr.* 40, 532–538. doi: 10.1037/a0015808

*Field, M., Santarcangelo, M., Sumnall, H., Goudie, A., and Cole, J. (2006). Delay discounting and the behavioral economics of cigarette purchases in

smokers: the effects of nicotine deprivation. *Psychopharmacology* 186, 255–263. doi: 10.1007/s00213-006-0385-4

Fields, S. A., Lange, K., Ramos, A., Thamotharan, S., and Rassu, F. (2014). The relationship between stress and delay discounting: a meta-analytic review. *Behav. Pharmacol.* 25, 434–444. doi: 10.1097/FBP.0000000000000044

Frederick, S., Loewenstein, G., and O'Donoghue, T. (2002). Time discounting and time preference: a critical review. *J. Econ. Lit.* 40, 351–401. doi: 10.1257/jel.40.2.351

Frost, R., and McNaughton, N. (2017). The neural basis of delay discounting: a review and preliminary model. *Neurosci. Biobehav. Rev.* 79, 48–65. doi: 10.1016/j.neubiorev.2017.04.022

Giordano, L. A., Bickel, W. K., Loewenstien, G., Jacobs, E. A., Marsh, L., and Badger, G. J. (2002). Mild opioid deprivation increases the degree that opioid-dependent outpatients discount delayed heroin and money. *Psychopharmacology* 163, 174–182. doi: 10.1007/s00213-002-1159-2

Gipson, C. D., and Bardo, M. T. (2009). Extended access to amphetamine self-administration increases impulsive choice in a delay discounting task in rats. *Psychopharmacology* 207, 391–400. doi: 10.1007/s00213-009-1667-4

Goulet-Pelletier, J. C., and Cousineau, D. (2018). A review of effect sizes and their confidence intervals, Part I: The Cohen's d family. *Quant. Methods Psychol.* 14, 242–265. doi: 10.20982/tqmp.14.4.p242

*Grabski, M., Curran, H. V., Nutt, D. J., Husbands, S. M., Ferguson, S. G., and Munaf,ò, M. R. (2020). The development and validation of a human screening model of tobacco abstinence. *Drug Alcohol Depend.* 206:107720. doi: 10.1016/j.drugalcdep.2019.107720

Grant, B. F., Shmulewitz, D., and Compton, W. M. (2020). Nicotine use and DSM-IV nicotine dependence in the United States, 2001-2002 and 2012-2013. *Am. J. Psychiatry* 177, 1082–1090. doi: 10.1176/appi.ajp.2020.19090900

Green, L., and Myerson, J. (2004). A discounting framework for choice with delayed and probabilistic rewards. *Psychol. Bull.* 130:769. doi: 10.1037/0033-2909.130.5.769

Green, L., Myerson, J., Lichtman, D., Rosen, S., and Fry, A. (1996). Temporal discounting in choice between delayed rewards: the role of age and income. *Psychol. Aging* 11:79. doi: 10.1037/0882-7974.11.1.79

Haisley, E., Mostafa, R., and Loewenstein, G. (2008). Subjective relative income and lottery ticket purchases. *J. Behav. Decis. Mak.* 21, 283–295. doi: 10.1002/bdm.588

Harvey-Lewis, C., Brisebois, A. D., Yong, H., and Franklin, K. B. (2015). Naloxone-precipitated withdrawal causes an increase in impulsivity in morphine-dependent rats. *Behav. Pharmacol.* 26, 326–329. doi: 10.1097/FBP.0000000000000106

Haufroid, V., and Lison, D. (1998). Urinary cotinine as a tobacco-smoke exposure index: a minireview. *Int. Arch. Occup. Environ. Health* 71, 162–168. doi: 10.1007/s004200050266

Haushofer, J., and Fehr, E. (2014). On the psychology of poverty. *Science* 344, 862–867. doi: 10.1126/science.1232491

Haynes, J. M., Galizio, A., Frye, C. C., Towse, C. C., Morrissey, K. N., Serang, S., et al. (2021). Discounting of food and water in rats shows trait-and state-like characteristics. *J. Exp. Anal. Behav.* 115, 495–509. doi: 10.1002/jeab.677

Heatherton, T. F., Kozlowski, L. T., Frecker, R. C., and Fagerstrom, K. O. (1991). The Fagerström test for nicotine dependence: a revision of the Fagerstrom Tolerance Questionnaire. *Br. J. Addict.* 86, 1119–1127. doi: 10.1111/j.1360-0443.1991.tb01879.x

*Heckman, B. W., MacQueen, D. A., Marquinez, N. S., MacKillop, J., Bickel, W. K., and Brandon, T. H. (2017). Self-control depletion and nicotine deprivation as precipitants of smoking cessation failure: a human laboratory model. *J. Consult. Clin. Psychol.* 85, 381–396. doi: 10.1037/ccp0000197

Heishman, S. J., Kleykamp, B. A., and Singleton, E. G. (2010). Meta-analysis of the acute effects of nicotine and smoking on human performance. *Psychopharmacology* 210, 453–469. doi: 10.1007/s00213-010-1848-1

Hughes, J. R. (2007). Effects of abstinence from tobacco: valid symptoms and time course. *Nicotine Tobacco Res.* 9, 315–327. doi: 10.1080/14622200701188919

Hughes, J. R. (2011). The hardening hypothesis: is the ability to quit decreasing due to increasing nicotine dependence? A review and commentary. *Drug Alcohol Depend.* 117, 111–117. doi: 10.1016/j.drugalcdep.2011.02.009

*Hughes, J. R., Budney, A. J., Muellers, S. R., Lee, D. C., Callas, P. W., Sigmon, S. C., et al. (2017). Does tobacco abstinence decrease reward sensitivity? A human laboratory test. *Nicotine Tobacco Res.* 19, 677–685. doi: 10.1093/ntr/ntw204

Hughes, J. R., Dash, M., and Callas, P. W. (2014). Is impulsivity a symptom of initial tobacco withdrawal? A meta-analysis and qualitative systematic review. *Nicotine Tobacco Res.* 17, 503–509. doi: 10.1093/ntr/ntu220

Hughes, J. R., and Hatsukami, D. (1986). Signs and symptoms of tobacco withdrawal. *Arch. Gen. Psychiatry* 43, 289–294. doi: 10.1001/archpsyc.1986.01800030107013

Hughes, J. R., Keely, J., and Naud, S. (2004). Shape of the relapse curve and long-term abstinence among untreated smokers. *Addiction* 99, 29–38. doi: 10.1111/j.1360-0443.2004.00540.x

Hullett, C. R., and Levine, T. R. (2003). The overestimation of effect sizes from f values in meta-analysis: The cause and a solution. *Commun. Monogr.* 70, 52–67. doi: 10.1080/715114664

Hurwitz, H. M. B., and Davis, H. (1983). Depriving rats of food: a reappraisal of two techniques. *J. Exp. Anal. Behav.* 40:211. doi: 10.1901/jeab.1983.40-211

Jatlow, P., Toll, B. A., Leary, V., Krishnan-Sarin, S., and O'Malley, S. S. (2008). Comparison of expired carbon monoxide and plasma cotinine as markers of cigarette abstinence. *Drug Alcohol Depend.* 98, 203–209. doi: 10.1016/j.drugalcdep.2008.05.013

Johnson, M. W., and Bickel, W. K. (2002). Within-subject comparison of real and hypothetical money rewards in delay discounting. *J. Exp. Anal. Behav.* 77, 129–146. doi: 10.1901/jeab.2002.77-129

Johnson, M. W., and Bruner, N. R. (2012). The sexual discounting task: HIV risk behavior and the discounting of delayed sexual rewards in cocaine dependence. *Drug Alcohol Depend.* 123, 15–21. doi: 10.1016/j.drugalcdep.2011.09.032

Jorenby, D. E., Hays, J. T., Rigotti, N. A., Azoulay, S., Watsky, E. J., Williams, K. E., et al. (2006). Efficacy of varenicline, an α4β2 nicotinic acetylcholine receptor partial agonist, vs. placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA* 296, 56–63. doi: 10.1001/jama.296.1.56

Kayir, H., Semenova, S., and Markou, A. (2014). Baseline impulsive choice predicts the effects of nicotine and nicotine withdrawal on impulsivity in rats. *Prog. Neuropsychopharmacol. Biol.* 48, 6–13. doi: 10.1016/j.pnpbp.2013.09.007

Killgore, W. D. (2010). Effects of sleep deprivation on cognition. *Prog. Brain Res.* 185, 105–129. doi: 10.1016/B978-0-444-53702-7.00007-5

Kirby, K. N., Petry, N. M., and Bickel, W. K. (1999). Heroin addicts have higher discount rates for delayed rewards than non-drug-using controls. *J. Exp. Psychol.* 128:78. doi: 10.1037/0096-3445.128.1.78

Kirk, J. M., and Logue, A. W. (1997). Effects of deprivation level on humans' self-control for food reinforcers. *Appetite* 28, 215–226. doi: 10.1006/appe.1996.0071

*Kolokotroni, K. Z., Rodgers, R. J., and Harrison, A. A. (2014). Trait differences in response to chronic nicotine and nicotine withdrawal in rats. *Psychopharmacology* 231, 567–580. doi: 10.1007/s00213-013-3270-y

Kosten, T. R., and Baxter, L. E. (2019). Effective management of opioid withdrawal symptoms: a gateway to opioid dependence treatment. *Am. J. Addict.* 28, 55–62. doi: 10.1111/ajad.12862

Landolt, H. P., Holst, S. C., Sousek, A., Bassetti, C., Dogas, Z., and Peigneux, P. (2014). "Effects of acute and chronic sleep deprivation," in *Sleep Medicine Textbook,* eds C. Bassetti, Z. Dogas, and P. Peigneux (Regensburg: European Sleep Research Society), 49–61. doi: 10.5167/uzh-107182

Levitt, E., Sanchez-Roige, S., Palmer, A. A., and MacKillop, J. (2020). Steep discounting of future rewards as an impulsivity phenotype: a concise review. *Recent Adv. Res. Impuls. Impuls. Behav.* 47, 113–138. doi: 10.1007/7854_2020_128

*Libedinsky, C., Massar, S. A. A., Ling, A., Chee, W., Huettel, S. A., and Chee, M. W. L. (2013). Sleep deprivation alters effort discounting but not delay discounting of monetary rewards. *Sleep* 36, 899–904. doi: 10.5665/sleep.2720

Lin, H., and Epstein, L. H. (2014). Living in the moment: effects of time perspective and emotional valence of episodic thinking on delay discounting. *Behav. Neurosci.* 128:12. doi: 10.1037/a0035705

Loewenstein, G. (1996). Out of control: visceral influences on behavior. *Organ. Behav. Hum. Decis. Proces.* 65, 272–292. doi: 10.1006/obhd.1996.0028

Loganathan, K., Lv, J., Cropley, V., Ho, E. T. W., and Zalesky, A. (2021). Associations between delay discounting and connectivity of the valuation-control system in healthy young adults. *Neuroscience* 452, 295–310. doi: 10.1016/j.neuroscience.2020.11.026

Logue, A. W. (1988). Research on self-control: an integrating framework. *Behav. Brain Sci.* 11, 665–679. doi: 10.1017/S0140525X00053978

Logue, A. W., Chavarro, A., Rachlin, H., and Reeder, R. W. (1988). Impulsiveness in pigeons living in the experimental chamber. *Anim. Learn. Behav.* 16, 31–39. doi: 10.3758/BF03209040

Logue, A. W., and Peña-Correal, T. E. (1985). The effect of food deprivation on self-control. *Behav. Process.* 10, 355–368. doi: 10.1016/0376-6357(85)90036-1

MacKillop, J., Amlung, M. T., Few, L. R., Ray, L. A., Sweet, L. H., and Munafò, M. R. (2011). Delayed reward discounting and addictive behavior: a meta-analysis. *Psychopharmacology* 216, 305–321. doi: 10.1007/s00213-011-2229-0

Madden, G. J., Begotka, A. M., Raiff, B. R., and Kastern, L. L. (2003). Delay discounting of real and hypothetical rewards. *Exp. Clin. Psychopharmacol.* 11:139. doi: 10.1037/1064-1297.11.2.139

Malin, D. H., Lake, J. R., Newlin-Maultsby, P., Roberts, L. K., Lanier, J. G., Carter, V. A., et al. (1992). Rodent model of nicotine abstinence syndrome. *Pharmacol. Biochem. Behav.* 43, 779–784. doi: 10.1016/0091-3057(92)90408-8

Masento, N., Golightly, M., Field, D., Butler, L., and Van Reekum, C. (2014). Effects of hydration status on cognitive performance and mood. *Br. J. Nutr.* 111, 1841–1852. doi: 10.1017/S0007114513004455

Mazur, J. E. (1987). *The Effect of Delay and of Intervening Events on Reinforcement Value: Quantitative Analyses of Behavior*. Hillsdale, NJ: Psychology Press.

McLaughlin, I., Dani, J. A., and De Biasi, M. (2015). Nicotine withdrawal. *Neuropharmacol. Nicotine Depend.* 24, 99–123. doi: 10.1007/978-3-319-13482-6_4

Metcalfe, J., and Mischel, W. (1999). A hot/cool-system analysis of delay of gratification: dynamics of willpower. *Psychol. Rev.* 106, 3–19. doi: 10.1037/0033-295X.106.1.3

Michael, J. (1982). Distinguishing between discriminative and motivational functions of stimuli. *J. Exp. Anal. Behav.* 37, 149–155. doi: 10.1901/jeab.1982.37-149

*Miglin, R., Kable, J. W., Bowers, M. E., and Ashare, R. L. (2017). Withdrawal-related changes in delay discounting predict short-term smoking abstinence. *Nicotine Tobacco Res.* 19, 694–702. doi: 10.1093/ntr/ntw246

Miller, L. K. (2006). *Principles of Everyday Behavior Analysis*. Monterey, CA: Cengage Learning.

Mitchell, S. (1999). Measures of impulsivity in cigarette smokers and non-smokers. *Psychopharmacology* 146, 455–464. doi: 10.1007/PL00005491

*Mitchell, S. H. (2004). Effects of short-term nicotine deprivation on decision-making: delay, uncertainty and effort discounting. *Nicotine Tobacco Res.* 6, 819–828. doi: 10.1080/14622200412331296002

*Moeini-Jazani, M., Albalooshi, S., and Seljeseth, I. M. (2019). Self-affirmation reduces delay discounting of the financially deprived. *Front. Psychol.* 10:1729. doi: 10.3389/fpsyg.2019.01729

*Moses, T. E. H., Burmeister, M., and Greenwalk, M. K. (2019). Heroin delay discounting and impulsivity: modulation by DRD1 genetic variation. *Addict. Biol.* 25:e12777. doi: 10.1111/adb.12777

Myerson, J., Green, L., and Warusawitharana, M. (2001). Area under the curve as a measure of discounting. *J. Exp. Anal. Behav.* 76, 235–243. doi: 10.1901/jeab.2001.76-235

Neave, N., Scholey, A. B., Emmett, J. R., Moss, M., Kennedy, D. O., and Wesnes, K. A. (2001). Water ingestion improves subjective alertness, but has no effect on cognitive performance in dehydrated healthy young volunteers. *Appetite* 37, 255–256. doi: 10.1006/appe.2001.0429

Noda, Y., Barr, M. S., ElSalhy, M., Masuda, F., Tarumi, R., Ogyu, K., et al. (2020). Neural correlates of delay discount alterations in addiction and psychiatric disorders: a systematic review of magnetic resonance imaging studies. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* 99:109822. doi: 10.1016/j.pnpbp.2019.109822

Nowland, M. H., Hugunin, K., and Rogers, K. L. (2011). Effects of short-term fasting in male Sprague-Dawley rats. *Comp. Med.* 61, 138–144.

Odum, A. L. (2011a). Delay discounting: i'm a k, you're a k. *J. Exp. Anal. Behav.* 96, 427–439. doi: 10.1901/jeab.2011.96-423

Odum, A. L. (2011b). Delay discounting: trait variable? *Behav. Process.* 87, 1–9. doi: 10.1016/j.beproc.2011.02.007

Odum, A. L., and Baumann, A. A. (2010). "Delay discounting: state and trait variable," in *Impulsivity: The Behavioral and Neurological Science of Discounting*, eds G. J. Madden and W. K. Bickel (Washington, DC: American Psychological Association), 39–65. doi: 10.1037/12069-002

Odum, A. L., Becker, R. J., Haynes, J. M., Galizio, A., Frye, C. C. J., Downey, H., et al. (2020). Delay discounting of different outcomes: review and theory. *J. Exp. Anal. Behav.* 113, 657–679. doi: 10.1002/jeab.589

*Oliveira, L., Calvert, A. L., Green, L., and Myerson, J. (2013). Level of deprivation does not affect degree of discounting in pigeons. *Learn. Behav.* 41, 148–158. doi: 10.3758/s13420-012-0092-4

Quisenberry, A. J., Snider, S. E., and Bickel, W. K. (2016). The return of rate dependence. *Behav. Anal.* 16:215. doi: 10.1037/bar0000042

Reynolds, B. (2006). A review of delay-discounting research with humans: relations to drug use and gambling. *Behav. Pharmacol.* 17, 651–667. doi: 10.1097/FBP.0b013e3280115f99

Reynolds, B., and Schiffbauer, R. (2004). Measuring state changes in human delay discounting: an experiential discounting task. *Behav. Process.* 67, 343–356. doi: 10.1016/j.beproc.2004.06.003

*Richards, J. B., Mitchell, S. H., De Wit, H., and Seiden, L. S. (1997). Determination of discount functions in rats with an adjusting-amount procedure. *J. Exp. Anal. Behav.* 67, 353–366. doi: 10.1901/jeab.1997.67-353

Robinson, J. D., Li, L., Chen, M., Lerman, C., Tyndale, R. F., Schnoll, R. A., et al. (2019). Evaluating the temporal relationships between withdrawal symptoms and smoking relapse. *Psychol. Addict. Behav.* 33:105. doi: 10.1037/adb0000434

*Roewer, I., Wiehler, A., and Peters, J. (2015). Nicotine deprivation, temporal discounting and choice consistency in heavy smokers. *J. Exp. Anal. Behav.* 103, 62–76. doi: 10.1002/jeab.134

Rohatgi, A. (2018). *WebPlotDigitalizer: Web Based Tool to Extract Data From Plots, Images, and Maps. Version 4.1.* Available online at: http://arohatgi.info/WebPlotDigitizer/app/

Rung, J. M., and Madden, G. J. (2018). Experimental reductions of delay discounting and impulsive choice: a systematic review and meta-analysis. *J. Exp. Psychol.* 147:1349. doi: 10.1037/xge0000462

Schelling, T. (1984). Self-command in practice, in policy, and in a theory of rational choice. *Am. Econ. Rev.* 74, 1–11.

Schneider, W., and Shiffrin, R. M. (1977). Controlled and automatic human information processing: I. Detection, search, and attention. *Psychol. Rev.* 84, 1–66. doi: 10.1037/0033-295X.84.1.1

Shah, A. K., Mullainathan, S., and Shafir, E. (2012). Some consequences of having too little. *Science* 338, 682–685. doi: 10.1126/science.1222426

Shoaib, M., and Bizarro, L. (2005). Deficits in a sustained attention task following nicotine withdrawal in rats. *Psychopharmacology* 178, 211–222. doi: 10.1007/s00213-004-2004-6

*Skrynka, J., and Vincent, B. T. (2019). Hunger increases delay discounting of food and non-food rewards. *Psychon. Bull. Rev.* 26, 1729–1737. doi: 10.3758/s13423-019-01655-0

Stanger, C., Elton, A., Ryan, S. R., James, C. A., Budney, A. J., and Kilts, C. D. (2013). Neuroeconomics and adolescent substance abuse: individual differences in neural networks and delay discounting. *J. Am. Acad. Child Adolesc. Psychiatry* 52, 747–755. doi: 10.1016/j.jaac.2013.04.013

Stanger, C., Ryan, S. R., Fu, H., Landes, R. D., Jones, B. A., Bickel, W. K., et al. (2012). Delay discounting predicts adolescent substance abuse treatment outcome. *Exp. Clin. Psychopharmacol.* 20, 205–212. doi: 10.1037/a0026543

Stein, J. S., Wilson, A. G., Koffarnus, M. N., Daniel, T. O., Epstein, L. H., and Bickel, W. K. (2016). Unstuck in time: episodic future thinking reduces delay discounting and cigarette smoking. *Psychopharmacology* 233, 3771–3778. doi: 10.1007/s00213-016-4410-y

*Stoltman, J. J. K., Woodcock, E. A., Lister, J. J., Lundahl, L. H., and Greenwald, M. K. (2015). Heroin delay discounting: modulation by pharmacological state, drug-use impulsivity, and intelligence. *Exp. Clin. Psychopharmacol.* 23, 455–463. doi: 10.1037/pha0000054

Strickland, J. C., and Johnson, M. W. (2021). Rejecting impulsivity as a psychological construct: A theoretical, empirical, and sociocultural argument. *Psychol. Rev.* 128, 336–361. doi: 10.1037/rev0000263

Sweeney, A. M., and Culcea, I. (2017). Does a future-oriented temporal perspective related to body mass index, eating, and exercise? A meta-analysis. *Appetite* 112, 272–285. doi: 10.1016/j.appet.2017.02.006

Sweeny, M. M., Berry, M. S., Johnson, P. S., Herrmann, E. S., Meredith, S. E., and Johnson, M. W. (2020). Demographic and sexual risk predictors of delay discounting of condom-protected sex. *Psychol. Health* 35, 366–386, doi: 10.1080/08870446.2019.1631306

Thaler, R. H., and Shefrin, H. M. (1981). An economic theory of self-control. *J. Polit. Econ.* 89, 392–406. doi: 10.1086/260971

Tiffany, S. T., and Drobes, D. J. (1991). The development and initial validation of a questionnaire on smoking urges. *Br. J. Addict.* 86, 1467–1476. doi: 10.1111/j.1360-0443.1991.tb01732.x

Van den Bergh, B., Dewitte, S., and Warlop, L. (2008). Bikinis instigate generalized impatience in intertemporal choice. *J. Consum. Res.* 35, 85–97. doi: 10.1086/525505

Van den Bos, W., and McClure, S. M. (2012). Towards a general model of temporal discounting. *J. Exp. Anal. Behav.* 99, 58–73. doi: 10.1002/jeab.6

Wang, X. T., and Dvorak, R. D. (2010). Sweet future: fluctuating blood glucose levels affect future discounting. *Psychol. Sci.* 21, 183–188. doi: 10.1177/0956797609358096

Wang, X. T., and Huangfu, G. (2017). Glucose-specific signaling effects on delay discounting in intertemporal choice. *Physiol. Behav.* 169, 195–201. doi: 10.1016/j.physbeh.2016.12.001

Wesson, D. R., and Ling, W. (2003). The clinical opiate withdrawal scale (COWS). *J. Psychoact. Drugs* 35, 253–259. doi: 10.1080/02791072.2003.10400007

Wilson, M., and Daly, M. (2004). Do pretty women inspire men to discount the future? *R. Soc.* 271, 177–179. doi: 10.1098/rsbl.2003.0134

*Yi, R., and Landes, R. D. (2012). Temporal and probability discounting by cigarette smokers following acute smoking abstinence. *Nicotine Tobacco Res.* 14, 547–558. doi: 10.1093/ntr/ntr252

*Yoon, J. H., Higgins, S. T., Bradstreet, M. P., Badger, G. J., and Thomas, C. S. (2009). Changes in the relative reinforcing effects of cigarette smoking as a function of initial abstinence. *Psychopharmacology* 205, 305–318. doi: 10.1007/s00213-009-1541-4

Yoon, J. H., Higgins, S. T., Heil, S. H., Sugarbaker, R. J., Thomas, C. S., and Badger, G. J. (2007). Delay discounting predicts postpartum relapse to cigarette smoking among pregnant women. *Exp. Clin. Psychopharmacol.* 15, 176–186. doi: 10.1037/1064-1297.15.2.186

Zajac, I., Herreen, D., Hunkin, H., James-Martin, G., Doyen, M., Kakoschke, N., and Brindal, E. (2021). Modified fasting compared to true fasting improves blood glucose levels and subjective experiences of hunger, food cravings and mental fatigue, but not cognitive function: results of an acute randomised cross-over trial. *Nutrients* 13, 65–68. doi: 10.3390/nu13010065

*Denotes that we computed an effect size for that study.

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Behavioral Neuroscience

BRIEF RESEARCH REPORT
published: 16 February 2022
doi: 10.3389/fnbeh.2022.809963

Differential Probability Discounting Rates of Gamblers in an American Indian Population

*Tadd D. Schneider[1,2], Jordyn A. Gunville[3], Vlad B. Papa[4], Morgan G. Brucks[4], Christine M. Daley[3], Laura E. Martin[2,4] and David P. Jarmolowicz[1,2,5]**

[1] Department of Applied Behavioral Science, University of Kansas, Lawrence, KS, United States, [2] Cofrin Logan Center for Addiction Research and Treatment, University of Kansas, Lawrence, KS, United States, [3] Center for American Indian Community Health, University of Kansas Medical Center, Kansas City, KS, United States, [4] Hoglund Biomedical Imaging Center, University of Kansas Medical Center, Kansas City, KS, United States, [5] Healthcare Institute for Improvements in Quality, University of Missouri-Kansas City, Kansas City, MO, United States

Probability discounting, a subset of behavioral economic research, has a rich history of investigating choice behavior, especially as it pertains to risky decision making. Gambling involves both choice behavior and risky decision making which makes it an ideal behavior to investigate with discounting tasks. With proximity to a casino being one of the biggest risk factors, studies into the American Indian population have been a neglected population of study. Using outcome measures from a pre-scan probability discounting task, the current study equated the scan task to evaluate behavioral and neurobiological differences in gamblers vs. non-gamblers. Gamblers showed differences in behavioral tasks (lower discounting rates) but not in patterns of neural activation.

Keywords: probability discounting, gambling, American Indian, fMRI, behavioral economics

OPEN ACCESS

Edited by:
Gregory J. Madden, Utah State University, United States

Reviewed by:
Christopher Olsen, Medical College of Wisconsin, United States
Mikhail Koffarnus, University of Kentucky, United States

***Correspondence:**
David P. Jarmolowicz
DPJ@ku.edu

Specialty section:
This article was submitted to Motivation and Reward, a section of the journal Frontiers in Behavioral Neuroscience

Received: *05 November 2021*
Accepted: *10 January 2022*
Published: *16 February 2022*

Citation:
Schneider TD, Gunville JA, Papa VB, Brucks MG, Daley CM, Martin LE and Jarmolowicz DP (2022) Differential Probability Discounting Rates of Gamblers in an American Indian Population. Front. Behav. Neurosci. 16:809963. doi: 10.3389/fnbeh.2022.809963

INTRODUCTION

In the United States, more than 80% of adults engage in some form of gambling each year (Barnes et al., 2017). This pattern is particularly pervasive amongst American Indians (AI). For example, in the past year, 76.9% of white Americans engaged in gambling, whereas 80.1% of AI gambled (Barnes et al., 2017). The discrepancies become even more pronounced as we consider those that frequently gamble and/or engage in problem gambling. Specifically, 9.3% of white Americans engaged in frequent gambling, with 1.8% reaching pathological criteria. By contrast, 12.6% of AI's frequently gambled with 10.5% meeting pathological gambling criteria (Welte et al., 2001). Although gambling availability and types are constantly changing, high percentages of pathological gamblers (PG) engage in traditional casino games (22.5%), electronic gambling machines (18%), and numbers/lotto (5%; Binde et al., 2017).

One reason that PG risk may be elevated in AIs is that many live near casinos. Of the 562 AI tribes, The National Indian Gaming Commission estimates more than 240 tribes offer gambling activities at nearly 500 casinos (Ashton, 2002). Further, approximately half of AIs residing in the continental United States belong to tribes that operate a casino-style gaming operations on tribal lands (Evans and Topoleski, 2002). Of note, those who reside within 10 miles of a casino were twice as likely to have issues with problem gambling (Welte et al., 2004). In a study of 7th–12th grade AI children, approximately 75% had gambled in the last year (Peacock et al., 1999); much higher than the national average of 45–55% (Winters and Anderson, 2000; Stinchfield, 2011). Further, in a survey of public school students in Minnesota, 17.4% of the AI children reported daily/weekly gambling behavior, compared to 12.3% of the white children (Stinchfield et al., 1997).

Although there are economic benefits to allowing casinos on their lands, it also brings a potential for unintended problems that put this population at risk.

Gambling often entails wagering a small amount of money for the chance to win a larger sum of cash. In behavioral economics, these sorts of tradeoffs are analoged via probability discounting tasks. Probability discounting (PD) tasks have subjects choose between smaller but guaranteed sums of money and larger yet uncertain sums of money. For example, a subject may choose between $50 and 95% chance of receiving $100. The presented options are typically titrated until the value of the two alternatives are subjectively equivalent (e.g., a subject may find a 95% chance of receiving $70 is as appealing as receiving $50). These points of subjective equivalence—called indifference points—are typically collected across a range of probabilities. By using Rachlin et al.'s (1991) hyperboloid equation to fit a function through those indifference points, the rate (h) at which the subject value (V) of some amount (A) the uncertain reward declines as rewards become less probable (represented as increasing odds against ([θ = (1-p)/p]; Rachlin et al., 1991) can be calculated using:

$$V = A/(1 + h\theta^s) \quad (1)$$

In doing so, h represents the speed at which V declines as uncertainty increases, frequently called the PD rate (Green et al., 1999; Estle et al., 2006). In simpler terms, smaller h values demonstrate a willingness to take risks, whereas larger values reflect aversiveness to risk (Peters and Buchel, 2009). Gamblers, who are more prone to risky behaviors (Hewig et al., 2010), demonstrate more shallow discounting across probabilities than controls (Holt et al., 2003; Madden et al., 2009; Miedl et al., 2012). Additionally, PD rates have a negative correlation with scores on the South Oaks Gambling Screener (Holt et al., 2003; Madden et al., 2009). These relations, however, have not been widely investigated in AIs (cf. Weatherly et al., 2012)—despite their elevated risk of PG. Specifically, although Weatherly et al. (2012) examined PD in AI's the comparison between subjects suffering from GD and controls was not made.

Moreover, relatively little is known about the neurobiological processes driving PG. One approach to uncovering these important neuro-correlates is Functional Magnetic Resonance Imaging (fMRI). fMRI studies use Blood Oxygenation Level Dependence (BOLD) measures to evaluate changes in blood oxygenation levels during task involvement. Higher levels of activity require more oxygen, and therefore, require more blood flow for oxygenation. Measurements are collected while participants simultaneously complete a behavioral and/or neuropsychological tasks, such as simulated casino games (Miedl et al., 2010) or probability discounting (Peters and Buchel, 2009; Miedl et al., 2012).

Using probability discounting tasks in combination with fMRI, Peters and Buchel (2009) examined specific ROIs [ventral striatum (VS) and orbito-frontal cortex (OFC)] as participants completed discounting tasks. Using pre-scan indifference points from a probability discounting task, researchers equated the scan tasks so that each participant would make approximately 50% of choices for the smaller/certain and 50% for the larger/uncertain outcomes. This assured that there were enough trials wherein the subject chose each reward type (i.e., smaller certain, larger uncertain) to make valid comparisons. Significant results were seen in both the VS and OFC when subjects were coding for subjective value of the delayed or probabilistic rewards. Peters and Buchel (2009) noted that the VS and OFC are part of an integrated system that is activated when subjects are making decisions about rewards. Additionally, studies have found decreased activity in the VS and OFC when subjects were making decisions about delayed/probabilistic rewards during risky (low probability or long delay) reward trials (Miedl et al., 2012).

Studies examining the neuro-correlates of PD have added and will continue to add to our understanding of this behavioral process and its relation to PG. The extent which prior findings generalize to AIs—with their elevated risk of GD—remains unknown. The purpose of the current study was to examine PD and its neuro- correlates among AIs with and without PG—with the hope of extending the generality of prior findings.

MATERIALS AND METHODS

Participants

American Indians (ages of 18–65) were recruited by the Center for American Indian Community Health (CAICH). Participants were 24 AIs of differing tribes spanning the Midwest plains. Using DSM-V criteria 12 gamblers and 12 controls were recruited with mean ages of 39 for gamblers (SD = 19.05) and 36 for controls (SD = 11.51). During recruitment, care was taken to ensure participants' demographic characteristics were representative of the overall AI population. Participants were excluded from participation if they reported any condition contraindicating fMRI, current use of psychotropic medication, current or past abuse of illicit substances, diagnosis of severe neurological or psychiatric illness, inability to read and speak English fluently, left-handedness, or pregnancy. All participants were compensated $115 and a $20 gas card for their time in the study.

Procedures

Upon arriving at Hoglund Biomedical Imaging Center at Kansas University Medical Center, participants were escorted to a consultation room. The consultation room was 8′ × 12′ with a bank of windows along one wall. The other wall had a door and bookshelf. There was a round table with chairs in the middle of the room and a couch to the side. Written consent was obtained, then all other paperwork was completed, including demographics, payment form, and the MR safety screener. Participants then completed a PD task. Participants were then brought to a locker room and instructed to change into scrubs and remove any jewelry. Once changed into scrubs, participants were taken into the scanner. Participants requiring glasses were fitted with scanner compatible prescription goggles, and sight was checked by technician before their fMRI session.

Probability Discounting Task (Pre-scan)

Participants completed a probability discounting task conducted on an encrypted laptop computer. In this task, participants were told,

> *"Now, you'll be making decisions about some probability of receiving some amount of money. You'll see different probabilities of receiving amounts of money. Although you will not receive these amounts, pretend you will have the chance of receiving the amount and answer honestly. You can select between the two options by pressing the 1 and 2 buttons on this line of numbers. Press the 1 button for the option on the left and the 2-button for the option on the right."*

Participants then completed four rounds of PD decision making, one round at each of the probabilities (90, 70, 50, and 10%). Probabilities were presented in descending order and all trials were completed for each probability before moving on to the next. On the first trial, participants are presented with a choice between a smaller, yet certain outcome (100% chance of $50), vs. a larger, probabilistic outcome (probabilistic chance of $100). If the participant chose the larger, uncertain reward, the value of the smaller, certain reward increased by 50% of the previous titration value (initially $25), but if the participant chose the smaller, certain reward, the value of the smaller, certain reward was reduced by 50% of the previous titration value. After the sixth titration at each probability the value of the smaller, certain reward was the participant's indifference point. After completion of the task, research assistants retrieved the indifference points from the computer. These values were later entered into the task program in the scanner to equate the tasks for all participants.

Functional Magnetic Resonance Imaging Scan

Scanning was performed on a 3-Tesla full body Siemens Skyra scanner (Siemens, Erlangen, Germany) fitted with a 20-channel head and neck coil.

Scans collected included an anatomical scan and three functional probability discounting task runs. T1-weighted 3D MPRAGE anatomic images were obtained (TR/TE 2,300/2.95 ms, flip angle 9°, FOV = 256 mm, matrix = 240 × 256, slice thickness = 1.2 mm). These images provided slice localization for functional scans and co-registration with fMRI data. Gradient echo blood oxygen level dependent (BOLD) scans were acquired in 43 interleaved slices at a 40° angle to the AC/PC line (TR/TE = 2,500/25.0 ms, flip angle = 90, matrix = 80 × 80, slice thickness = 3 mm, in-plane resolution = 2.9 mm). The duration of each functional run varied based on individual participant reaction times.

Anatomical scans were acquired for participant positioning. Indifference points from the practice rounds were entered for each participant to equate the difficulty of the task across participants. The task adjusted the dollar amounts presented at each probability to offer the same number of choices above and below pre-scan indifference points to each participant. The function of equating the tasks across participants was to prevent markedly different patterns of choice to more easily investigate the processes that support choice, rather than the choices that were made.

Participants were given a control pad with two buttons, side-by-side, that correlated with the choices projected onto the screen. The MR tech made sure the screen was visible by the participant and any last-minute adjustments were made. Instructions were given by the research assistant about the PD trials. Instructions were verbally delivered as before:

> *"Now, you'll be making decisions about some probability of receiving some amount of money. You'll see different probabilities of receiving amounts of money. Although you will not receive these amounts, pretend you will have the chance of receiving the amount and answer honestly. You can select between the two options by pressing the left and right buttons on the controller. Press the left button for the option on the left and the right button for the option on the right."*

Once instructions were delivered, the program was loaded and automatically triggered by the start of the scanner. All stimuli (PD choices) were presented using E-Prime (Psychology Software Tools, Inc., Sharpsburg, PA) for the scan portion of the task. The same adjusting amount PD procedure was used from the pre-scan testing, however, for the scan task, percentages were displayed in a pseudorandomized order. The screen above the participant showed the two options (the certain and probabilistic outcomes) the participant was to choose from. Options were presented in black text on a white background, with the certain outcome being randomized between the right and left side of the screen for each trial. Participants are presented with a choice between a smaller, yet certain outcome (100% chance of $50), vs. a larger, probabilistic outcome (probabilistic chance of $100). If the participant chose the larger, uncertain reward, the value of the smaller, certain reward increased by 50% of the previous titration value, but if the participant chose the smaller, certain reward, the value of the smaller, certain reward was reduced by 50% of the previous titration value. Participants made 32 choices per round, for three total rounds (total of 96 choices), to determine an indifference point at each probability. Between trials the instructions were repeated by the MR tech and each trial ended with a fixation cross that turned from black to gray to signify the end of the round.

After completing the scans, participants were escorted to a small office (5′ × 7′) in which they completed additional questionnaires including timeline follow-back and SOGS questionnaire. Following completion of questionnaires, participants were escorted to the changing rooms to return to their street clothes. After changing, participants received their compensation and were thanked for their time.

ANALYSIS

Behavioral Analysis

Probability discounting data were screened for orderliness using the criteria outlined by Johnson and Bickel (2008). Specifically, participants' data were removed if an increase of more than 20% of the undiscounted amount was noted from one condition to

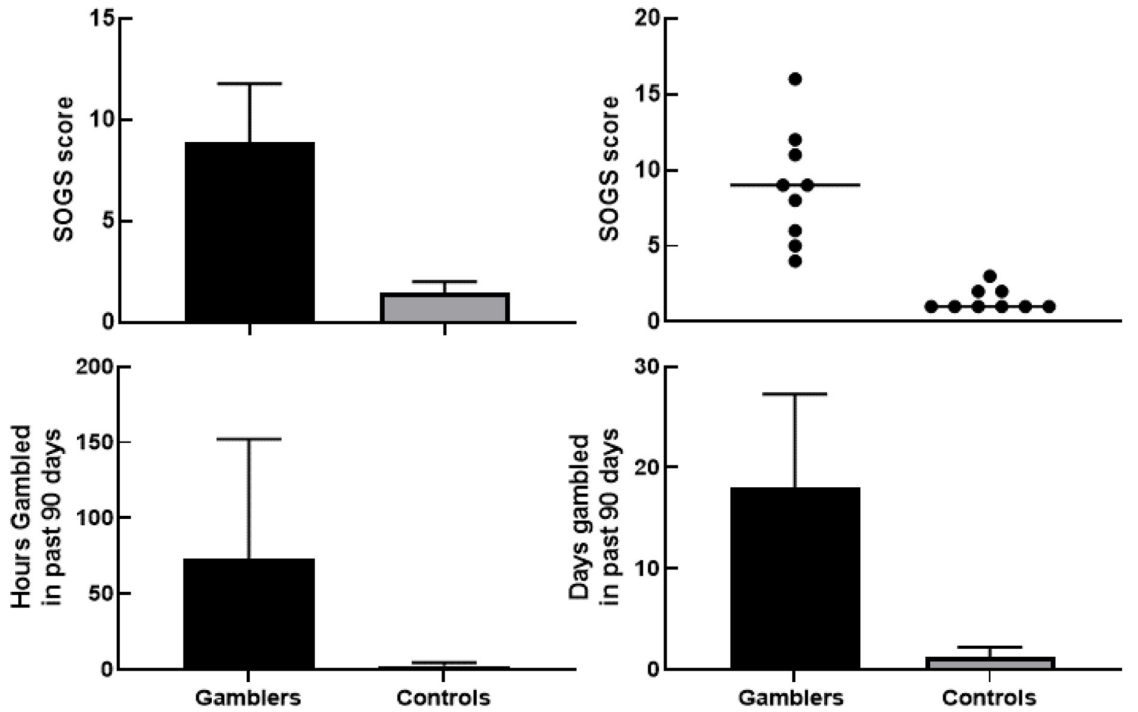


FIGURE 1 | Upper left panel shows group differences in South Oaks Gambling Screener between gamblers and controls with 95% confidence interval using an independent samples *t*-test with Welch's correction [$t(16) = 5.837$, $p < 0.001$]. **Upper right panel** shows scatterplot of individual South Oaks Gambling Screener values with the line representing median score per group. **Bottom left panel** shows group differences of number of hours gambled in the last 90 days with 95% confidence interval using a one-tailed independent samples *t*-test with Welch's correction [$t(8) = 2.034$, $p = 0.038$]. **Bottom right panel** shows group differences in number of days gambled in last 90 days with 95% confidence interval using a one-tailed independent samples *t*-test with Welch's correction [$t(8) = 4.142$, $p < 0.002$].

the next, starting with the second indifference point, or if the final condition indifference point was not less than the first by at least 10%. Applying these criteria to the participant pool, three Gamblers and three Controls were removed for analyses of behavioral components.

Probability Discounting analyses and curve fitting were performed in GraphPad Prism (version 8), specifically Equation 1 (Rachlin's Hyperboloid) was separately fit to the median indifference points for gamblers and controls using least squares regression. In doing so, the scaling parameter (s) was shared across groups, isolating the discounting rate (h) as the sole free parameter. Next, that shared scaling value (s) was input into the equation, and h values were calculated for each participant. These h values were used to examine correlations (Spearman) between discounting rates and SOGS scores. Additionally, PD rates were calculated using the AUC analysis. AUC is calculated using the trapezoid method that calculates the aggregate data (area) under the data path (curve) (Myerson et al., 2001). AUC provided a measure suitable for use with the parametric statistics used to examine between group differences in discounting rate.

Functional Magnetic Resonance Imaging Analysis

All imaging data was collected and managed using RedCap electronic data capture tools hosted at University of Kansas Medical Center (Harris et al., 2009, 2019) for data quality checks. The quality of the fMRI data was checked for processing errors, alignment, and motion issues. Four subjects (two gambler and two control) were removed from imaging analysis due to not completing scans and two gamblers were removed due to excessive motion (i.e., > 50% censoring).

Data preprocessing and statistical analyses for imaging data were performed in AFNI (Cox, 1996). Preprocessing steps included motion correction, alignment, spatial smoothing and normalization. The fMRI images were realigned to the minimum outlier in each run to correct for motion. The images were spatially smoothed to 4 mm FWHM Gaussian kernel. Anatomic images were aligned to functional images and spatially normalized to Montreal Neurological Institute space using non-linear warping implemented with AFNI's automated algorithm. Within each functional run were registered to the minimum outlier. Data points were censored if motion within a volume was greater than 0.3 mm. Statistical contrasts were conducted using multiple regression analysis with motion parameters included as nuisance regressors. Regressors representing the experimental conditions of interest (i.e., High, Mid, and Low Probability) were entered into the regression analysis using a duration modulated basis function. Timing files were created in Microsoft Excel to identify the beginning and end of each individual trial. Trials were separated into three groups (High, Mid and Low Probability). High probability trials consisted

of the 90% probabilities, Mid probability trials consisted of the 70 and 50% probabilities, and the Low probability trials were set for the 10% probabilities. The quality of the fMRI data was checked for processing errors, alignment, and motion issues.

The data analysis focused on a whole-brain voxel-wise analysis of variance (ANOVA) implemented by AFNI's 3 dMVM (Chen et al., 2014) to determine brain activation (i.e., percent signal change from baseline) main effects and interactions [Probability (Low, Mid, Hight) × Group (Gambler, Control). AFNI's 3 dClustSim was used to estimate the probability of false positives and correct for multiple comparisons at $p < 0.005$ and $\alpha < 0.05$.

RESULTS

Figure 1 (top) shows South Oaks Gambling Scale scores for gamblers (range 4–16; $M = 8.88$. $SD = 3.76$) and controls (range 1–3; $M = 1.44$, $SD = 0.73$), with a significant difference between groups using an independent samples t-test [$t(16) = 5.837$, $p < 0.001$]. **Figure 1** (bottom) shows participants' histories of gambling involvement (hours and days). Results of previous studies have reported variance of gambling behaviors being unidirectional (gamblers). Our analytical hypothesis, therefore, was past gambling behavior variance would occur in one direction (gamblers). Using a one-tailed independent samples t-test with Welch's correction resulted in a statistically significant [$t(8) = 2.034$, $p = 0.038$] difference in the number of hours gambled (**Figure 1**—bottom left) over the last 90 days between Gamblers ($M = 65.73$, $SD = 94.02$) and Controls ($M = 2.00$, $SD = 2.68$). Using the same analysis on self-reported days gambled in the last 90 days (**Figure 1**—bottom right) shows a statistically significant difference [$t(8) = 4.142$, $p < 0.002$] in the number of days gambled amongst Gamblers ($M = 17.91$, $SD = 11.09$) than Controls ($M = 1.00$, $SD = 1.26$).

Figure 2 (top) shows the probability discounting curves fit to the median indifference points for PG (circles) and controls (squares) using Rachlin et al.'s (1991) hyperboloid discounting equation (Equation 1). This equation allows for two free parameters (discounting rate, h, and psychosocial scaling of delay, s) during analysis. To control for this, the scaling parameter (s) was held constant (i.e., shared) across all participants ($s = 0.8165$). Analysis showed an excellent fit for gamblers ($R^2 = 0.9955$) and controls ($R^2 = 0.9703$) to the group median. Additionally, discounting rates demonstrated a much more-shallow discounting rate by the gamblers ($h = 0.6038$) compared to controls ($h = 2.134$). When fitting Equation 1 to individual subjects' data the group mean fit was fair for PG ($R^2 = 0.8642$) and controls ($R^2 = 0.8926$), with the mean log-transformed discounting rate (LN[h]) significantly differing between groups. As a confirmatory step, this analysis was also conducted using Area under the Curve. Area Under the Curve measures of indifference points were lower for Gamblers ($M = 0.427$, $SD = 0.212$) than Controls ($M = 0.672$, $SD = 0.057$). An unpaired t-test comparing AUC showed a statistically significant group difference [$t(20) = -3.714$, $p \leq 0.001$]. **Figure 2** (bottom) shows Spearman correlations between SOGS scores to discounting rates. Using a Spearman correlation analysis, results showed a significant negative correlation $r(18) = -0.617$, $p = 0.006$.

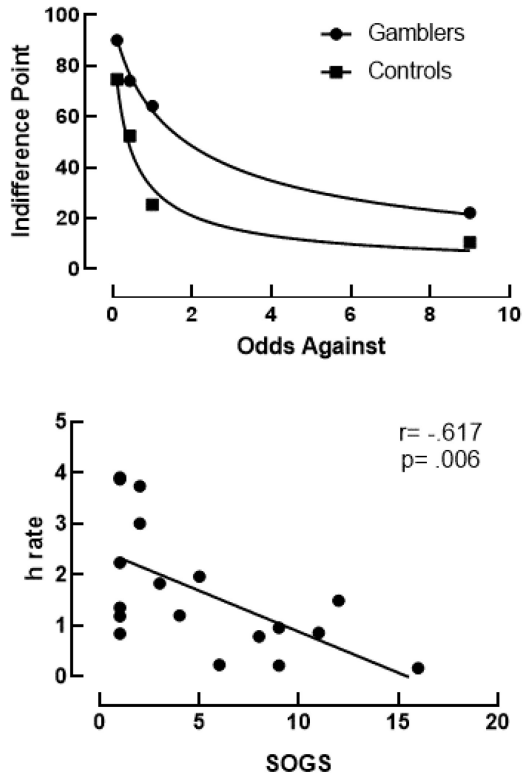


FIGURE 2 | Top panel shows probability discounting curves using Rachlin's Hyperboloid equation for gamblers ($R^2 = 0.9955$) and controls ($R^2 = 0.9703$). **Bottom panel** shows results of a Spearman correlation between discounting rates (h) on the y-axis and SOGS scores on the x-axis. The trendline shows a negative correlation of $r(18) = -0.617$, $p = 0.006$.

Whole brain analysis found no significant ($p > 0.05$) Group × Condition interaction or main effect of Group. A main effect of probability condition (**Figure 3**) was found in decision-making regions of the dorsal medial prefrontal cortex (dmPFC; x, y, z = -2, 44, 33, $p < 0.005$, corrected) and attention regions of the precuneus (x, y, z = -5, -69, 58), $p < 0.005$, corrected) demonstrating greater activation in low compared to high probability conditions.

DISCUSSION

Consistent with prior reports (Holt et al., 2003; Madden et al., 2009; Miedl et al., 2012) probability discounting rates were lower in PG relative to controls. Also consistent with prior studies, SOGS scores were negatively correlated with discounting rates (Holt et al., 2003; Madden et al., 2009). Also consistent with prior studies (Miedl et al., 2012), we did not obtain differences in task-related neural activation while PG and controls completed the PD task. There are four additional points we would like to make about these data.

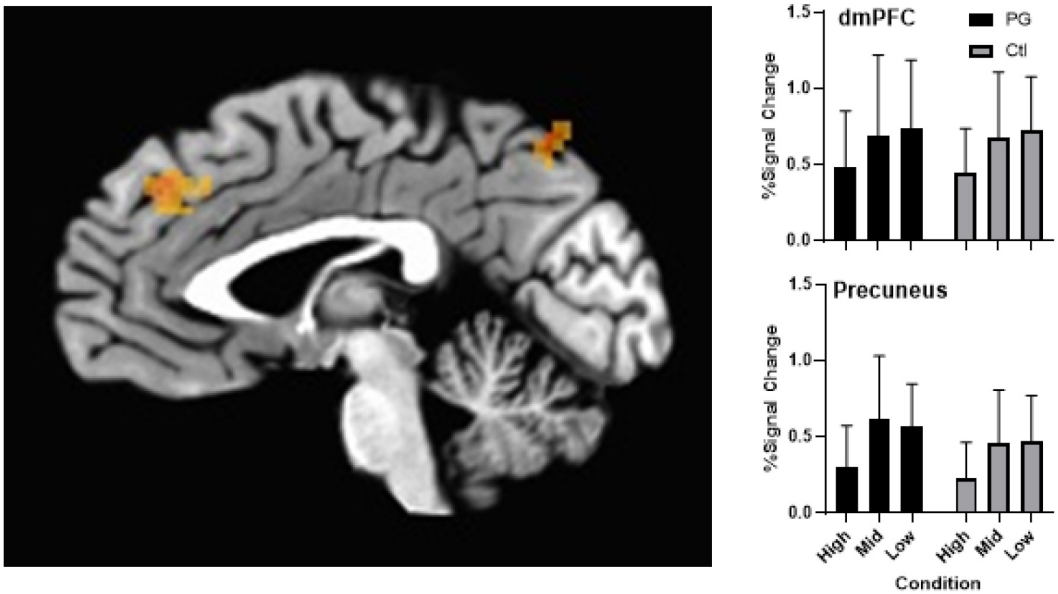


FIGURE 3 | Left panel shows activation differences in the dmPFC and precuneus as an effect of condition (probability) of the probability discounting task during fMRI scan. **Upper right panel** shows group differences across probabilities in the dmPFC with a main effect of condition (error bars represent mean and SD). Controlling for multiple comparisons, results were significant at $p < 0.005$. **Bottom right panel** shows group differences across probabilities in the precuneus with a main effect of condition (error bars represent mean and SD). Controlling for multiple comparisons, results were significant at $p < 0.005$.

First, despite the limited sample size, the between-group differences in probability discounting rate were robust. While this modest sample size is a limitation, the consistency of this finding with findings from prior studies (Holt et al., 2003; Madden et al., 2009) suggests that we were not capturing a spurious relation. As a systematic replication (Sidman, 1960) of prior studies in this novel and relevant population, the current findings strengthen our understanding of the relation between PD and GD. In light of prior findings, the current findings suggest probability discounting rates may be a behavioral process undergirding the risk taking seen in problem gambling. This possibility is strengthened by the replication of the negative relation between SOGS scores and PD seen in prior studies (Holt et al., 2003; Madden et al., 2009).

Second, the current study failed to find group-based differences in task-related neural activation when PG and controls completed the probability discounting task. This is consistent with prior studies (Peters and Buchel, 2009; Miedl et al., 2012), but may be based on the sample size providing insufficient power to demonstrate significant relations once corrected for multiple comparisons. Similar neurobiological profiles associated with differing behavioral profiles, however, is not unprecedented. Ersche et al. (2012), for example, found that siblings of individuals suffering from stimulant-dependence had the same underlying neural abnormalities—despite their abstaining from stimulant use. Future studies with a larger sample size are needed to determine if the between group consistency was due to low power or similar neural processing between groups.

Third, while the sample size may have been insufficient to reveal neurobiological differences between groups, it was sensitive to task related differences. Specifically, we found differences between condition activation in the dmPFC and precuneus. Previous studies have found elevated activation of the dmPFC during complex decision-making tasks (Paulus et al., 2002; Pochon et al., 2008; Venkatraman et al., 2009)—consistent with the complexity of making judgements regarding probabilities during the current task. These neural response patterns, however, differ slightly from Abidi et al. (2018) who found elevated activation in the OFC and VS during severe side effect conditions and Miedl et al. (2012) who found a trend toward less pronounced activation in the OFC and VS in gamblers compared to controls during a PD task. Specifically, results showed neural values were attenuated for gamblers during PD tasks (Miedl et al., 2012). Although inconsistent, these results contribute to our overall understanding of the neural correlates of this understudied behavioral process. Additional work is needed to determine the reasons for these discrepancies.

Finally, there were limitations to the study that can be addressed in future research. The first limitation is the small group sizes and large amounts of variability within and between groups that reduced statistical power needed to identify some group level differences. The next limitation is that indifference points from the pre-scan task were entered into the scan computer to equate the task. By equating the tasks, it could be preventing some differences from being identified. It does, however, functionally equate the tasks which reduce differences in task difficulty and differential responding. Equating the tasks sets the expected outcomes equal across groups. This means that observed regional differences are reflective of neurological differences and not tied to task difficulty.

For future studies, neurobiological differences could be investigated as to differences in non-task dependent, resting state activity, outside and inside a gambling environment. Those differences could then be compared to neural activity while gambling in a real-world gambling environment. Additionally, behaviors specific to the gambling environment, such as betting, collecting their winnings or watching their losses being removed could highlight some subtleties that are easily lost in translation to a research study. Further, auditory stimuli need to be investigated to study the impact on neural activity underlying behavioral processes during decision making.

In summary, this study replicated previous findings of PG using PD tasks in an fMRI study, but also highlighted new findings that need to be further investigated. Additionally, these differences need to be evaluated in a larger cohort to gain the necessary statistical power to evaluate some subtleties noted in regional activation differences. Further research is needed to replicate and extend these findings to treatments that may target the mediation of the risky outcome with the reward drive.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the University of Kansas Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TS contributed to the study's design, conduct, analysis of data, and writing of the final report. JG, VP, and MB contributed substantially to the conduct of the experiment. CD contributed to the design of the experiment and conduct of the experiment. LM contributed to the design of the study, its conduct, data analysis, and writing of the final report. DJ contributed to the conceptualization and design of the study, its conduct, data analysis, and writing of the final report. All authors contributed to the article and approved the submitted version.

FUNDING

Funding was provided by the Institute for General Medical Sciences (1ULTR002366).

ACKNOWLEDGMENTS

We would like to thank Derek Reed for his comments during study design and Shea Lemley for her help in developing this study. We would also like to thank the Center for American Indian Community Health for help with recruiting.

REFERENCES

Abidi, M., Bruce, J., Le Blanche, A., Bruce, A., Jarmolowicz, D. P., Csillik, A., et al. (2018). Neural mechanisms associated with treatment decision making: an fMRI study. *Behav. Brain Res.* 349, 54–62. doi: 10.1016/j.bbr.2018.04.034

Ashton, S. J. (2002). The role of the national indian gaming commission in the regulation of tribal gaming symposium: the role of jurisdiction in the quest for sovereignty. *New Eng. Law Rev.* 3, 545–552.

Barnes, G. M., Welte, J. W., and Tidwell, M.-C. O. (2017). Gambling involvement among native americans, blacks, and whites in the united states. *Am. J. Addict.* 26, 713–721. doi: 10.1111/ajad.12601

Binde, P., Romild, U., and Volberg, R. A. (2017). Forms of gambling, gambling involvement and problem gambling: evidence from a Swedish population survey. *Int. Gambling Stud.* 17, 490–507. doi: 10.1080/14459795.2017.1360928

Chen, G., Adleman, N. E., Saad, Z. S., Leibenluft, E., and Cox, R. W. (2014). Applications of multivariate modeling to neuroimaging group analysis: a comprehensive alternative to univariate general linear model. *NeuroImage* 99, 571–588. doi: 10.1016/j.neuroimage.2014.06.027

Cox, R. W. (1996). AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Comput. Biomed. Res.* 29, 162–173.

Ersche, K. D., Jones, P. S., Williams, G. B., Turton, A. J., Robbins, T. W., and Bullmore, E. T. (2012). Abnormal brain structure implicated in stimulant drug addiction. *Science* 335, 601–604. doi: 10.1126/science.1214463

Estle, S. J., Green, L., Myerson, J., and Holt, D. D. (2006). Differential effects of amount on temporal and probability discounting of gains and losses. *Memory Cogn.* 34, 914–928. doi: 10.3758/bf03193437

Evans, W. N., and Topoleski, J. H. (2002). *The Social and Economic Impact of Native American Casinos*. Cambridge, MA: National Bureau of Economic Research.

Green, L., Myerson, J., and Ostaszewski, P. (1999). Amount of reward has opposite effects on the discounting of delayed and probabilistic outcomes. *Exp. Psychol. Learn. Memory Cogn.* 25, 418–427. doi: 10.1037//0278-7393.25.2.418

Harris, P. A., Taylor, R., Minor, B. L., Elliott, V., Fernandez, M., O'Neal, L., et al. (2019). The REDCap consortium: building an international community of software platform partners. *J. Biomed. Inform.* 95:103208. doi: 10.1016/j.jbi.2019.103208

Harris, P. A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., and Conde, J. G. (2009). A metadata-driven methodology and workflow process for providing translational research informatics support. *J. Biomed. Inform.* 42, 377–381. doi: 10.1016/j.jbi.2008.08.010

Hewig, J., Kretschmer, N., Trippe, R. H., Hecht, H., Coles, M. G. H., Holroyd, C. B., et al. (2010). Hypersensitivity to reward in problem gamblers. *Biol. Psychiatry* 67, 781–783. doi: 10.1016/j.biopsych.2009.11.009

Holt, D. D., Green, L., and Myerson, J. (2003). Is discounting impulsive? Evidence from temporal and probability discounting in gambling and non-gambling college students. *Behav. Proc.* 64, 355–367. doi: 10.1016/S0376-6357(03)00141-4

Johnson, M. W., and Bickel, W. K. (2008). An algorithm for identifying nonsystematic delay-discounting data. *Exp. Clin. Psychopharmacol.* 16, 264–274. doi: 10.1037/1064-1297.16.3.264

Madden, G. J., Petry, N. M., and Johnson, P. S. (2009). Pathological gamblers discount probabilistic rewards less steeply than matched controls. *Exp. Clin. Psychopharmacol.* 17, 283–290. doi: 10.1037/a0016806

Miedl, S. F., Fehr, T., Meyer, G., and Herrmann, M. (2010). Neurobiological correlates of problem gambling in a quasi-realistic blackjack scenario as revealed by fMRI. *Psychiatry Res. Neuroimaging* 181, 165–173. doi: 10.1016/j.pscychresns.2009.11.008

Miedl, S. F., Peters, J., and Buchel, C. (2012). Altered neural reward representations in pathological gamblers revealed by delay and probability discounting. *Arch. General Psychiatry* 69, 177–186. doi: 10.1001/archgenpsychiatry.2011.1552

Myerson, J., Green, L., and Warusawitharana, M. (2001). Area under the curve as a measure of discounting. *J. Exp. Anal. Behav.* 76, 235–243. doi: 10.1901/jeab.2001.76-235

Paulus, M. P., Hozack, N., Frank, L., and Brown, G. G. (2002). Error rate and outcome predictability affect neural activation in prefrontal cortex and anterior cingulate during decision-making. *NeuroImage* 15, 836–846.

Peacock, T. D., Day, P. A., and Peacock, R. B. (1999). At what cost? The social impact of american indian gaming. *J. Health Soc. Policy* 10, 23–34. doi: 10.1300/J045v10n04_02

Peters, J., and Buchel, C. (2009). Overlapping and distinct neural systems code for subjective value during intertemporal and risky decision making. *J. Neurosci.* 29, 15727–15734. doi: 10.1523/JNEUROSCI.3489-09.2009

Pochon, J.-B., Riis, J., Sanfey, A. G., Nystrom, L. E., and Cohen, J. D. (2008). Functional imaging of decision conflict. *J. Neurosci.* 28, 3468–3473. doi: 10.1523/jneurosci.4195-07.2008

Rachlin, H., Raineri, A., and Cross, D. (1991). Subjective probability and delay. *J. Exp. Anal. Behav.* 55, 233–244. doi: 10.1901/jeab.1991.55-233

Sidman, M. (1960). *Tactics of Scientific Research: Evaluating Experimental Data in Psychology*. New York: Basic Books, Inc.

Stinchfield, R. (2011). Gambling among minnesota public school students from 1992-2007: declines in youth gambling. *Psychol. Addict. Behav.* 25, 108–117. doi: 10.1037/a0021266

Stinchfield, R., Cassuto, N., Winters, K., and Latimer, W. (1997). Prevalence of gambling among minnesota public school students in 1992 and 1995. *J. Gambling Stud.* 13, 25–48. doi: 10.1023/a:1024987131943

Venkatraman, V., Rosati, A. G., Taren, A. A., and Huettel, S. A. (2009). Resolving response, decision, and strategic control: evidence for a functional topography in dorsomedial prefrontal cortex. *J. Neurosci.* 29, 13158–13164. doi: 10.1523/JNEUROSCI.2708-09.2009

Weatherly, J. N., McDonald, J. D., and Derenne, A. (2012). Probability discounting in a sample of american indians: gambling as an escape predicts discounting of monetary, but not non-monetary, outcomes. *Anal. Gambling Behav.* 6, 37–45.

Welte, J., Barnes, G., Wieczorek, W., Tidwell, M.-C., and Parker, J. (2001). Alcohol and gambling pathology among US adults: prevalence, demographic patterns and comorbidity. *J. Stud. Alcohol* 62, 706–712. doi: 10.15288/jsa.2001.62.706

Welte, J. W., Wieczorek, W. F., Barnes, G. M., Tidwell, M.-C., and Hoffman, J. H. (2004). The relationship of ecological and geographic factors to gambling behavior and pathology. *J. Gambling Stud.* 20, 405–423. doi: 10.1007/s10899-004-4582-y

Winters, K. C., and Anderson, N. (2000). Gambling involvement and drug use among adolescents. *J. Gambling Stud.* 16, 175–198. doi: 10.1023/a:1009480930810

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Behavioral Neuroscience

ORIGINAL RESEARCH
published: 25 April 2022
doi: 10.3389/fnbeh.2022.837654

Large-N Rat Data Enables Phenotyping of Risky Decision-Making: A Retrospective Analysis of Brain Injury on the Rodent Gambling Task

Cole Vonder Haar[1,2], Michelle A. Frankot[1], A. Matthew Reck[1], Virginia Milleson[1] and Kris M. Martens[1,2]*

[1] Department of Psychology, West Virginia University, Morgantown, WV, United States, [2] Department of Neuroscience, Ohio State University, Columbus, OH, United States

Decision-making is substantially altered after brain injuries. Patients and rats with brain injury are more likely to make suboptimal, and sometimes risky choices. Such changes in decision-making may arise from alterations in how sensitive individuals are to outcomes. To assess this, we compiled and harmonized a large dataset from four studies of TBI, each of which evaluated behavior on the Rodent Gambling Task (RGT). We then determined whether the following were altered: (1) sensitivity to overall contingencies, (2) sensitivity to immediate outcomes, or (3) general choice phenotypes. Overall sensitivity was evaluated using the matching law, immediate sensitivity by looking at the probability of switching choices given a win or loss, and choice phenotypes by k-means clustering. We found significant reductions in sensitivity to the overall outcomes and a bias toward riskier alternatives in TBI rats. However, the substantial individual variability led to poor overall fits in matching analyses. We also found that TBI caused a significant reduction in the tendency to repeatedly choose a given option, but no difference in win- or loss-specific sensitivity. Finally, clustering revealed 5 distinct decision-making phenotypes and TBI reduced membership in the "optimal" type. The current findings support a hypothesis that TBI reduces sensitivity to contingencies. However, in the case of tasks such as the RGT, this is not a simple shift to indiscriminate or less discriminate responding. Rather, TBI rats are more likely to develop suboptimal preferences and frequently switch choices. Treatments will have to consider how this behavior might be corrected.

Keywords: Iowa Gambling Task (IGT), impulsivity, controlled cortical impact (CCI), statistical approaches, rat

OPEN ACCESS

Edited by:
Gregory J. Madden,
Utah State University, United States

Reviewed by:
Shane Alan Perrine,
Wayne State University, United States
Patrick Johnson,
California State University, Chico, United States

****Correspondence:***
Cole Vonder Haar
Cole.VonderHaar@osumc.edu

Specialty section:
This article was submitted to Motivation and Reward, a section of the journal Frontiers in Behavioral Neuroscience

Received: *16 December 2021*
Accepted: *18 March 2022*
Published: *25 April 2022*

Citation:
Vonder Haar C, Frankot MA, Reck AM, Milleson V and Martens KM (2022) Large-N Rat Data Enables Phenotyping of Risky Decision-Making: A Retrospective Analysis of Brain Injury on the Rodent Gambling Task. Front. Behav. Neurosci. 16:837654. doi: 10.3389/fnbeh.2022.837654

INTRODUCTION

Traumatic brain injury (TBI) affects 2.8 million Americans every year and is associated with impairments in decision-making (Bhalerao et al., 2013; Zgaljardic et al., 2015). Though these psychiatric-like symptoms are well-cataloged in this population, the underlying behavioral and neurological mechanisms are not clear. A better understanding of the behaviors that lead to

these symptoms may yield effective rehabilitative strategies which could readily be implemented. Moreover, study of this population may lead to additional insights regarding the fundamentals of behavior. Patients with TBI display altered performance of numerous neuropsychological assessments related to decision-making, however, as described below, findings are not necessarily in line with a simple hypothesis of "injury increases risk taking." Shifts in behavior such as reduced sensitivity to outcomes or reduced learning rates may also be sufficient to explain such findings.

In the Iowa Gambling Task (IGT), which evaluates preference for safe vs. risky alternatives as people interact with the choices, patients with TBI make increased risky decisions (Sigurdardottir et al., 2010; Cotrena et al., 2014; Visser-Keizer et al., 2016). On the Game of Dice Task, which explicitly presents probabilities in the form of dice, patients with TBI made significantly fewer advantageous (safer) choices (Rzezak et al., 2012). However, in the Balloon Analog Risk Task, which presents a visual representation of risk/reward in the form of a virtual "balloon" that participants "inflate" to earn points, patients with TBI demonstrate no differences (in adolescents, Chiu et al., 2012), or even risk aversion (in adults, Fecteau et al., 2013). While the IGT is the most widely used of these tasks, a large confound is that outcomes must be learned over time through interaction. However, this also likely yields the best translational value as explicit consequences of an action are rarely specified in real life at the time of a decision. In contrast, the Game of Dice Task gives indicators of probability, but some level of math equivalency must be carried out (e.g., 4/6 numbers on a die = 0.67 probability for $100, weighed by cost of bet). Finally, the Balloon Analog Risk Task likely provides the simplest representation of risk in the form of a (virtual) balloon which inflates to a point of popping. However, even with this task, some level of learning is required to determine the elasticity of the balloon and maximize gains. In the case of the Fecteau study, the "risk aversion" observed in patients with TBI was largely due to a lack of adaptation. This suggests more general deficits of learning over time as opposed to a fundamental change in preferences regarding risk.

While TBI clearly alters decision-making, given the somewhat discrepant findings and the nature of the assessments, it is difficult to conclude that injury explicitly increases risky decision-making. Instead, insensitivity to outcomes (e.g., a winning or losing trial) or reduced learning from those outcomes over time may also account for these same symptoms. Indeed, earlier work explicitly tested this in patients with TBI and found that they had difficulty discriminating outcomes and adjusting their own actions based on those outcomes (Schlund and Pace, 2000; Schlund, 2002). To evaluate these findings with greater control, animal models may be used. With the appropriate motivation, animals can be trained on an array of behaviors similar to the human condition. In a rat model of TBI, we have reported findings strikingly similar to the human condition. Rats with either a frontal or unilateral TBI demonstrated reduced optimal decision-making on an analog of the IGT, the Rodent Gambling Task (RGT) (Shaver et al., 2019; Ozga-Hess et al., 2020), in which rats can make safe or risky choices by nosepoking in different holes in an operant chamber. Moreover, they distributed their choices to both a less risky (but suboptimal) choice, and riskier choices. This suggests a more indiscriminate style of decision-making as opposed to a pure increase in riskiness. Indeed, in studies of simple discrimination after TBI in rats, impairments are substantial (Martens et al., 2012; Vonder Haar et al., 2014; Muelbl et al., 2018). However, while these deficits resolve, more complex decision-making tasks such as the RGT may present less explicit feedback than discrimination tasks and present a much greater challenge to detection of contingencies.

A large drawback to the existing studies described above are the relatively small samples sizes. With heterogenous behaviors such as decision-making, individual differences may make it difficult to determine whether patients or animals are truly more risk-preferring or if there have merely been reductions in sensitivity to outcomes. The use of larger scale, harmonized datasets may provide an opportunity to gain insight and evaluate different potential explanations for changes in choice behavior. In the field of behavioral science, two theoretical approaches are commonly used to describe many types of decision-making. The molar viewpoint takes the perspective that behavior is sensitive to the overall rates of reinforcement amongst alternatives (Baum, 1989). In contrast, the molecular viewpoint suggests that immediate outcomes drive subsequent decisions (Shimp, 2020). Indeed, experimental setups can be designed which provide evidence for both, but some combination of the two are likely at work for everyday behaviors. The molar view is epitomized by the Matching Law, a mathematical description that relative rates of behavior closely match relative rates of reinforcement (Baum, 1974). The strongest evidence for this comes from data collected at a steady state, after the contingencies have been learned, using experimental setups in which effort is independent of time spent on an alternative (i.e., interval schedules as opposed to ratio schedules) (Rider, 1981). The strongest evidence for molecular viewpoints comes from tasks in which change occurs rapidly or frequently and behavior must be adapted to new contingencies (Dalton et al., 2014). Because changes to either molar or molecular sensitivities after TBI could drive changes to decision-making, both must be evaluated. Moreover, if neither are sufficient to describe behavior at the group and/or subject level, atheoretical statistical data reduction techniques may provide insight into these changes underlying changes to decision-making.

In the current set of analyses, we used a dataset collected across four studies to evaluate molar (overall contingencies), molecular (immediate contingencies), and atheoretical accounts (purely descriptive) of behavior. This large dataset was able to power analyses which would have been impossible with data from any single one of these studies. The RGT captures decisions across four distinct alternatives, each associated with a different probability and magnitude of reinforcement (sucrose pellets) and punishment (time out from reinforcement). Because choices are mutually exclusive and probabilistic, decisions should collapse into exclusive preference of the most optimal option. However, this is rarely observed at a subject level, and never at the population level. Thus, there is rationale to evaluate if behavior is allocated according to relative rates of reinforcement (i.e., matching: molar sensitivity) or if there are high sensitivities to

immediate outcomes (i.e., shifting behavior based on a "win" or "loss": molecular sensitivity). TBI causes changes to decision-making behavior on this task (Shaver et al., 2019; Ozga-Hess et al., 2020) and may disrupt sensitivity to either molar or molecular outcome dynamics. In the current study, we aimed to compare molar, molecular, and atheoretical accounts of RGT choice behavior.

MATERIALS AND METHODS

The Dataset: Rodent Gambling Task Performance in a Large Cohort of Traumatic Brain Injury and Sham Rats

The dataset analyzed in the current study was compiled from four separate experiments (**Table 1**). Common methods are described below in brief. All rats performed the Rodent Gambling Task, a measure of probabilistic decision-making and motor impulsivity. The first study assessed the effects of a bilateral frontal TBI delivered either before ("acquisition" condition), or after ("trained" condition), learning the RGT (Shaver et al., 2019). The second assessed the effects of a unilateral TBI on acquisition of RGT learning (Ozga-Hess et al., 2020). The remaining two are in preparation for publication, but both used bilateral frontal TBI. One assessed the effects of a dietary manipulation before injury (RGT trained pre-injury), and the other a drug treatment after injury (RGT tested in acquisition). For these two studies, the control conditions of sham surgery or TBI surgery (no additional treatment/manipulation) were isolated for the current analysis. For all experiments, stable performance was evaluated (i.e., sessions ≥ 15 for pre-injury and sessions > 10 for post-surgery) to mitigate learning effects in acquisition experiments. Thus, the sessions selected represent approximately weeks 4–8 post-injury. To maximize control numbers, both pre-TBI and post-surgery sham data were pooled for any Sham-only analyses (e.g., single-subject plots). This resulted in 80 Sham animals, and 51 TBI animals with an average of 17 sessions each. Analyses comparing Sham and TBI performance were carried out using only post-injury data (Sham = 58, TBI = 51). Three types of analysis (representing molar, molecular, and atheoretical perspectives) were evaluated on this dataset to better understand (1) normal probabilistic decision-making, and (2) how this was disrupted by brain injury.

Subjects

Subjects were 109 male Long-Evans rats, between 3 and 5 months of age at time of injury. Rats were either pair-housed in standard cages (Allentown, Allentown NJ) or triple-housed in larger, pentagonal cages (Animal Care Systems, Centennial CO) prior to injury and single-housed after injury. Rats were restricted to 12–14 g of chow daily plus pellets earned during the task. Water was available *ad libitum*.

Apparatus

Behavioral testing was conducted in a set of 16 standard 5-choice operant chambers (Med Associates, St Albans, VT). Each was enclosed in a sound-attenuating box, and white noise played in the room. The right side was equipped with a food hopper and light. The left wall of the chamber was equipped with a 5-hole array in which rats' nosepokes were recorded. The chamber was also equipped with a houselight.

The Rodent Gambling Task

Rats were trained as previously reported on the RGT (Zeeb and Winstanley, 2013; Shaver et al., 2019; Ozga-Hess et al., 2020). In brief, nosepoking behavior was shaped by reinforcing pokes to an illuminated hole. The stimulus duration was gradually decreased until rats responded within 10 s and responses made prior to illumination were recorded as "premature" and punished with a timeout. Rats then began "forced-choice" RGT training in which only one option was available, but the RGT contingencies were in effect. Following 7 sessions of forced choice, rats were tested on the free-choice RGT.

The choice contingencies on the RGT are designed such that four options are available, named for the number of pellets they deliver: P1 (90% 1 pellet; 10% 5-s timeout), P2 (80% 2 pellets; 20% 10-s timeout), P3 (60% 3 pellets; 40% 30-s timeout), and P4 (40% 4 pellets; 60% 40-s timeout). The P2 option is optimal (13.71 pellets/min), the P1 suboptimal, but low risk (9.81 pellets/min), while the P3 (4.5 pellets/min) and P4 (3.31 pellets/min; least advantageous outcome) are high risk but with large magnitudes.

Multiple other variables were collected on the RGT, including the number of premature/impulsive responses, omitted trials, total trials, total reinforcers, response latency, collection latency, and perseverative pokes to the 5-choice array.

Traumatic Brain Injury: Controlled Cortical Impact

A controlled cortical impact procedure was used to administer moderate-severe, focal TBI (Hoffman et al., 1994). Rats were anesthetized with isoflurane (5% induction, 2–4% maintenance) in 0.5 L/min oxygen. Then rats were placed into a stereotaxic frame and administered a local analgesic (Bupivacaine; 0.25%, s.c.) at the incision site and a subcutaneous general analgesic (ketoprofen; 5 mg/kg, s.c.). Then, the surgical site was sanitized, and rats were given a midline incision. A craniectomy was performed above the injury location and a controlled cortical impact delivered (bilateral frontal: + 3 mm/ + 0 mm/−2.5 mm @ 3 m/s; unilateral parietal: −2.4 mm/ + 2.4 mm/−2.5 mm @ 3 m/s). Sham surgeries consisted of either craniectomy shams (all procedures except impact) or "intact" shams which only received an incision. Rats resumed testing starting at week 2 post-injury and continued until week 8–12 (varied by study). Sessions evaluated here would represent approximately weeks 4–8 post-injury, a relatively chronic time point for rats.

Data Processing

Raw trial-by-trial data were imported into R for processing. Any manipulations/treatments other than TBI were filtered away. Sessions prior to stable post-injury performance were filtered away. For each subject, session and choice option, total choices,

earned pellets, and total timeout were summed. Additional calculations were performed as described below.

Experiment 1—Molar Accounts of Behavior: The Generalized Matching Law

To maximize pellets earned, the P2 option should be chosen exclusively. However, this is not observed at the population level (even in Sham rats) and rarely observed in individual rats. To determine if this heterogeneity in choice performance was related to relative reinforcement rates amongst the choice options, the generalized matching law was evaluated. The matching law stipulates that behavioral allocation will approximate relative reinforcement rate (Baum, 1974). While this typically breaks down under ratio schedules (probabilistic delivery in this task is analogous to variable ratio), it may account for some behavior.

The ratio of choices for each option was calculated per subject and for the last 10 sessions of performance. The obtained reinforcers and punishers were used to calculate a reinforcement rate for each option. When total choices were less than 4, the programmed reinforcement rate was used. When choice of an option was 0, this was replaced with a 1 and added to the total of choices. These adjustments were necessary to prevent 0 s and infinite values since this experiment was not designed to eliminate those from the data as would be typical in a matching experiment. The ratios of choice and reinforcement rate [e.g., P1/(P2 + P3 + P4)] were then calculated for each option, subject, and session. These were log transformed and fit to the generalized matching law using linear regression [$\log(R_T/R_O) = a^*\log(B_T/B_O) + \log(b)$, where R_T is the reinforcement rate of the target option and R_O is the sum of reinforcement rate of other options, B_T is the number of choices on the target option, B_O is the sum of choices on other options, and b is the bias].

From this linear regression, values representing the sensitivity to reinforcement (slope), bias (y-intercept) and the overall fit (R^2) were calculated. Plots of individual subjects were used to visualize how many rats demonstrated matching, and a quantitative comparison (*t*-test) was made between TBI and Sham. Average values were used to also fit the matching law at the population level to Sham and TBI.

Experiment 2—Molecular Accounts of Behavior: Win/Loss Sensitivity

It is possible that in tasks such as these, greater sensitivity is given to immediate consequences. Thus, if a choice is reinforced on a given trial, this may increase what is commonly referred to as "win-stay" behavior, or an increase in probability of staying on that option. Conversely, punishment may increase "lose-shift" behaviors, or the probability of switching away from that option. To maximize performance on the RGT, rats must persist through punishment on optimal choices (i.e., P2 option) and switch away from reinforcement on riskier choices (e.g., P3, P4).

The probability of staying with the same choice on a subsequent trial was evaluated as a function of the preceding outcome ("win" or "loss"). Overall data were calculated for the last 10 sessions from a given study. To power analyses at the individual choice option level, data from the last 10 sessions for each choice option were summed to a single value and filtered so that only choices with greater than 4 observations were used. Overall switching, probability given a win, and probability given a loss were evaluated in a linear mixed-effects regression with Injury and Session as predictors. Individual subjects were plotted to visually examine the range of sensitivity between the two groups. The same analyses were then carried out for each choice option (i.e., P1:P4) but using ANOVA since data were aggregated.

Experiment 3—Atheoretical Accounts of Behavior: k-Means Clustering

Given that neither opposing theories of behavior strongly accounted for RGT data, a third experiment was conducted to determine if an unbiased approach might better describe the data. A simple k-means clustering approach was used. In this, the distance from a multidimensional centroid was minimized by categorizing subjects into *k* number of clusters. Data were averaged on a per subject basis from the last 10 sessions of a given study. A series of clusters was evaluated, starting at 2, and increasing to 10. Clusters were evaluated using the gap statistic to determine optimal number and validated by visual inspection of the elbow plot of the sum of squares. To reduce risk of overfitting/overestimation given the relatively small dataset, the number of subjects in each cluster were also monitored to ensure that any given cluster contained at least 5% of the sample. Sham data were assessed alone first, followed by TBI alone, and then the full dataset together. Visualization of the cluster averages were used to generate descriptive names as "phenotypes."

Supplemental Analyses

The supplement provides several comparisons between the various sub-group variables in the current study. Specifically, comparisons were made between craniectomy and intact shams, bilateral frontal and unilateral parietal TBI, and within-subjects pre- and post-injury effects. These subgroup comparisons (with the exception of intact vs. craniectomy) are of lower power than the main document, and so should be interpreted with caution.

TABLE 1 | Brief description of studies.

Study	References	Injury	Trained or acquisition	N (TBI)
1	Shaver et al., 2019	Bilateral frontal	Both (separate cohorts)	44 (21)
2	Ozga-Hess et al., 2020	Unilateral parietal	Acquisition	25 (11)
3	Under review	Bilateral frontal	Trained	18 (8)
4	In preparation	Bilateral frontal	Acquisition	22 (11)

RESULTS

General Rodent Gambling Task Performance and Effects of Traumatic Brain Injury

An examination of the relation between non-choice and other variables is presented in **Supplementary Figure 1**. There were substantial correlations between overall choice and multiple

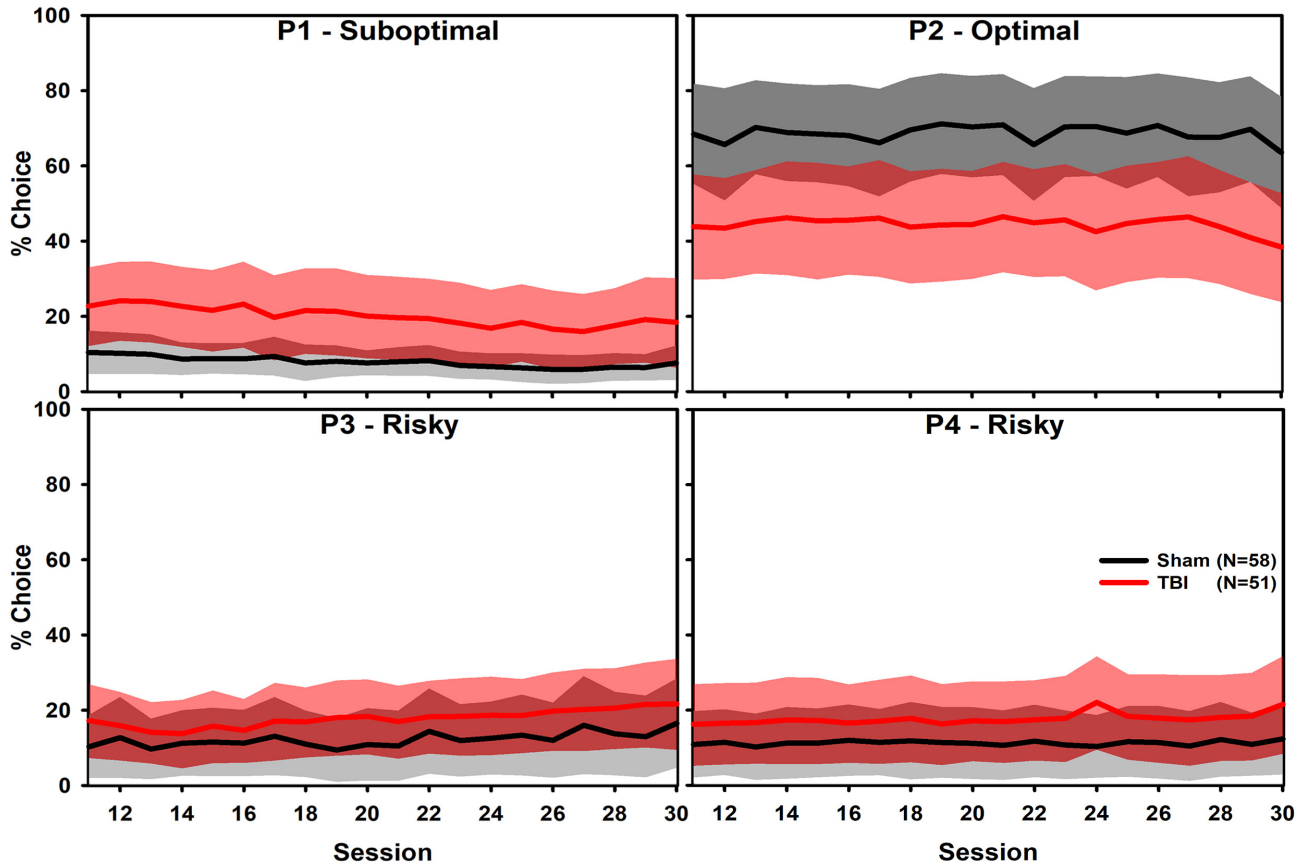


FIGURE 1 | Overall choice of the four RGT options shown as mean (solid line) and one standard deviation band (fill). Only sessions after 10 are shown to maximize visualization of stable choice preference, which represents approximately weeks 4–8 post-injury. There were significant Injury effects on each choice option (P1 and P2: $p < 0.001$; P3: $p = 0.048$; P4: $p = 0.022$) and P1 had a slight, but significant decline over time ($p = 0.001$). Analyses indicated substantial individual variation in choice.

variables of interest, including premature responses and "Win-Stay" and "Lose-Shift" behaviors. Choice of each option was analyzed in independent linear mixed effects regressions, interacting Injury and Session as fixed effects, and allowing slope and intercepts to vary by subject as random effects. Sessions from 11 to 30 were selected to minimize early change after TBI and learning (**Figure 1**). For P1 choice, there were significant increases due to Injury and across Session ($\beta = 0.68$, $t = 4.25$, $p < 0.001$; $\beta = -0.10$, $t = 4.00$, $p < 0.001$), but not with regard to their interaction ($\beta = -0.05$, $t = 1.26$, $p = 0.209$). Individual subjects also varied considerably in their intercept but not in slope (SD = 1.04; SD = 0.03). For P2 choice, there was a significant decrease due to Injury ($\beta = -0.79$, $t = 4.76$, $p < 0.001$), but no effect of Session nor their interaction ($\beta = 0.02$, $t = 0.80$, $p = 0.427$; $\beta = 0.01$, $t = 0.22$, $p = 0.825$). Individual subjects also varied considerably in their intercept but not in slope (SD = 0.98; SD = 0.03). For P3 choice, there was a significant increase due to Injury ($\beta = 0.35$, $t = 2.00$, $p = 0.048$), but not because of Session nor their interaction ($\beta = 0.03$, $t = 1.07$, $p = 0.288$; $\beta = 0.01$, $t = 0.17$, $p = 0.863$). Individual subjects also varied considerably in their intercept but not in slope (SD = 0.86; SD = 0.03). For P4 choice, there was a significant increase due to Injury ($\beta = 0.41$, $t = 2.32$, $p = 0.022$), but no effect of Session nor their interaction ($\beta = -0.01$, $t = 0.30$, $p = 0.767$; $\beta = 0.02$, $t = 0.63$, $p = 0.529$). Individual subjects also varied considerably in their intercept but not in slope (SD = 1.03; SD = 0.03).

Although the P2 option had a large TBI effect, others were considerably smaller and likely only significant due to the large power given the number of subjects. Moreover, there was substantial individual variability as shown by the standard deviation of the random effects. This variability is described further in individual subject-level plots below. The magnitude of these individual differences were of similar or larger magnitude than the group-level effect. These reinforce the need to examine data on an individual subject level in subsequent analyses.

Experiment 1: Molar Accounts of Behavior

The generalized matching law was fit to each individual subject. In Sham rats, a large number were sensitive to the reinforcement contingencies as indicated by steep slopes in **Figure 2**. However, a portion also demonstrated anti-matching or preference for the riskier option as well as indifference to the

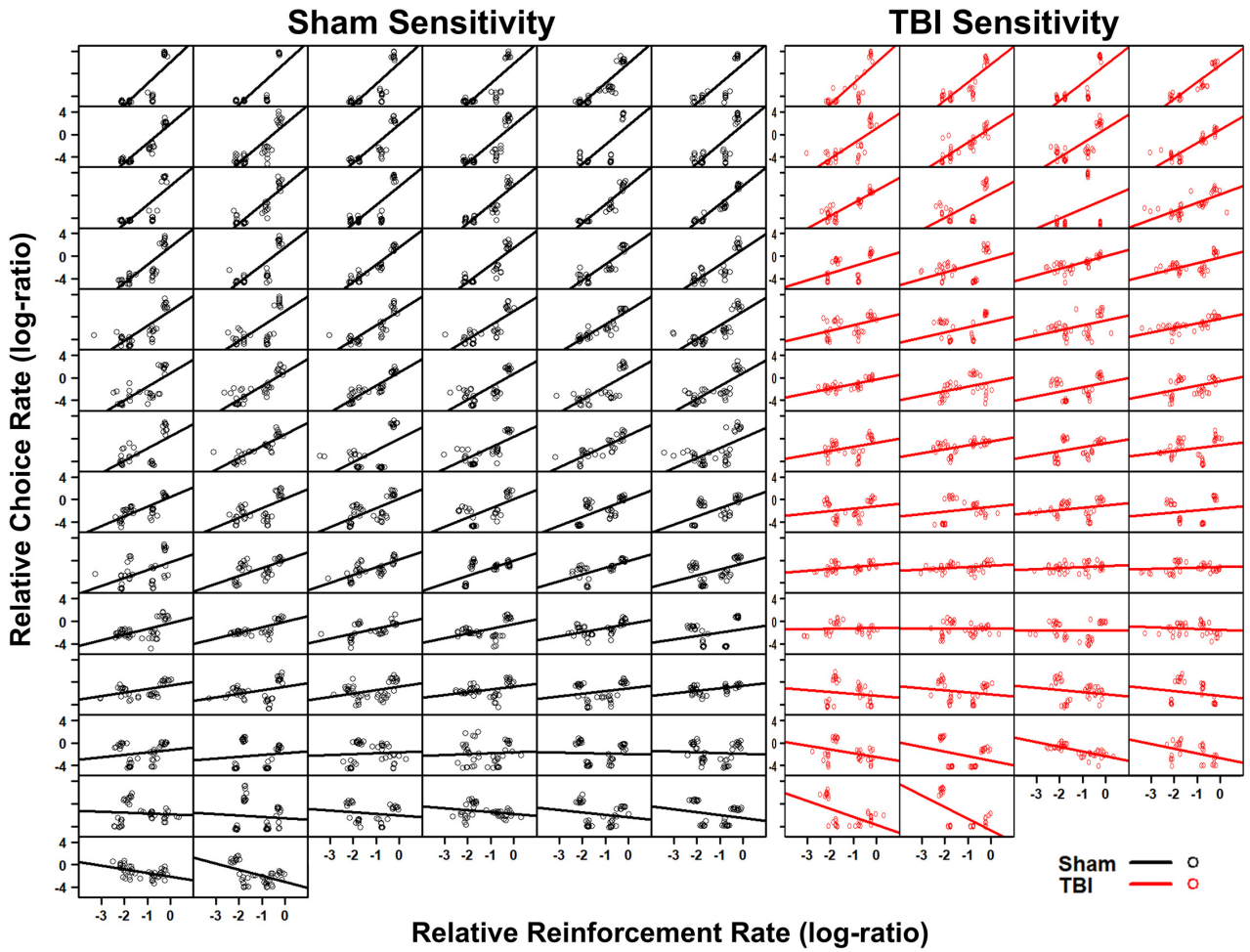


FIGURE 2 | Individual subject fits to the matching law show Sham (left, black) and TBI (right, red) subjects. A wide degree of sensitivity was present across subjects. The matching law only described a very small subset of animals.

relative rates of reinforcement. For the TBI rats, similar styles were present at the individual level (**Figure 2**). However, in the aggregate, TBI rats had reduced sensitivity to reinforcement rates [$t_{(107.21)} = 4.15$, $p < 0.001$], increased bias toward risky alternatives [$t_{(104.02)} = 3.96$, $p < 0.001$], and worse fits to the equation [$t_{(107.25)} = 3.64$, $p < 0.001$] relative to Sham rats (**Figures 3A–C**). Further, the matching law fit poorly at the population level (Sham $R^2 = 0.39$, TBI $R^2 = 0.11$; **Figures 3D,E**).

Experiment 2: Molecular Accounts of Behavior

To determine if immediate outcomes influenced decision-making on the RGT, likelihood of switching after a choice was analyzed, including session as a covariate. Aggregate distributions of switching are shown as density plots in **Figures 4A,B**. The overall tendency to stay was significantly reduced in TBI rats [$F_{(1,\ 155.25)} = 7.07$, $p = 0.009$]. When analyzed by the prior trial being a win or loss, TBI rats still were significantly less likely to stay with an option regardless of win or loss [$F_{(1,\ 153.1)} = 7.29$, $p = 0.008$], and overall rats were less likely to stay following a loss [$F_{(1,3710)} = 5.85$, $p = 0.016$], but there was no differential sensitivity to losses in the TBI group [$F_{(1,3710)} = 0.00$, $p = 0.966$].

While useful to capture global changes in propensity to stay with a choice, analyzing the overall data could miss important differences related to individual choice contingencies. Thus, a similar analysis was conducted, but data from the 10 sessions were summed for each option to ensure sufficient resolution. Aggregate distributions are shown as density plots in **Figures 4C,D**. For overall tendency to switch, there was an interaction of Injury and Choice Option [$F_{(3,\ 407)} = 12.74$, $p < 0.001$], so each was analyzed separately. TBI rats were significantly more likely to stay on P1, but less likely on P2 choices [$F_{(1,\ 105)} = 11.44$, $p = 0.001$; $F_{(1,\ 106)} = 19.43$, $p < 0.001$], but not P3 or P4 [$F_{(1,\ 99)} = 0.75$, $p = 0.388$; $F_{(1,\ 97)} = 2.32$, $p = 0.131$]. When analyzed by win- and loss-trials, there was also an Injury × Choice Option interaction [$F_{(3,\ 812)} = 23.28$, $p < 0.001$], so each was analyzed separately. TBI rats were significantly more likely to stay on P1 and P4 choice options, but less likely on P2 [$F_{(1,\ 208)} = 20.04$, $p < 0.001$; $F_{(1,\ 194)} = 5.41$,

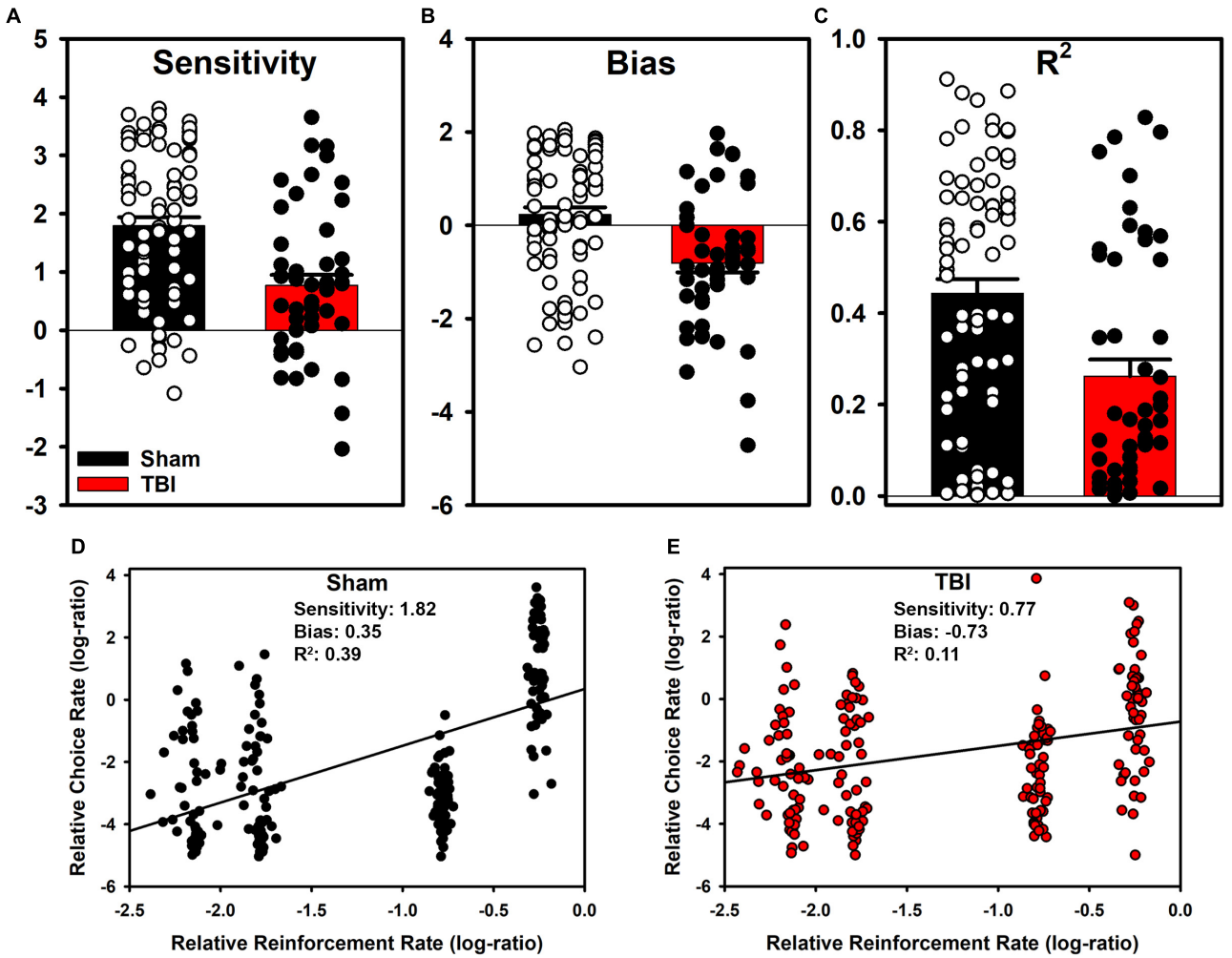


FIGURE 3 | Aggregate matching law parameters and group-level fits. **(A)** TBI reduced sensitivity ($p < 0.001$), and **(B)** shifted bias toward suboptimal options ($p < 0.001$). **(C)** The matching law described TBI rats more poorly than Sham ($p < 0.001$), however the matching law did not describe data well at the individual or **(D,E)** at the aggregate level.

$p = 0.021$; $F_{(1,\ 212)} = 38.08$, $p < 0.001$], and not significantly different on P3 [$F_{(1,\ 198)} = 1.37$, $p = 0.243$]. There was no injury-related difference in tendency to switch given a win vs. a loss (p's > 0.134).

These wide distributions suggest considerable individual variability. Indeed, this was confirmed from viewing the average probability of staying with an option at the subject level (**Figure 5**). Both Sham and TBI groups had some rats which exploited options, and others which were frequently switching amongst choices.

Experiment 3: Atheoretical Accounts of Behavior

For the Sham cohort, four clusters were the optimal fit to the data according to the gap statistic, and it was not until six clusters that any given one approached the < 5% sample threshold we established. For the TBI cohort, nine clusters was the optimal fit according to the gap statistic. However, examination showed that eight or more clusters resulted in clusters with less than 5% of the sample. A re-analysis of the TBI cohort, limited to a max of seven clusters identified seven as optimal on the gap statistic.

Once the data were combined, the gap statistic identified four clusters as optimal, and six or more clusters resulted in at least one with < 5% of a given group. Because the k-means algorithm is agnostic to injury condition, when four clusters were examined, the group-level fits were imprecise. The cluster number was increased to five and group-level data fit the clusters much better while still staying within the previously set parameters.

The clusters that emerged represented five choice phenotypes (**Figure 6**): An Optimal (strong P2 preference), an Exploratory (moderate P2 preference), two Risky (a P3-preferring and a P4-preferring), and an Indeterminate (P1 + P3 preference). When these clusters were examined by group, a Fisher's Exact Test revealed a significantly uneven distribution of cluster membership ($p = 0.001$; **Figure 7A**). TBI animals were less likely to be in the Optimal phenotype and displayed small increases in

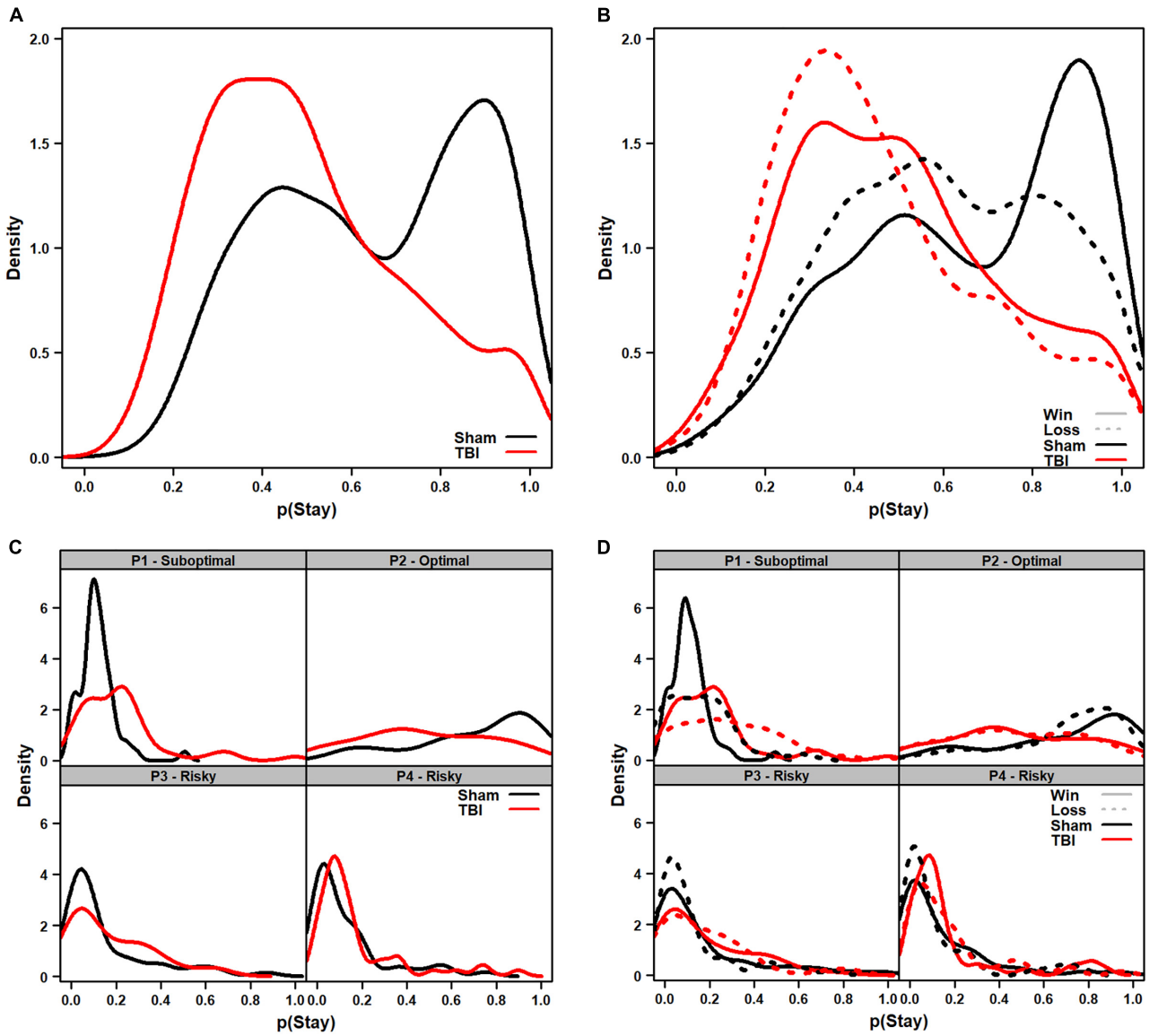


FIGURE 4 | Density plots of distributions of the probability of staying with a choice in TBI vs. Sham animals. **(A)** Overall tendency to stay on a choice (regardless of outcome) was higher in Sham than TBI rats ($p = 0.008$). Sham rats displayed a bimodal set of peaks around 40 and 90% likelihood of staying on an outcome. **(B)** Breakdown of tendency to stay depending on whether the prior outcome was a win (solid) or loss (dashed). The same overall differences were present in TBI ($p = 0.008$), and losses reduced the probability of staying (leftward shift in curve; $p = 0.016$) but TBI rats did not show differential sensitivity to wins or losses ($p = 0.966$). **(C)** When broken down to each choice option, TBI rats were more likely to stay with P1 ($p = 0.001$), but less likely to stay with P2 ($p < 0.001$) regardless of outcome. **(D)** When choice option data were analyzed depending on whether prior outcome was a win (solid) or loss (dashed), similar overall effects in tendency to stay were observed with TBI rats more likely to stay with P1 ($p < 0.001$) and P4 ($p = 0.021$), but less likely for P2 ($p < 0.001$). There were no differential effects in sensitivity to wins vs. losses (p's > 0.134).

the remaining phenotypes. TBI animals were the only ones to demonstrate the Indeterminate phenotype.

For each cluster, an ANOVA (Pct Choice ~ Injury * Choice Option) was conducted to see if groups differed despite being grouped together in the k-means process (**Figures 7B–F**). TBI were significantly different in the Optimal (Injury*Choice: $p = 0.018$) and Risky (P3) cluster (Injury*Choice: $p = 0.001$). To obtain a coarse measure of differences in variance, the standard deviations were calculated for each choice option for both groups and then summed for each phenotype to provide a qualitative comparison of variance. TBI had higher variance in the Risky (P4) cluster (48.11 vs. 35.76) and Exploratory cluster (43.77 vs. 36.73), less variance in the Risky (P3) cluster (31.34 vs. 43.94), and similar variance in the Optimal cluster (24.13 vs. 24.67).

Supplemental Analyses

There were no differences on overall behavior between craniectomy and intact shams (**Supplementary Figure 2**), and

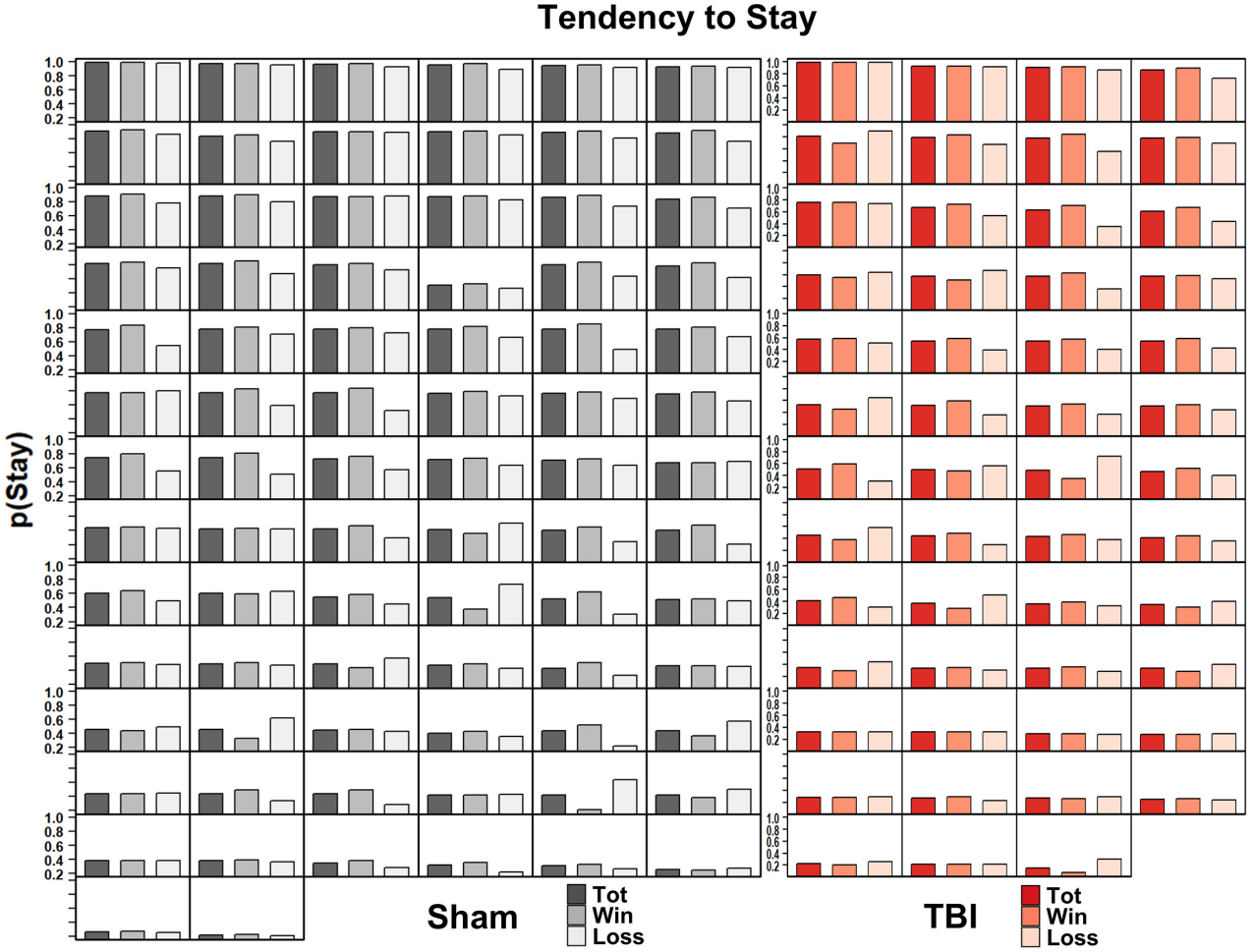


FIGURE 5 | Individual subject's probability of staying with a choice across total trials, winning trials, and losing trials in Sham (left, black) and TBI (right, red) subjects. There was considerable variability in the tendency to stay with a choice across subjects.

so molar/molecular/atheoretical analyses were not applied to this group. Unilateral parietal TBI significantly decreased molar sensitivities, but increased tendency to stay with those options relative to bilateral frontal TBI (**Supplementary Figures 3–5**). With regard to the subset where pre- and post-injury performance was available, TBI significantly decreased molar and molecular sensitivity (**Supplementary Figures 6–8**).

DISCUSSION

To understand how to treat the psychiatric-like symptoms which stem from TBI, more research is needed regarding changes in behaviors which underlie these conditions. In the current report, we pooled data collected over multiple studies to better explore these fundamental changes. This enabled evaluation of the impact of individual variability and analyses of conditional data (e.g., a switch in choice after a loss). Rats performed more poorly on the RGT after TBI and choices tend to be allocated away from optimal options and toward both safer, suboptimal choices and riskier choices, suggesting a reduced sensitivity to the outcomes of choices (**Figure 1**). Notably, this could be explained by reduced molar sensitivity (i.e., sensitivity to overall contingencies) or by changes in molecular sensitivity (i.e., immediate outcomes: a "win" or "loss").

An evaluation of the molar perspective of behavior was carried out in Experiment 1. There were substantial, statistically significant reductions in sensitivity to reinforcement and increased bias toward lower reinforcement rates in TBI rats (**Figure 3**). On the surface, this could potentially explain how TBI changes decision-making. However, a closer consideration of the data reveals significant problems with this interpretation. From a pure optimization standpoint, a task such as this theoretically should generate exclusive preference of the P2 option to maximize reinforcement. However, this is clearly not the case for almost any rats. This means that theoretically, the matching law should poorly describe the data. Indeed, at the subject level, we see this is the case for many subjects (**Figures 2**, **3**). True matching behavior would result in a sensitivity (slope) of 1, and a bias (intercept) of 0. However, even in sham rats, there are a

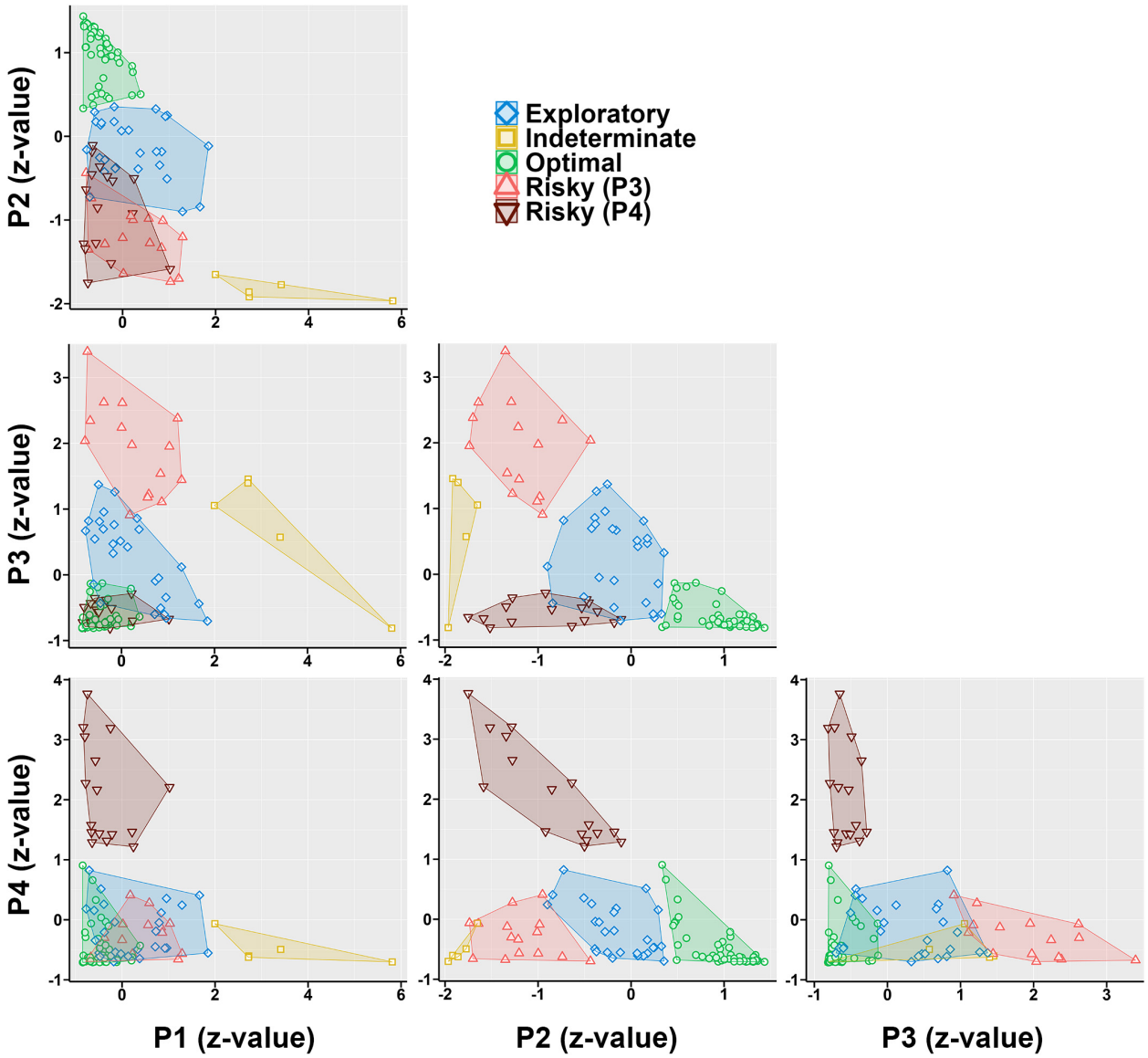


FIGURE 6 | Normalized preference (z score) for a given option plotted against each other, with clusters superimposed on top. Points represent individual rats. An Optimal phenotype (green) can be seen as rats that have high P2 values and relatively low values of all others. An Exploratory phenotype (blue) can be seen with values across all options around 0 (average). Two risky phenotypes can be seen, one which highly prefers P3 (light red), and another which prefers P4 (dark red). Finally, a small cluster of indeterminate rats (yellow) can be seen with unique preference for P1.

number with negative sensitivity and bias, otherwise understood as a preference for lower rates of reinforcement. Despite this problem, a shift in overall sensitivity to outcomes cannot be ruled out as this task was not explicitly designed to test this hypothesis. Rather, data of convenience were used to provide a rough evaluation. Indeed, studies explicitly controlled to examine matching under similar conditions find that adjustment of choice probabilities across blocks will generate matching in a 3-alternative probabilistic task (Kangas et al., 2009). Moreover, in patients with TBI, when a similar adjusting probability procedure is used, patients displayed reduced sensitivity to changes and some tended to overestimate their own performance in self-report (Schlund and Pace, 2000). Thus, while the matching law provides some marginal utility to describe behavior on the RGT, it does not capture the full range of individual subjects nor the depth of changes in choice behavior after TBI.

Because the RGT, with its fixed contingencies, is not well-suited for evaluating matching performance, an alternative might be to evaluate molecular sensitivity to immediate outcomes (i.e., "wins" and "losses") on the task. This molecular perspective could potentially explain post-injury changes in which reduced sensitivity to negative outcomes ("losses") or increased sensitivity to positive and/or large magnitude outcomes ("wins") may have an outsized influence on behavioral impairment. Patient data

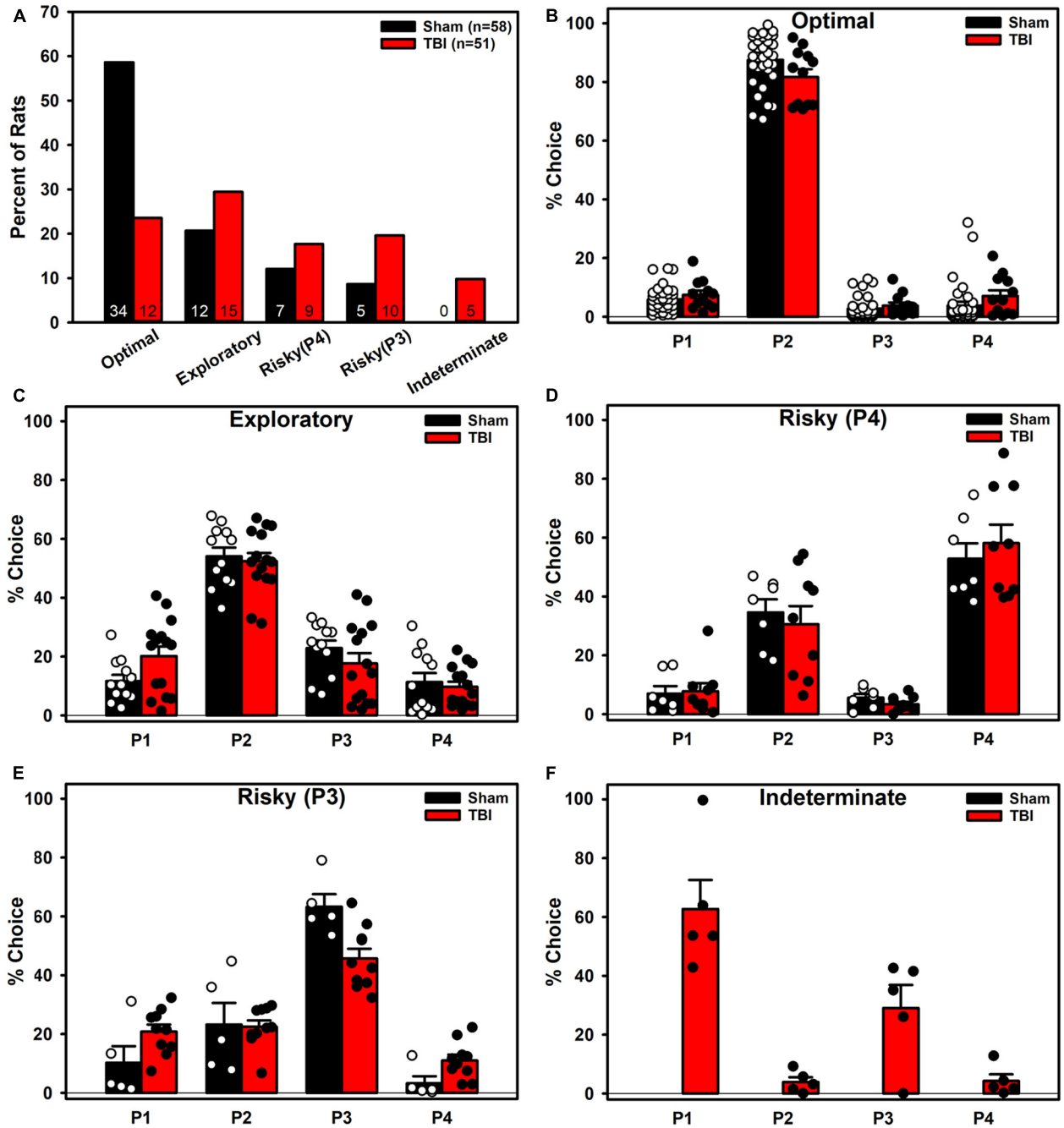


FIGURE 7 | Phenotypes broken down by Injury. **(A)** TBI rats were significantly less likely to be in the Optimal phenotype and instead were increased across the other phenotypes. Only TBI rats were classified into the Indeterminate phenotype. **(B)** TBI was significantly different than Sham ($p = 0.018$) in the Optimal phenotype, with lower P2 and higher P4 choice. **(C)** TBI was not significantly different than Sham but had high variability in the Exploratory phenotype. **(D)** TBI was not significantly different than Sham but had high variance in the Risky (P4) phenotype as well. **(E)** TBI was significantly different than Sham ($p = 0.001$), with higher P1 and lower P3 preference in the Risky (P3) phenotype. **(F)** Only TBI animals were present in the Indeterminate phenotype.

suggest that TBI leads to less sensitivity to negative outcomes because they display less reactivity to fearful stimuli alongside poor IGT performance (Visser-Keizer et al., 2016). Despite this, in the current data, we did not find any significant differences in sensitivity to wins vs. losses on the RGT. TBI rats were significantly changed overall in their tendency to stay with a given option (**Figure 4**), but both TBI and sham had downward shifts in probability following losses. Further, this was not uniquely affected by the choice options with more frequent wins or losses. Interestingly, we again observed drastic individual differences

(**Figure 5**), with both sham and TBI rats displaying a range from exclusive choice to almost absolute alternation amongst options. Thus, it seems that some level of differential sensitivity to immediate outcomes is not a driver of TBI-induced deficits on the RGT. Rather, the overall changes suggest further support for a more molar viewpoint as discussed above.

Neither the molar nor molecular approach fully explained choice behavior on the RGT. To determine if a theory-agnostic approach would provide more explanatory power, k-means clustering was performed on the full dataset. This generated five total choice phenotypes: Optimal, Exploratory, two Risky, and Indeterminate. There was minimal overlap between the pattern of choices for rats in any given phenotype and can be visualized by plotting each choice against each other (**Figure 6**), yielding distinct patterns which clearly segregate even optimal from exploratory rats. These phenotypes described choice behavior very well, and moreover, the changes in TBI animals were accounted for almost entirely by a reduction in the Optimal phenotype (**Figure 7**). However, clustering results should always be approached with some level of caution. K-means and similar algorithms are designed to maximize variance accounted for, and so further explorations should be performed to determine if the phenotypes found here hold up across future studies or in other laboratories. Another consideration is that these phenotypes may merely recapitulate the matching data. Rats who were true matchers (i.e., sensitivity approximately 1) are likely those in the Exploratory phenotype, while those with the highest sensitivity and positive bias are the Optimizers, and those with negative matching or bias are likely the Risky rats. Still, these phenotypes illustrate that the matching data are less continuous than might be inferred from the aggregated plots and that distinct clusters of preference emerge on the RGT. Finally, these phenotypes open new avenues of investigation into the underlying neurobiology or behavioral drivers of such choice. For example, differences in phasic dopamine activity and/or dopamine receptor and transporter density may underly TBI-mediated cognitive deficits (Bales et al., 2009) as well as reactivity to conditioned stimuli (e.g., the choice hole) and primary reinforcers (e.g., the sucrose pellets) for intact rats (Singer et al., 2016).

The current data do not fully explain how choice behavior develops on a probabilistic task such as the RGT. However, they do inform our interpretation of how stable behavior is best described and how it is altered by a brain injury. A prior study using similar retrospective data (in intact rats) suggested a combination of immediate consequences and molar contingencies drove acquisition of behavior on this task using a model of reinforcement learning (Langdon et al., 2019). Specifically, it was suggested that reductions in loss sensitivity would allow for a riskier phenotype and this could be augmented by pairing complex audiovisual cues with riskier options. Interestingly, given the current data demonstrating large-scale shifts in phenotypes immediately following TBI, a lack of explicit changes in loss sensitivity, and a tendency toward molar-level insensitivity, the prior study may not fully explain the development of risky decisions. Unfortunately, these comparisons are somewhat limited by our current selection of only stable post-injury data (i.e., 4 + weeks post-injury). While this gave the ability to compare a large amount of data, it limited what could be interpreted about acquisition of this task in TBI rats. Ultimately, the current study highlights the need to experimentally manipulate these parameters so that we can dissociate molar from molecular tendencies in decision-making and evaluate whether the reported phenotypes have underlying neurobiological substrates. Further data collection in TBI animals both before and after the injury (N = 19 in current study; **Supplementary Figures 6–8**), exploration of differences in unilateral parietal and bilateral frontal TBI (N = 10 unilateral in current study; **Supplementary Figures 3–5**), and evaluation of effective therapeutics may also provide insights on the biobehavioral pathologies which drive maladaptive decision-making. Using data collected from such studies, we may be able to devise rehabilitative strategies to treat the devastating consequences of TBI.

DATA AVAILABILITY STATEMENT

Raw data are available via the TBI Open Data Commons (https://odc-tbi.org/), ODC-TBI accession ID 703 (Vonder Haar et al., 2022). Processing/analysis syntax may be requested by contacting the authors.

ETHICS STATEMENT

The animal study was reviewed and approved by the West Virginia University IACUC.

AUTHOR CONTRIBUTIONS

CV, MF, VM, AR, and KM collected the data, drafted, and edited the manuscript. CV, MF, VM, and AR performed the analyses. All authors contributed to the article and approved the submitted version.

FUNDING

Funding for this project was provided by the NIH (NINDS R01-NS1109; NIGMS P20-GM103434), West Virginia University, and Ohio State University.

ACKNOWLEDGMENTS

These analyses were made possible by many laboratory personnel who helped to collect behavioral data or assisted with surgeries over multiple years.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnbeh.2022.837654/full#supplementary-material

REFERENCES

Bales, J. W., Wagner, A. K., Kline, A. E., and Dixon, C. E. (2009). Persistent cognitive dysfunction after traumatic brain injury: A dopamine hypothesis. *Neurosci. Biobehav. Rev.* 33, 981–1003. doi: 10.1016/j.neubiorev.2009.03.011

Baum, W. M. (1974). On two types of deviation from the matching law: Bias and undermatching. *J. Exp. Anal. Behav.* 22, 231–242. doi: 10.1901/jeab.1974.22-231

Baum, W. M. (1989). Quantitative prediction and molar description of the environment. *Behav. Anal.* 12, 167–176. doi: 10.1007/bf03392493

Bhalerao, S. U., Geurtjens, C., Thomas, G. R., Kitamura, C. R., Zhou, C., and Marlborough, M. (2013). Understanding the neuropsychiatric consequences associated with significant traumatic brain injury. *Brain Injury* 27, 767–774. doi: 10.3109/02699052.2013.793396

Chiu, C.-Y. P., Tlustos, S. J., Walz, N. C., Holland, S. K., Eliassen, J. C., Bernard, L., et al. (2012). Neural correlates of risky decision making in adolescents with and without traumatic brain injury using the balloon analog risk task. *Dev. Neuropsychol.* 37, 176–183. doi: 10.1080/87565641.2011.632796

Cotrena, C., Brancoa, L. D., Zimmermanna, N., Cardosoa, C. O., Grassi-Oliveiraa, R., and Fonseca, R. P. (2014). Impaired decision-making after traumatic brain injury: The Iowa Gambling Task. *Brain Injury* 28, 1070–1075. doi: 10.3109/02699052.2014.896943

Dalton, G. L., Phillips, A. G., and Floresco, S. B. (2014). Preferential involvement by nucleus accumbens shell in mediating probabilistic learning and reversal shifts. *J. Neurosci.* 34, 4618–4626. doi: 10.1523/JNEUROSCI.5058-13.2014

Fecteau, S., Levasseur-Moreau, J., García-Molina, A., Kumru, H., Vergara, R. P., Bernabeu, M., et al. (2013). Risk taking in hospitalized patients with acute and severe traumatic brain injury. *PloS One* 8:e83598. doi: 10.1371/journal.pone.0083598

Hoffman, S. W., Fülöp, Z., and Stein, D. G. (1994). Bilateral frontal cortical contusion in rats: behavioral and anatomic consequences. *J. Neurotrau.* 11, 417–431. doi: 10.1089/neu.1994.11.417

Kangas, B. D., Berry, M. S., Cassidy, R. N., Dallery, J., Vaidya, M., and Hackenberg, T. D. (2009). Concurrent performance in a three-alternative choice situation: Response allocation in a Rock/Paper/Scissors game. *Behav. Proc.* 82, 164–172. doi: 10.1016/j.beproc.2009.06.004

Langdon, A. J., Hathaway, B. A., Zorowitz, S., Harris, C. B. W., and Winstanley, C. A. (2019). Relative insensitivity to time-out punishments induced by win-paired cues in a rat gambling task. *Psychopharmacology* 236, 2543–2556. doi: 10.1007/s00213-019-05308-x

Martens, K. M., Vonder Haar, C., Hutsell, B. A., and Hoane, M. R. (2012). A discrimination task used as a novel method of testing decision-making behavior following traumatic brain injury. *J. Neurotrau.* 29, 2505–2512. doi: 10.1089/neu.2012.2388

Muelbl, M. J., Slaker, M. L., Shah, A. S., Nawarawong, N. N., Gerndt, C. H., Budde, M. D., et al. (2018). Effects of mild blast traumatic brain injury on cognitive-and addiction-related behaviors. *Sci. Rep.* 8:9941. doi: 10.1038/s41598-018-28062-0

Ozga-Hess, J. E., Whirtley, C., O'Hearn, C., Pechacek, K., and Vonder Haar, C. (2020). Unilateral parietal brain injury increases risk-taking on a rat gambling task. *Exp. Neurol.* 327:113217. doi: 10.1016/j.expneurol.2020.113217

Rider, D. P. (1981). Concurrent fixed-interval variable-ratio schedules and the matching relation. *J. Exp. Anal. Behav.* 36, 317–328. doi: 10.1901/jeab.1981.36-317

Rzezak, P., Antunes, H. K. M., Tufik, S., and Mello, M.T.d (2012). Translation and cultural adaptation of the Game Dice Task to Brazilian population. *Arquivos de Neuro-Psiquiatria* 70, 929–933. doi: 10.1590/s0004-282x2012001200005

Schlund, M. W. (2002). Effects of acquired brain injury on adaptive choice and the role of reduced sensitivity to contingencies. *Brain Injury* 16, 527–535. doi: 10.1080/02699050110113679

Schlund, M. W., and Pace, G. (2000). The effects of traumatic brain injury on reporting and responding to causal relations: An investigation of sensitivity to reinforcement contingencies. *Brain Injury* 14, 573–583. doi: 10.1080/026990500120475

Shaver, T. K., Ozga, J. E., Zhu, B., Anderson, K. G., Martens, K. M., and Vonder Haar, C. (2019). Long-term deficits in risky decision-making after traumatic brain injury on a rat analog of the Iowa gambling task. *Brain Res.* 1704, 103–113. doi: 10.1016/j.brainres.2018.10.004

Shimp, C. P. (2020). Molecular (moment-to-moment) and molar (aggregate) analyses of behavior. *J. Exp. Anal. Behav.* 114, 394–429. doi: 10.1002/jeab.626

Sigurdardottir, S., Jerstad, T., Andelic, N., Roe, C., and Schanke, A.-K. (2010). Olfactory dysfunction, gambling task performance and intracranial lesions after traumatic brain injury. *Neuropsychology* 24:504. doi: 10.1037/a0018934

Singer, B. F., Guptaroy, B., Austin, C. J., Wohl, I., Lovic, V., Seiler, J. L., et al. (2016). Individual variation in incentive salience attribution and accumbens dopamine transporter expression and function. *Euro. J. Neurosci.* 43, 662–670. doi: 10.1111/ejn.13134

Visser-Keizer, A. C., Westerhof-Evers, H. J., Gerritsen, M. J., van der Naalt, J., and Spikman, J. M. (2016). To fear is to gain? The role of fear recognition in risky decision making in TBI patients and healthy controls. *PloS One* 11:e0166995. doi: 10.1371/journal.pone.0166995

Vonder Haar, C., Maass, W. R., Jacobs, E. A., and Hoane, M. R. (2014). Deficits in discrimination following experimental frontal brain injury are mediated by motivation and can be improved by nicotinamide administration. *J. Neurotrau.* 31, 1711–1720. doi: 10.1089/neu.2014.3459

Vonder Haar, C., Martens, K. M., and Frankot, M. A. (2022). *Combined Dataset of Rodent Gambling Task in Rats After Brain Injury [Data set]*. Open Data Commons for Traumatic Brain Injury (ODC-TBI), 703. doi: 10.34945/F5Q597

Zeeb, F. D., and Winstanley, C. A. (2013). Functional disconnection of the orbitofrontal cortex and basolateral amygdala impairs acquisition of a rat gambling task and disrupts animals' ability to alter decision-making behavior after reinforcer devaluation. *J. Neurosci.* 33, 6434–6443. doi: 10.1523/jneurosci.3971-12.2013

Zgaljardic, D. J., Seale, G. S., Schaefer, L. A., Temple, R. O., Foreman, J., and Elliott, T. R. (2015). Psychiatric Disease and Post-Acute Traumatic Brain Injury. *J. Neurotrau.* 32, 1911–1925. doi: 10.1089/neu.2014.3569

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers | Frontiers in Behavioral Neuroscience

ORIGINAL RESEARCH
published: 28 April 2022
doi: 10.3389/fnbeh.2022.806944

Beyond Systematic and Unsystematic Responding: Latent Class Mixture Models to Characterize Response Patterns in Discounting Research

Shawn P. Gilroy[1], Justin C. Strickland[2], Gideon P. Naudé[2], Matthew W. Johnson[2], Michael Amlung[3,4] and Derek D. Reed[3,4]*

[1] Department of Psychology, Louisiana State University, Baton Rouge, LA, United States, [2] Behavioral Pharmacology Research Unit, Department of Psychiatry and Behavioral Sciences, Johns Hopkins University, Baltimore, MD, United States, [3] Department of Applied Behavioral Science, University of Kansas, Lawrence, KS, United States, [4] Cofrin Logan Center for Addiction Research and Treatment, University of Kansas, Lawrence, KS, United States

Operant behavioral economic methods are increasingly used in basic research on the efficacy of reinforcers as well as in large-scale applied research (e.g., evaluation of empirical public policy). Various methods and strategies have been put forward to assist discounting researchers in conducting large-scale research and detecting irregular response patterns. Although rule-based approaches are based on well-established behavioral patterns, these methods for screening discounting data make assumptions about decision-making patterns that may not hold in all cases and across different types of choices. Without methods well-suited to the observed data, valid data could be omitted or invalid data could be included in study analyses, which subsequently affects study power, the precision of estimates, and the generality of effects. This review and demonstration explore existing approaches for characterizing discounting and presents a novel, data-driven approach based on Latent Class Analysis. This approach (Latent Class Mixed Modeling) characterizes longitudinal patterns of choice into classes, the goal of which is to classify groups of responders that differ characteristically from the overall sample of discounters. In the absence of responders whose behavior is characteristically distinct from the greater sample, modern approaches such as mixed-effects models are robust to less-systematic data series. This approach is discussed, demonstrated with a publicly available dataset, and reviewed as a potential supplement to existing methods for inspecting and screening discounting data.

Keywords: discounting, mixed-effects models, statistical analysis, non-systematic data, latent factor

OPEN ACCESS

Edited by:
Marco Bortolato,
The University of Utah, United States

Reviewed by:
Sara McMullin,
University of Missouri, United States
Michael Young,
Kansas State University, United States

****Correspondence:***
Shawn P. Gilroy
sgilroy1@lsu.edu

Specialty section:
This article was submitted to Motivation and Reward, a section of the journal Frontiers in Behavioral Neuroscience

Received: *01 November 2021*
Accepted: *07 March 2022*
Published: *28 April 2022*

Citation:
Gilroy SP, Strickland JC, Naudé GP, Johnson MW, Amlung M and Reed DD (2022) Beyond Systematic and Unsystematic Responding: Latent Class Mixture Models to Characterize Response Patterns in Discounting Research. Front. Behav. Neurosci. 16:806944. doi: 10.3389/fnbeh.2022.806944

INTRODUCTION

Delay discounting and probability discounting are two key behavioral mechanisms. These are defined as the devaluation of a relevant consequence resulting from the delay or uncertainty associated with its receipt. Clinical research has focused on discounting given empirical work describing and conceptual frameworks positing that many of the behaviors observed in

neuropsychiatric (and other) health conditions mechanistically relate to one's sensitivity to delay and/or uncertainty (Bickel et al., 2014, 2017; MacKillop, 2016; Amlung et al., 2019). For example, research in addiction science has shown that people with substance use disorders have a greater tendency to devalue delayed rewards than healthy controls, a mechanism thought to underlie decisions to use drugs (e.g., cigarettes) and forgo long-term health benefits (e.g., increased later lung cancer risk; MacKillop et al., 2011; Amlung et al., 2017). Although research on probability discounting is more mixed in its relationship with substance use outcomes, similar associations with clinically relevant behaviors have been observed, particularly when outcome-specific discounting tasks rather than monetary-based discounting tasks are used (e.g., probabilistic risk of STI transmission; Johnson et al., 2020). More recently, discounting research has been extended to behavioral addictions such as Internet gaming and gambling, finding comparable predictive associations between specific discounting profiles and health behavior engagement (e.g., Petry and Madden, 2010; Kyonka and Schutte, 2018; Chung et al., 2021). Continued advances in the analysis of discounting data are needed to ensure that the growing emphasis on discounting as a candidate marker of neuropsychiatric health is accompanied by a retained focus on the rigor of the analytic procedures used to generate those conclusions.

The available literature shows that delay and uncertainty tend to decrease reinforcing value and behavioral scientists often regard any deviations from a monotonically decreasing function as erred responding by the participant and/or methodological flaws of the task (Smith et al., 2018). Thus, researchers typically label such deviations as "non-systematic" response patterns. In the seminal account of this issue, Johnson and Bickel (2008) proposed a general framework for assessing whether discounting data are systematic. Previous methods had often used an arbitrary R^2 value when fitting the data to a model such as the hyperbolic decay equation, a method that conflates model fit with the extent of discounting itself as shown by Johnson and Bickel (2008). Rather, they recommended the use of simple rules for the empirical data (i.e., indifference points) based on the most basic expectations of the data. For the data sets they presented, they classified data as non-systematic using two criteria: when (1) an indifference point is greater than the preceding indifference point by a magnitude of 20% of the undiscounted reward value (i.e., JB1), and/or when (2) the last indifference point (i.e., at the largest delay or odds against receipt) is not less than the first indifference point (i.e., shortest delay or smallest odds against receipt) by at least a magnitude of 10% of the undiscounted reward (i.e., JB2). They argued that depending on the data set, the specific criteria should be modified (e.g., adjustment of parameters, dropping the second criterion). They also noted that while the framework can be used to eliminate flagged data, it can be used simply to characterize data without elimination, and if used for elimination, variations such as allowing a single violation of the first criterion may be appropriate. Despite encouragement for such flexibility and some examples of that flexibility (e.g., Johnson and Bruner, 2012; Johnson et al., 2015), the specific non-systematic criteria noted in Johnson and Bickel (2008) have since become the *de facto* gold standard metrics of data quality in the discounting literature. That is, information on systematic responding may be grounds for manuscript rejection or at least substantial revision (e.g., requested to exclude those participants from analysis).

A recent meta-analysis of non-systematic responding in discounting studies sought to identify the prevalence of these patterns in published works (Smith et al., 2018). In their meta-analysis, Smith and colleagues identified 114 discounting experiments in human participants that explicitly reference the use of the Johnson and Bickel (2008) algorithm. Of these, 95 experiments used both criteria from the algorithm (i.e., JB1, JB2), and 14 of those 95 modified the criteria to account for procedural nuances. Across all experiments reviewed, approximately 18% of participant datasets failed at least 1 of the criteria. Rates of non-systematic responding were not found to differ between types of discounting, adults vs. youth, specified samples vs. general samples, hypothetical vs. real/potentially real outcomes, or whether the algorithm was modified. However, non-systematic rates were higher for non-monetary outcomes than monetary ones, as well as higher for university samples versus non-university samples. Findings from Smith et al. (2018) indicated that discounting data are robust and reliable concerning systematic patterns; however, the finding that 18% of datasets featured some degree of non-systematic responding is concerning and questions remain regarding the factors that account for these deviations.

Latent Class Analyses, Mixed Models, and Discounting Data

As an alternative to set criteria for characterizing discounters (i.e., systematic, non-systematic), Latent Class Analyses (LCAs) can be performed to explore subgroups of responders that comprise a given data set (e.g., systematic, mostly systematic, non-systematic, and so on). The term LCA refers to a collection of methods that are used to extract classes from data (Hagenaars and McCutcheon, 2002; Muthén, 2004). Class membership here refers to a latent feature, extracted from variance in the data, that distinguishes groups or classes of individuals that appear to be distinct from others within the overall sample (Lazarsfeld and Henry, 1968; Weller et al., 2020). Broadly, LCA and derivatives of this methodology are often used as a way of characterizing latent groups concerning some phenomena (Muthén, 2004; Proust-Lima et al., 2015). Derivatives of LCA expand upon the general process, which includes categorical variables, to evaluate changes in class membership over time (Latent Transition Analysis), to evaluate differential shapes and patterns of growth [Latent Class Growth Analysis (LCGA)], and to determine class membership while simultaneously modeling individual-level changes [LCGA + Mixing Modeling (LCMM), Muthén and Muthén, 2000]. Before discussing LCMMs further, we note that LCA is distinct from other clustering approaches (e.g., K-means), wherein the emphasis is on minimizing the distance between some metric (e.g., rate parameter k) and the values associated with each of the n fitted clusters. In data-driven approaches such as K-means, classes are determined by a process of minimizing individual

data distance from *n* centroids, and class membership is established based on proximity to the nearest centroid. That is, such approaches view class membership as determined by proximity rather than probability. Approaches such as K-means are readily applied to large datasets and demonstrate reliable convergence; however, such approaches are more strongly influenced by initial starting values, outliers, and conditions where cluster sizes vary significantly in terms of density and size (Morissette and Chartier, 2013).

Derivatives of the LCA such as LCMM can be extended to include linear modeling and to accommodate a range of longitudinal data types (e.g., continuous, binary; Proust-Lima et al., 2015). The flexibility provided by LCMM is particularly suited to evaluating patterns of choice over time, such as discounting phenomena. When used in this context, LCMMs can be applied to patterns of intertemporal choice over time to identify sub-classes of decision-makers that comprise the greater sample. This approach is distinct from approaches such as K-means because class membership is based on modeling differences (e.g., slopes) across individual data rather than data distance from centroids. Furthermore, class membership in LCMMs is probabilistic for individuals and this differs from approaches such as K-means. For example, a sample is likely to be comprised of multiple classes (with larger samples likely manifesting greater classes) and the results of LCMM explore class membership in a probabilistic sense. That is, the variance regarding individual choice over time is analyzed and viewed in terms of the classes in which it most probabilistically emerged from. This is key in viewing the distinguishing between LCMM and K-means; that is, latent features are extracted from the results of a model and the results probabilistically determine which class best characterizes the individual's responses. In a relevant example of this approach, Campbell et al. (2021) applied a derivative of LCA – Latent Profile Analysis (LPA) – to evaluate various continuous outcomes (e.g., discounting rate, indicators of demand). Using a latent approach with continuous indicators, the authors found three distinct classes of college students who engage in heavy drinking: low reward value, high discounting (LRHD); moderate reward value, low discounting (MRLD); high reward value, high discounting (HRHD). These profiles corresponded with individuals demonstrating a low demand for alcohol but high rates of discounting, a medium level of demand for alcohol, but low rates of discounting, and high levels of demand and discounting, respectively.

Although the Campbell et al. (2021) study provides an excellent exemplar of methods derived from LCA to indicators of demand and decision-making *across* various tasks, the goal of the current work is more general and specific to responding *within* a decision-making task. That is, the sample of decision-makers in a discounting task is likely to include classes of responders that demonstrated monotonically decreasing choices (i.e., systematic) and those who varied from that expected trend (i.e., non-systematic). These non-systematic responders are likely to demonstrate characteristically different patterns of choice as *compared to* the overall sample (e.g., ascending trends in the presence of increasing delays). In this way, LCMM provides a means to detect responders that behave uncharacteristically of the greater sample and this provides information that may be useful to researchers when deciding how to analyze responding in these tasks.

Despite recommendations by Johnson and Bickel (2008) to adapt a flexible framework, and examples of the adaptive use of the proposed framework (e.g., Johnson and Bruner, 2012; Johnson et al., 2015), many researchers continue to use these criteria rotely. That is, the criteria are being used to distinguish between orderly decreasing data and data that does not conform to this pattern. We propose the use of LCMMs as an alternative to assuming that a single "true" pattern of discounting exists (i.e., systematic vs. unsystematic). That is, LCMMs can be applied to the data to characterize the various subgroups that behave in characteristic and uncharacteristic ways (e.g., increasing value with delays).

Research Aims

The goal of this study was to test the use of LCMMs with a publicly available data set. The Human Connectome Project (HCP) was a large-scale open-science collaboration sponsored by the National Institutes of Health. The HCP provides a repository of delay discounting data drawn from healthy young adults participating in neural and behavioral research (full recruitment and screening procedures are found in Van Essen et al., 2013). Included among the battery of assessments were two adjusting-amount tasks (Du et al., 2002) that measured delay discounting across $200 and $40,000 reward magnitudes. Previous research has found that HCP delay discounting data are well characterized by hyperbolic-like discount functions (Yeh et al., 2021), exhibit the reward magnitude effect (Naudé et al., 2021; Yeh et al., 2021), and demonstrate the well-published association between cigarette smoking and greater discounting (Naudé et al., 2021). The goals of this report were to apply both the two original Johnson and Bickel (2008) criteria and the LCMM approach to evaluate the correspondence between the two different approaches. Specifically, the goal was to evaluate how two different approaches correlated when LCMMs identified clusters of responders that responded in characteristically different ways from the overall sample.

MATERIALS AND METHODS

Participants

A total of 1206 adults were included in the HCP and discounting data was available for 1198 of those participants. As part of an effort to better understand the relationship between neurology and behavior, participants across various ages and demographics completed a range of neuropsychological and decision-making measures. The sample included comparable groups of male (n = 550; 45%) and female (n = 656; 54%) participants. The amount of participants in each of the 22–25, 26–30, 31–35, and 36 + age ranges was 247 (20%), 527 (43%), 418 (34%), and 14 (1%), respectively. Participants in the HCP project completed two hypothetical delay discounting tasks as part of the overall battery of assessments. All data used in this study were drawn from

the unrestricted set of data and no demographic information is analyzed here.

Hypothetical Delay Discounting Tasks

The core battery of the HCP included two discounting tasks. One featured a low magnitude Larger Later Reward (LLR; $200) and another high magnitude LLR ($40,000). Across both amounts, indifference points were calculated across delays of 1 month, 6 months, 1 year, 3 years, 5 years, and 10 years. Indifference points across each delay were calculated using methods consistent with Du et al. (2002). That is, the initial value of the Smaller Sooner Reward (SSR) at each delay was 50% of the LLR and the value of the SSR was adjusted following participant choices. Specifically, the value of the SSR would increase and decrease following the choice to select the LLR and SSR, respectively. The degree of adjustment for the SSR was half of the starting SSR value and halved in each subsequent iteration. Following a total of five choices, the final SSR value was considered the indifference point for that delay. This process was repeated for each delay, in ascending order, across both tasks. The results of each were used to construct a ratio of area under the interpolated series to the total area possible, i.e., point-based area under the curve (AUC; Myerson et al., 2001). In the presence of a monotonically decreasing data series, AUC provides a summary index of individual discounting (see Gilroy and Hantula, 2018, for a discussion on AUC interpretation).

Analytical Strategy

Participant responses on each of the discounting tasks included in the HCP were analyzed using multiple methods for characterizing discounters. Specifically, the criteria in Johnson and Bickel (2008) were compared to the best-fitting LCMMs for each of the Hypothetical Money Choice Tasks (HMCTs). These two approaches are expected to correspond to an unknown degree, with the Johnson and Bickel (2008) approach reflecting comparison to an absolute standard (i.e., JB1, JB2) and LCMMs relative to the trends observed in the sample overall. The methods used to apply the Johnson and Bickel (2008) indicators were adapted from source code included in the *discountingtools* R package (Gilroy, 2017). LCMMs were applied to the HCP data set using the *lcmm* R package (Proust-Lima et al., 2015) and the R Statistical Program (R Core Team, 2021). Data from each of the HMCTs were supplied to the *lcmm* method included in the R package. The *lcmm* package provides considerable flexibility in specifying models; however, this exploration used the most basic linear model to characterize individual data across delays. The use of a basic linear model was selected because it presented the simplest option to index the direction and rate of change for individual choices over time. Indeed, there are various competing options for representing the shape of individual discounting processes (e.g., exponential, hyperbolic) and the use of the linear model provided the simplest model with which to perform LCMM. Furthermore, in regards to comparison with the Johnson and Bickel (2008) comparison, we note that the rules provided did not reference any specific shape for the discounting process.

The *lcmm* method was used to evaluate the overall sample with *n* latent classes and these various fits were evaluated using the Sample-size Adjusted Bayesian Information Criterion (SABIC; Lubke and Neale, 2006). Briefly, the SABIC is a derivative of the Bayesian Information Criterion (BIC; Schwarz, 1978) adjusted for sample size. Lubke and Neale (2006) conducted various simulation studies and their results suggested that the Akaike Information Criterion (AIC; Akaike, 1974) and SABIC fared better overall as indices for determining mixture model fitness. The grouping structure with the lowest SABIC was inspected to evaluate subgroups of discounters.

RESULTS

Empirical Evaluations of Discounting Data

The results of screening using the Johnson and Bickel (2008) criteria are displayed across both decision-making tasks in **Table 1**. Results from the $200 task indicated that 80, 93, and 76% of the sample satisfy (i.e., were not flagged as non-systematic with) JB1, JB2, and both criteria, respectively. Similarly, results from the $40,000 task indicated that 81, 87, and 71% of the sample satisfied JB1, JB2, and both criteria, respectively. Across the sample, 59% (n = 715) demonstrated patterns of responding that satisfied both JB1 and JB2 across both tasks.

Class-Based Characterization of $200 Discounting Task

LCMMs were performed for the $200 discounting task and model fitness across each solution is displayed in the upper portion of **Table 2**. Model comparisons using SABIC favored a seven-class solution. A visualization of the favored solution is illustrated in the left panel of **Figure 1**. The range of decision-making patterns in the $200 dataset appeared best characterized by the presence of seven distinct subgroups of discounters. Among these subgroups, six demonstrated patterns of discounting that varied in terms of the estimated intercepts and rates of discounting. Additionally, modeling revealed that one subgroup did not correspond with most decision-makers in the sample. Whereas

TABLE 1 | Johnson and Bickel criteria applied to discounting tasks overall.

$200 Decision-making task		
	Count	**Percentage**
Systematic Local (JB1)	970	80.96
Systematic Global (JB2)	1125	93.91
Both Systematic	920	76.69
$40,000 Decision-making task		
	Count	**Percentage**
Systematic Local (JB1)	978	81.64
Systematic Global (JB2)	1045	87.23
Both Systematic	860	71.79

TABLE 2 | Evaluation of latest classes across discounting tasks.

	Fits with *N* Classes (200 USD)							
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
SABIC	75570.0	75581.7	75144.0	75131.6	75126.0	75152.0	**75122.9**	75134.1
AIC	75558.5	75564.5	75121.1	75102.9	75091.6	75111.8	**75077.0**	75082.4
Class 1%	100	∼100	23	3	<1	25	<1	0.668
Class 2%		<1	5	22	49	4	8	7
Class 3%			70	7	30	15	24	47
Class 4%				65	4	6	14	14
Class 5%					16	44	3	24
Class 6%						3	3	3
Class 7%							44	3
Class 8%								<1
	Fits with *N* Classes (40,000 USD)							
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
SABIC	75897.2	75623.2	75265.2	75115.4	75043.5	**75039.4**	75054.2	
AIC	75885.7	75606.0	75242.2	75086.8	75009.1	**74999.3**	75008.3	
Class 1%	100	36	36	22	26	24	26	
Class 2%		63	43	34	24	23	24	
Class 3%			19	35	22	20	22	
Class 4%				7	19	15	15	
Class 5%					6	11	<1	
Class 6%						4	8	
Class 7%							3	
Class 8%								

The best-performing model amongst fits is bolded for each dataset.

most demonstrated a trend of decreasing value as a function of time, this subgroup demonstrated responding in the opposing direction, see **Figure 2**. Additionally, 6 of the 7 responders failed both of the Johnson and Bickel (2008) criteria and 1 of the 7 failed the first of the Johnson and Bickel (2008) criteria. Additional information regarding the rates of systematic responding is provided in the right panel of **Figure 1** and **Table 3**. Information regarding the distribution of AUC within the $200 task across each of the classes is provided in **Table 4**.

Class-Based Characterization of $40,000 Discounting Task

LCMMs were performed for the $40,000 discounting task and model fitness across each solution is displayed in the lower portion of **Table 2**. Evaluations of model fitness using SABIC favored the six-group solution. A visualization of the favored solution is illustrated in the left panel of **Figure 3**. The range of decision-making patterns in the $40,000 dataset appeared best explained by the presence of six distinct subgroups of discounters that varied in terms of intercept and rate of discounting. The analysis did not indicate that there was any particular subgroup that varied meaningfully in terms of trends across increasing delays (i.e., in direction). As expected, the various subgroups of responders passed the Johnson and Bickel (2008) criteria in varying degrees, see the right panel of **Figure 3** and **Table 3**. Details regarding the distribution of AUC values within each class in the $40,000 task are provided in **Table 4**.

DISCUSSION

Methods for elucidating and analyzing discounting phenomena continue to be refined, with a growing push toward leveraging more sophisticated methods, such as mixed-effects models (Young, 2017, 2018). Mixed-effects models have many advantages and are more robust to issues that may exist regarding responders at extremes, e.g., non-systematic patterns (Young, 2017). However, it is common and expected for researchers evaluating discounting phenomena to characterize and describe the decision-makers that comprise the full sample. Although an improvement over previous methods based on the R^2 metric (Johnson and Bickel, 2008), based on historically observed behavioral patterns, and easily performed, the framework presented in Johnson and Bickel (2008) is only one means of characterizing a discounting dataset. As such, many approaches likely exist and are associated with benefits and drawbacks.

The approach reviewed in this work (LCMM) provides a novel means of evaluating for the presence of subgroups that appear qualitatively different than others in the sample. This extends the earlier Johnson and Bickel (2008) method by allowing the

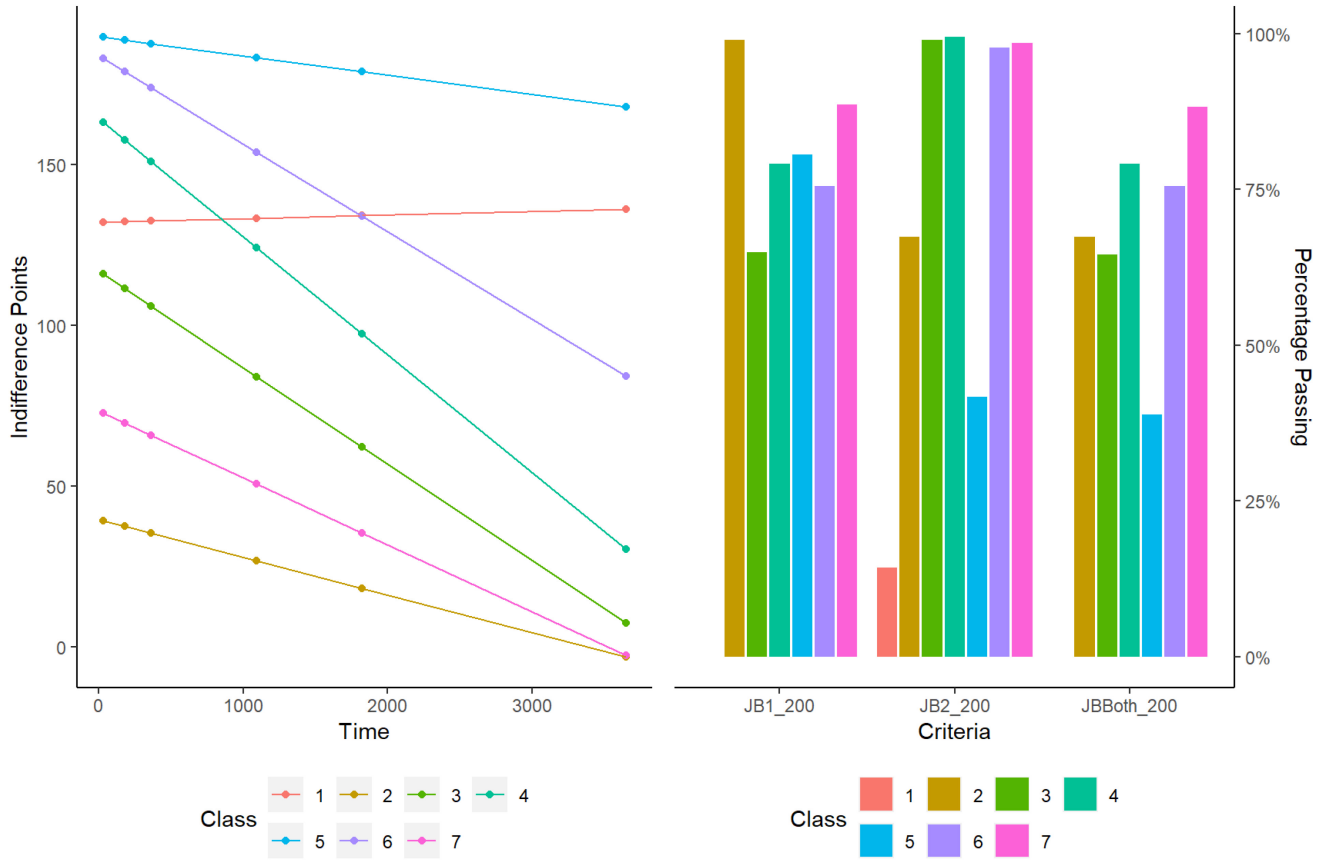


FIGURE 1 | Latent class analysis and systematic criteria of low magnitude task ($200).

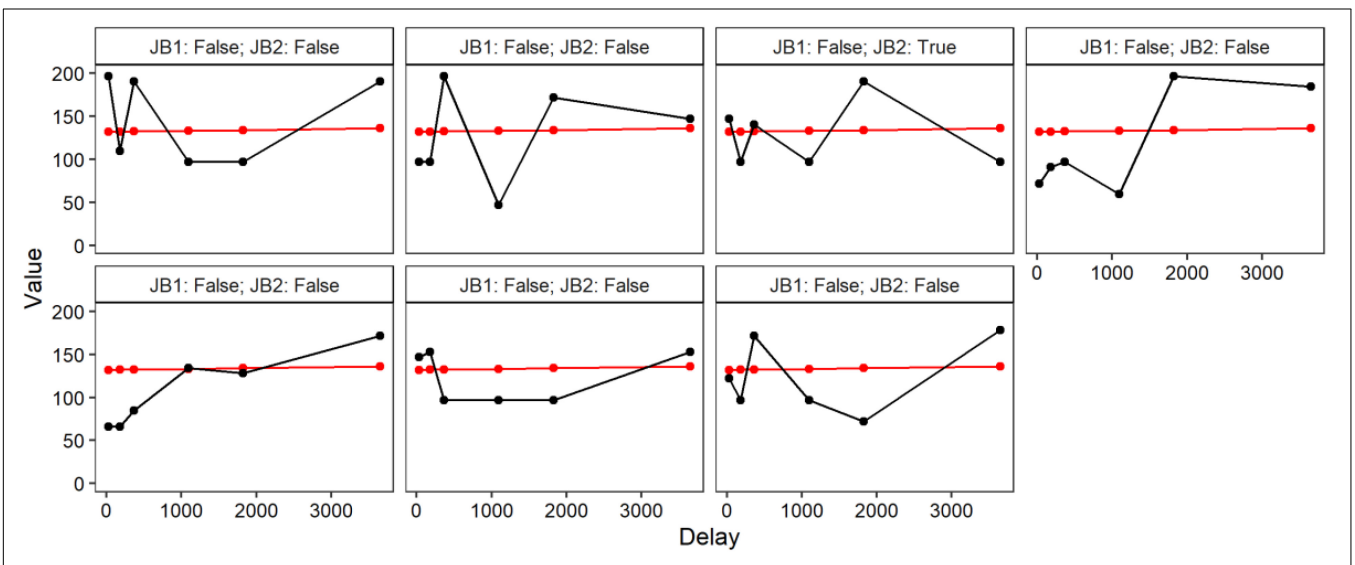


FIGURE 2 | Composition of Non-systematic discounter class.

standards for expected patterns to be derived from the sample itself (i.e., what the data will be compared against), rather than an *a priori* expectation of how individuals should respond in all instances. That is, no presumptions are necessary and researchers need not rely on any general criteria to make analytical decisions. However, it should be noted that the lack of presumptions

TABLE 3 | Latent class linear mixed modeling across discounting tasks.

	200 USD		
Class	**% Systematic local (JB1)**	**% Systematic global (JB2)**	**% Both systematic**
1 (*n* = 7)	0	14	0
2 (*n* = 101)	100	67	67
3 (*n* = 299)	64	98	64
4 (*n* = 172)	79	99	79
5 (*n* = 36)	80	41	38
6 (*n* = 45)	75	97	75
7 (*n* = 538)	88	98	88
	40,000 USD		
Class	**% Systematic local (JB1)**	**% Systematic global (JB2)**	**% Both systematic**
1 (*n* = 295)	82	98	81
2 (*n* = 284)	89	59	54
3 (*n* = 245)	79	97	78
4 (*n* = 180)	75	98	75
5 (*n* = 135)	75	94	75
6 (*n* = 59)	83	61	55

is not a universal positive. The Johnson and Bickel (2008) framework uses presumptions based on scientific observation to determine if data may be suspect. As such, the features noted in Johnson and Bickel (2008) provide a way to reference the greater population of decision-makers beyond the immediate sample and across multiple samples. The present framework of LCMM, while based on the data itself with no presumptions, categorizes participants into subgroups but is silent on whether responding deviates from expectations of orderly responding overall (i.e., correspond with the greater population from which they are derived). Furthermore, the number of subgroups is also likely to vary considerably across samples—with larger numbers of subsets being more likely with larger datasets.

In discussing how LCMMs can help guide discounting analysis, several points warrant noting as they relate to mixed-effects models. First, mixed-effects modeling already provides some means of accommodating responders at extremes because the manner of optimization (e.g., Maximum Likelihood Estimation) typically pulls estimates toward the group mean (Young, 2017). This effect, shrinkage, has the added benefit of drawing the more extreme (e.g., very low, very high) responses toward the mean of the group. These more extreme responses are typically those that result in participants failing one or more of the criteria provided in Johnson and Bickel (2008). As such, mixed-effects modeling alone can accommodate such challenges, to a degree. Second, it is necessary to note that the mixed-effects approach rests on the assumption that individual fits/estimates emerge from the same distribution of parameter values as the respective group. If the overall sample includes individuals or subgroups that differ characteristically from the overall sample (e.g., increasing rather than decreasing trends), then it is more appropriate to treat and analyze these groups separately (i.e., remove them from the planned analysis). When paired together, the LCMM approach complements the strengths of mixed-effects models quite nicely in this specific regard.

In furthering the argument for both LCMMs and mixed-effects modeling, this evokes questions regarding the framework provided by Johnson and Bickel (2008) and how these conventions fit in a data-driven approach. Indeed, the Johnson and Bickel (2008) criteria have been used as a proxy for data quality and the available literature is largely restricted to data that is considered to be "systematic" in nature. To address some of these questions, we wish to clarify that the Johnson and Bickel (2008) criteria have utility beyond their typical use as the basis for including or excluding responders. For instance, these have good descriptive utility for characterizing responding within a dataset and provide an easily interpreted index with which to appraise an overall sample. Indeed, this provides a standard with which to classify trends in responding that can be compared across various samples. As such, it is reasonable to apply both the Johnson and Bickel (2008) and LCMMs but base decisions on what data are included in mixed-effects modeling based on the clusters identified in the LCMMs. However, it warrants reiterating that using LCMMSs to include or exclude data relies on an individual data set's classification within the overall data set, meaning that decisions to include or exclude would be based on the entire class rather than on the specifics of any individual data set.

Limitations

Although data-driven, robust, and applicable to discounting, LCMMs do present several limitations. First, LCMMs entail

TABLE 4 | Distribution of point-based area under curve.

	$200 Choice task			$40,000 Choice task		
Class	**M (SD)**	**Mdn (Q1-Q3)**	**N**	**M (SD)**	**Mdn (Q1-Q3)**	**N**
1	0.66 (0.05)	0.62 (0.57–0.68)	7	0.42 (0.09)	0.36 (0.21–0.43)	295
2	0.05 (0.03)	0.03 (0.02–0.04)	101	0.88 (0.07)	0.82 (0.64–0.88)	284
3	0.28 (0.07)	0.22 (0.09–0.28)	299	0.67 (0.08)	0.61 (0.49–0.67)	245
4	0.46 (0.08)	0.41 (0.27–0.47)	172	0.25 (0.09)	0.18 (0.09–0.25)	180
5	0.89 (0.08)	0.84 (0.71–0.9)	36	0.13 (0.07)	0.08 (0.04–0.11)	135
6	0.7 (0.07)	0.65 (0.58–0.69)	45	0.06 (0.05)	0.03 (0.02–0.04)	59
7	0.13 (0.07)	0.08 (0.04–0.13)	538	—	—	—

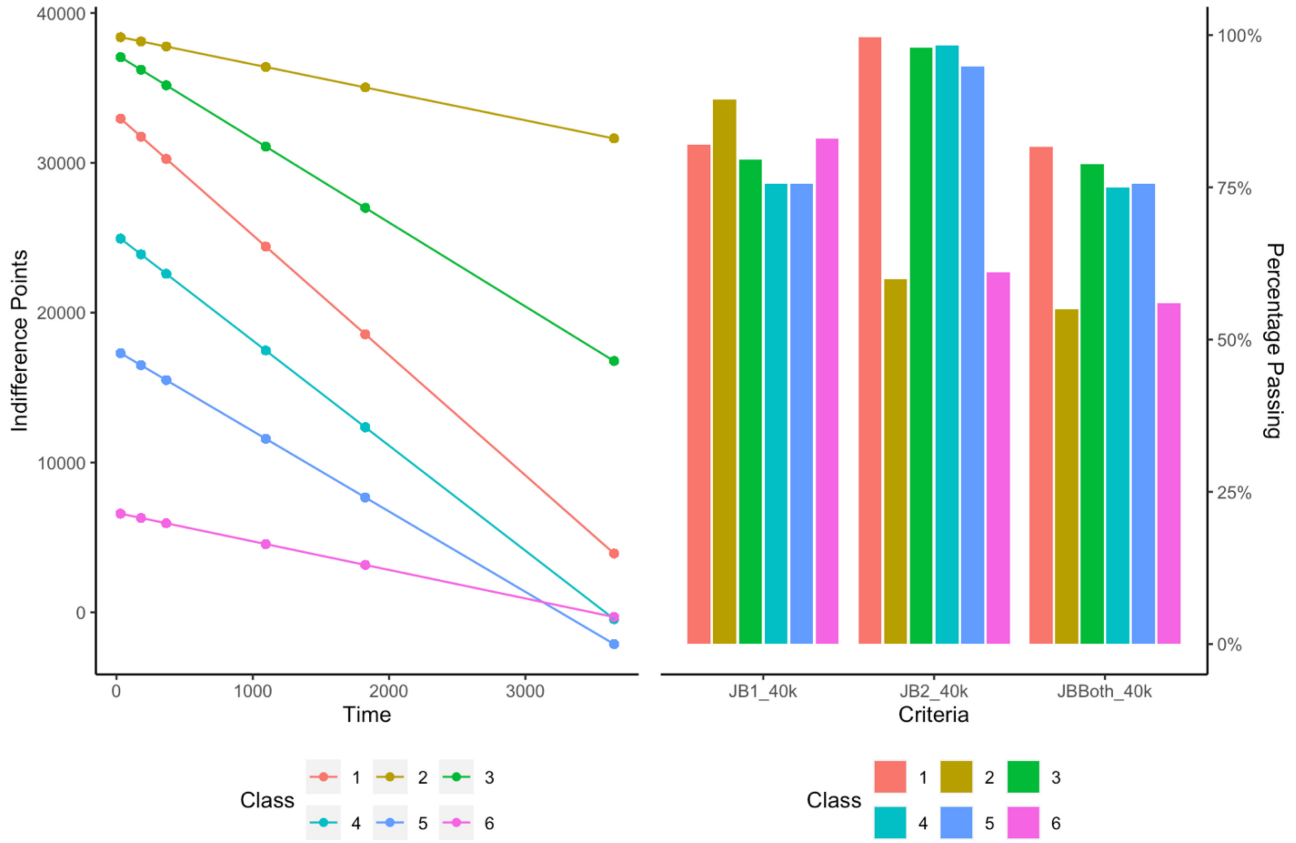


FIGURE 3 | Latent class analysis and systematic criteria of high magnitude task ($40,000).

both considerable flexibility and considerable complexity (van de Schoot et al., 2017). For example, the *lcmm* method applied provides a range of options for the researcher to fit individual data (e.g., linear, n-spline), to compare mixture models (e.g., 1- vs. 2- vs. 3-group fits), and to explore how many clusters might exist (e.g., 2 vs. 10). The decision to use a linear model in this evaluation was effective for providing initial support for LCMMs in this specific regard; however, additional research and study with models more commonly used in the literature is warranted (e.g., n-spline, hyperbolic, hyperboloid). Second, and this challenge is shared with mixed-effects modeling, computational requirements scale poorly with complexity. Even with modern hardware, individual LCMMs may take several minutes, perhaps hours, to converge with complex data sets. Third, few guidelines currently exist with which to perform and then evaluate the relative fitness of LCMMs (Weller et al., 2020). For example, initial fits can be judged based on the AIC, BIC, the SABIC, or the log of the likelihood itself, but ultimately, the analyst has considerable freedom concerning model building (e.g., to vary the number of classes or covariates; van de Schoot et al., 2017). As such, LCMMs entail far more complexity than the algorithm-based approaches to screening discounting data. Fourth, we acknowledge that level of access to HCP demographic data for the present report was restricted to broad sample estimates (e.g., multi-year age range) which precluded a careful analysis of associations between participant characteristics and latent-class membership. We note, though, that HCP data were drawn from healthy young adults with no pre-existing psychiatric or neuropsychiatric disorders, thereby representing only a subset of the larger population and potentially constraining the range of response variability used to identify latent classes. Lastly, the LCMM approach used in this study was evaluated with just one publicly available dataset. As such, researchers should continue to evaluate multiple methods for characterizing individual discounting patterns.

Although LCMMs and mixed-effects modeling increase the complexity of work in discounting, we suggest that researchers in this area consider the use of these methods for several reasons. First, mixed-effects methods already provide a means of accommodating responders at extremes (Young, 2017, 2018). Indeed, these methods should be explored before conducting planned analyses but should not be considered a replacement for carefully inspecting the empirical data. Second, when used together, both empirical reviews and LCMMs can be used to explore the degree to which the data correspond within the sample as well as to the greater population from which they are assumed to emerge. Combining these approaches balances the desire to both retain as much data as possible and exclude data that might limit the generality of the analysis.

AUTHOR'S NOTE

The source code necessary to recreate this work is publicly hosted in a repository at: https://github.com/miyamot0/LatentClassDiscounting. The terms of the Human Connectome Project require that all parties request access to the data from the following location: https://www.humanconnectome.org.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: http://www.humanconnectomeproject.org/.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Human Connectome Project and was managed and organized by the National Institute of Health. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SG, JS, and DR: study conception and design. SG, JS, DR, and MJ: analysis and interpretation of results. SG, GN, JS, DR, and MJ: draft manuscript preparation. All authors reviewed the results and approved the final version of the manuscript.

FUNDING

JS was supported by the National Institute on Drug Abuse (NIDA; R03 DA054098). GN was supported by NIDA (T32 DA07209). MJ was supported by NIDA grants R01DA042527 and R01 DA049814. MA was supported by NIAAA grant R01AA027255.

REFERENCES

Akaike, H. (1974). A new look at the statistical model identification. *IEEE Trans. Automat. Contr.* 19, 716–723. doi: 10.1109/tac.1974.1100705

Amlung, M. T., Marsden, E., Holshausen, K., Morris, V., Patel, H., Vedelago, L., et al. (2019). Delay discounting as a transdiagnostic process in psychiatric disorders: a meta-analysis. *JAMA Psychiatry* 76, 1176–1186. doi: 10.1001/jamapsychiatry.2019.2102

Amlung, M. T., Vedelago, L., Acker, J., Balodis, I., and MacKillop, J. (2017). Steep delay discounting and addictive behavior: a meta-analysis of continuous associations: delay discounting and addiction. *Addiction* 112, 51–62. doi: 10.1111/add.13535

Bickel, W. K., Koffarnus, M. N., Moody, L., and Wilson, A. G. (2014). The behavioral-and neuro-economic process of temporal discounting: a candidate behavioral marker of addiction. *Neuropharmacology* 76, 518–527. doi: 10.1016/j.neuropharm.2013.06.013

Bickel, W. K., Snider, S. E., Quisenberry, A. J., and Stein, J. S. (2017). Reinforcer pathology: the behavioral economics of abuse liability testing. *Clin. Pharmacol. Ther.* 101, 185–187. doi: 10.1002/cpt.443

Campbell, K. W., Voss, A. T., Acuff, S. F., Pebley, K., Berlin, K. S., Martens, M. P., et al. (2021). Statistically derived patterns of behavioral economic risk among heavy-drinking college students: a latent profile analysis. *Exp. Clin. Psychopharmacol.* 29, 191–202. doi: 10.1037/pha0000420

Chung, W., Sun, C.-K., Tsai, I.-T., Hung, K.-C., Chiu, H.-J., Tzang, R.-F., et al. (2021). A systematic review and meta-analysis on the clinical implications of probability discounting among individuals with Internet gaming disorder. *Sci. Rep.* 11:3177. doi: 10.1038/s41598-021-82822-z

Du, W., Green, L., and Myerson, J. (2002). Cross-cultural comparisons of discounting delayed and probabilistic rewards. *Psychol. Rec.* 52, 479–492. doi: 10.1007/bf03395199

Gilroy, S. P. (2017). *Discountingtools: R Package to Assist in analyzing Discounting Data*. Available Online at: https://github.com/miyamot0/discountingtools

Gilroy, S. P., and Hantula, D. A. (2018). Discounting model selection with areaâĂŘbased measures: a case for numerical integration. *J. Exp. Anal. Behav.* 109, 433–449. doi: 10.1002/jeab.318

Hagenaars, J. A., and McCutcheon, A. L. (2002). *Applied Latent Class Analysis*. Cambridge: Cambridge University Press.

Johnson, M. W., and Bickel, W. K. (2008). An algorithm for identifying nonsystematic delay-discounting data. *Exp. Clin. Psychopharmacol.* 16, 264–274. doi: 10.1037/1064-1297.16.3.264

Johnson, M. W., and Bruner, N. R. (2012). The sexual discounting task: HIV risk behavior and the discounting of delayed sexual rewards in cocaine dependence. *Drug Alcohol Depend.* 123, 15–21. doi: 10.1016/j.drugalcdep.2011.09.032

Johnson, M. W., Strickland, J. C., Herrmann, E. S., Dolan, S. B., Cox, D. J., and Berry, M. S. (2020). Sexual discounting: a systematic review of discounting processes and sexual behavior. *Exp. Clin. Psychopharmacol.* 29, 711–738. doi: 10.1037/pha0000402

Johnson, P. S., Herrmann, E. S., and Johnson, M. W. (2015). Opportunity costs of reward delays and the discounting of hypothetical money and cigarettes. *J. Exp. Anal. Behav.* 103, 87–107. doi: 10.1002/jeab.110

Kyonka, E. G., and Schutte, N. S. (2018). Probability discounting and gambling: a meta-analysis. *Addiction* 113, 2173–2181. doi: 10.1111/add.14397

Lazarsfeld, P., and Henry, N. (1968). *Latent Structure Analysis*. Boston, MA: Houghton Mifflin Harcourt.

Lubke, G., and Neale, M. C. (2006). Distinguishing between latent classes and continuous factors: resolution by maximum likelihood? *Multivariate Behav. Res.* 41, 499–532. doi: 10.1207/s15327906mbr4104_4

MacKillop, J. (2016). The behavioral economics and neuroeconomics of alcohol use disorders. *Alcohol. Clin. Exp. Res.* 40, 672–685. doi: 10.1111/acer.13004

MacKillop, J., Amlung, M. T., Few, L. R., Ray, L. A., Sweet, L. H., and Munafò, M. R. (2011). Delayed reward discounting and addictive behavior: a meta-analysis. *Psychopharmacology* 216, 305–321. doi: 10.1007/s00213-011-2229-0

Morissette, L., and Chartier, S. (2013). The k-means clustering technique: general considerations and implementation in Mathematica. *Tutor. Quant. Methods Psychol.* 9, 15–24. doi: 10.20982/tqmp.09.1.p015

Muthén, B. (2004). "Latent variable analysis: growth mixture modeling and related techniques for longitudinal data," in *Handbook of Quantitative Methodology for the Social Sciences*, ed. D. Kaplan (Newbury Park, CA: Sage), 345–368.

Muthén, B., and Muthén, L. K. (2000). Integrating person-centered and variable-centered analyses: growth mixture modeling with latent trajectory classes. *Alcohol. Clin. Exp. Res.* 24, 882–891. doi: 10.1111/j.1530-0277.2000.tb02070.x

Myerson, J., Green, L., and Warusawitharana, M. (2001). Area under the curve as a measure of discounting. *J. Exp. Anal. Behav.* 76, 235–243.

Naudé, G. P., Strickland, J. C., Reed, D. D., and Amlung, M. T. (2021). Delay discounting and neurocognitive performance in young adults with differential patterns of substance use: findings from the Human Connectome Project. *Exp. Clin. Psychopharmacol.* [Online ahead of print]. doi: 10.1037/pha0000469

Petry, N. M., and Madden, G. J. (2010). "Discounting and pathological gambling," in *Impulsivity: The Behavioral and Neurological Science of Discounting*, eds G. J. Madden and W. K. Bickel (Washington, DC: American Psychological Association), 273–294. doi: 10.1037/12069-010

Proust-Lima, C., Philipps, V., and Liquet, B. (2015). Estimation of extended mixed models using latent classes and latent processes: the R package lcmm. *arXiv [Preprint]* doi: 10.48550/arXiv.1503.00890

R Core Team (2021). *R: A Language and Environment for Statistical Computing*. Vienna: R Foundation for Statistical Computing.

Schwarz, G. (1978). Estimating the dimension of a model. *Ann. Stat.* 6, 461–464. doi: 10.1214/aos/1176344136

Smith, K. R., Lawyer, S. R., and Swift, J. K. (2018). A meta-analysis of nonsystematic responding in delay and probability reward discounting. *Exp. Clin. Psychopharmacol.* 26, 94–107. doi: 10.1037/pha0000167

van de Schoot, R., Sijbrandij, M., Winter, S. D., Depaoli, S., and Vermunt, J. K. (2017). The GRoLTS-checklist: guidelines for reporting on latent trajectory studies. *Struct. Equ. Modeling* 24, 451–467. doi: 10.1080/10705511.2016.1247646

Van Essen, D. C., Smith, S. M., Barch, D. M., Behrens, T. E., Yacoub, E., and Ugurbil, K. (2013). The WU-Minn human connectome project: an overview. *Neuroimage* 80, 62–79. doi: 10.1016/j.neuroimage.2013.05.041

Weller, B. E., Bowen, N. K., and Faubert, S. J. (2020). Latent class analysis: a guide to best practice. *J. Black Psychol.* 46, 287–311. doi: 10.1177/0095798420930932

Yeh, Y.-H., Myerson, J., and Green, L. (2021). Delay discounting, cognitive ability, and personality: what matters? *Psychon. Bull. Rev.* 28, 686–694. doi: 10.3758/s13423-020-01777-w

Young, M. E. (2017). Discounting: a practical guide to multilevel analysis of indifference data. *J. Exp. Anal. Behav.* 108, 97–112. doi: 10.1002/jeab.265

Young, M. E. (2018). Discounting: a practical guide to multilevel analysis of choice data. *J. Exp. Anal. Behav.* 109, 293–312. doi: 10.1002/jeab.316

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Advantages of publishing in Frontiers

OPEN ACCESS
Articles are free to read for greatest visibility and readership

FAST PUBLICATION
Around 90 days from submission to decision

HIGH QUALITY PEER-REVIEW
Rigorous, collaborative, and constructive peer-review

TRANSPARENT PEER-REVIEW
Editors and reviewers acknowledged by name on published articles

Frontiers
Avenue du Tribunal-Fédéral 34
1005 Lausanne | Switzerland

Visit us: www.frontiersin.org
Contact us: frontiersin.org/about/contact

REPRODUCIBILITY OF RESEARCH
Support open data and methods to enhance research reproducibility

DIGITAL PUBLISHING
Articles designed for optimal readership across devices

FOLLOW US
@frontiersin

IMPACT METRICS
Advanced article metrics track visibility across digital media

EXTENSIVE PROMOTION
Marketing and promotion of impactful research

LOOP RESEARCH NETWORK
Our network increases your article's readership