Perspectives on Behavior Science (2019) 42:419–432
https://doi.org/10.1007/s40614-019-00218-x

SPECIAL ISSUE ON ADDICTIONS

Linking Delay Discounting and Substance Use Disorders: Genotypes and Phenotypes

Suzanne H. Mitchell [1]

Published online: 10 July 2019

Abstract

Research supports the idea that "delay discounting," also known as temporal discounting, intertemporal choice, or impulsive choice, is a transdisease process with a strong connection to substance use disorders (SUDs) and other psychopathologies, like attention deficit hyperactivity disorder and depression. This article briefly reviews the evidence used to conclude that delay discounting is heritable and should be considered to be an endophenotype, as well as evidence of its behavioral and genetic associations with SUDs. It also discusses the limitations that should be considered when evaluating the strength of these associations. Finally, this article briefly describes research examining relationships among delay discounting and SUD-associated intermediate phenotypes to better understand the conceptual relationships underlying the links between SUDs and delay discounting, and identifies research gaps that should be addressed.

Keywords Behavioral genetics · Addiction · Nicotine · Alcohol · Delay discounting · Impulsivity

Introduction

Basic and applied behavior analysts have been growing more interested in the role of genetics in psychopathology. One such psychopathology is addiction, which the American Psychiatric Association (APA) defines as synonymous with "substance use disorder" (SUD) (APA, 2013): "a brain disease that is manifested by compulsive *substance use* despite harmful consequence" (emphasis added). However, recent conceptualizations of addiction have distinguished between substance and nonsubstance addiction (e.g., Zou et al., 2017). By definition, both require that individuals engage in

✉ Suzanne H. Mitchell
mitchesu@ohsu.edu

[1] Behavioral Neuroscience, Psychiatry, the Oregon Institute of Occupational Health Sciences, Oregon Health & Science University, 3181 SW Sam Jackson Park Road, Portland, OR 97239, USA

behaviors that result in problematic consequences. Further, both use subcategories to increase clinical precision. In terms of substance addiction, a diagnosis of a SUD usually specifies the particular substance being used, such as alcohol in alcohol use disorder or marijuana in cannabis use disorder. Likewise, diagnoses of nonsubstance or behavioral addictions specify the particular behavior that is problematic, such as gambling in pathological gambling disorder or sexual activity in sex addiction. However, substance and nonsubstance addictions differ substantially in the degree to which researchers have explored their characteristics. This may be partly attributable to national research funding priorities, which prioritize research on SUDs. As a result, the extent to which SUD and nonsubstance addiction share epidemiological, neurobiological, behavioral, and therapeutic features is currently unclear. Filling this knowledge gap is critical if researchers and practitioners are to determine whether lessons learned from research and treatment of SUDs can be applied to nonsubstance addictions.

Identifying Genetic and Phenotypic Correlates of SUD

The present article focuses only on addiction research associated with SUD because there is a significant body of research examining its genetic correlates, in contrast to the nascent state of research in the genetics of nonsubstance addiction. SUD has long been viewed as having a genetic component based on family pedigree studies, twin studies, and adoption studies that examined commonly used substances like alcohol, nicotine, and marijuana (e.g., Hopfer, Stallings, Hewitt, & Crowley, 2003; Walters, 2002). Studies using animal models have further supported the importance of genetics in substance use, e.g., alcohol: Barkley-Levenson and Crabbe (2014); and nicotine: Chen, Hiler, Tolley, Matta, and Sharp (2012). It is not surprising that human studies of SUD heritability for less frequently used substances, like cocaine or methamphetamine, are lacking; though studies using rodents indicate their use also involves a heritable component (e.g., Eastwood, Barkley-Levenson, & Phillips, 2014).

Unfortunately, although there is clearly a genetic contribution to SUD, identifying specific genes has been difficult due to a number of complicating factors, which could be addressed by additional research. First, SUDs can easily be demonstrated to involve both genetic (G) and environmental (E) factors, and there are compelling data indicating that G x E interactions are also critical to determining whether a particular individual manifests a SUD or not (e.g., Chartier, Karriker-Jaffe, Cummings, & Kendler, 2017). Oft-provided examples to demonstrate the importance of G x E interactions in SUD include the lack of alcohol use disorders in populations for whom alcohol drinking is culturally or religiously forbidden, increased vulnerability to SUD during adolescence or increased likelihood of relapse to use during periods of heightened stress at any age. Second, it is difficult to disentangle the genetics of SUDs from the genetics of commonly comorbid psychiatric disorders, such as attention deficit hyperactivity disorder or depression. Partly this difficulty stems from the high probability that nongenetic etiological commonalities, such as early life trauma, affect the occurrence and severity of both the SUD and the psychiatric disorder. It is further exacerbated by the action of positive feedback processes by which substance use augments the symptoms of the psychiatric disorder, such as anxiety, which in turn

increases subsequent substance use (Carey et al., 2016; Kendler, Prescott, Myers, & Neale, 2003; Reginsson et al., 2018). A third complicating factor is related to the complex biological mechanisms by which genes affect an individual's behavior. Multiple biological processes intervene between the possession of a specific genotype and an individual's behavior. Considering the nature of genes and an individual's genotype will make the source of this complication clearer. Each individual's genome is composed of numerous chromosomes, 23 pairs in humans, 21 in rats, and 20 in mice, and each chromosome contains multiple genes. The genes themselves are made up of double strands of deoxyribonucleic acid (DNA), formed from connected pairs of molecules or bases (adenine paired with thymine and guanine paired with cytosine). Although the strands are continuous, different genes are associated with different lengths and so are composed of different number of pairs of bases. Individual differences in the specific set of these bases at a particular locus in the gene are called genetic polymorphisms. For example, at one locus (SNP rs 4680 in humans) there can be either two adenine nucleobases, an adenine and a guanine or two guanines. It is interesting that studies examining individuals with each of these three genetic polymorphisms at this locus have demonstrated that having a pair of two adenine nucleobases, rather than either the adenine + guanine or two guanines, is associated with heightened choice of the delayed alternative in the monetary choice task used to assess delay discounting, as discussed in more depth later in this article. However, the precise intervening steps by which these differences at a single SNP locus on the genome are translated into behavior is not entirely known. It is currently unclear how much the lack of basic biological knowledge illustrated in this example will slow progress in confirming the identity of genes and G x E interactions affecting the SUD phenotype, or whether it will merely retard our understanding of the mechanisms explaining the linkage. Finally, a fourth complicating factor of particular interest to behavior analysts is that a SUD diagnosis requires an individual to engage in multiple behaviors associated with substance use, each of which could be linked to multiple genes. These behavioral phenotypes include, but are not limited to, drug seeking, drug taking, and reporting particular subjective and physiological effects acutely and chronically. Underscoring their importance, many are explicitly incorporated into the diagnostic elements required for a SUD diagnosis by the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*), 5th edition (APA, 2013). As an aside, qualitative and quantitative changes in these behaviors would potentially be required to accommodate those less established, nonsubstance addictions such as gambling, self-tanning, or social media use mentioned earlier (Byun et al., 2009; Nolan, Taylor, Liguori, & Feldman, 2009; Reed, Kaplan, Becirevic, Roma, & Hursh, 2016). Such an expansion in the behavioral phenotypes might result in additional genetic polymorphisms needing to be identified, or may weaken the importance assigned to some, already-identified polymorphisms.

A critical strategy to address this fourth complication is that researchers must characterize SUD-associated phenotypes and factors that affect their manifestation substantially, that is, the operating three term contingencies, before trying to confirm their genetic bases. Behavior analysts are in an excellent position to add to the understanding of the role of genetics in SUDs because they have a sophisticated understanding of the complexity of delineating the three term contingencies in substance use. This understanding provides an excellent basis when thinking about how individual differences in sensitivity to stimuli and reinforcer contingencies can

influence the initiation, maintenance, and resistance to the extinction of problematic substance use. Only clear delineations of the individual differences in the SUD-related behavioral phenotypes and the variables influencing their expression will provide a workable foundation for researchers to link these behaviors to particular genes.

One approach to delineating these phenotypes can be characterized as "splitting," in which behavioral or nonbehavioral phenotypes specific to *individual* SUDs are identified. For example, research clearly indicates that faster metabolism of nicotine is associated with shorter intercigarette-intervals and an increased susceptibility to nicotine dependence, and this biological process has been linked to single nucleotide polymorphisms of the cytochrome P450 2A6 (CYP2A6) gene (see Chenoweth & Tyndale, 2013, for review). An alternative approach to splitting is "lumping," in which phenotypes associated with *multiple* SUDs or addictions are identified (Morrow & Flagel 2016). For example, Billieux, Schimmentic, Khazaal, Mauragea, and Heerena (2015) focused on the degree of functional impairment experienced by an individual and the stability of this dysfunction as a molar characteristic of SUD. Others have focused more on biological markers as phenotypes. For example, Everitt and Robbins (2005) created a SUD diagnostic criterion based on there being a transition from occasional, casual substance use activity to compulsive, stimulus-/contingency-independent activity. However, a key feature of their definition is that there must be alterations in the location of neural activity from prefrontal cortex to striatal regions accompanying the behavioral change (Everitt & Robbins, 2005).

There are advantages and disadvantages to adopting splitting or lumping approaches. Although lumping may provide "big-picture" phenotypes and genotypes, it also results in researchers ignoring possibly important differences amongst SUDs. This disadvantage can be illustrated by considering an extreme case, a hypothetical study in which comparisons are made between the phenotypes and genotypes of healthy controls and those diagnosed with a SUD, be those nicotine dependent smokers or methamphetamine dependent individuals. Although not as extreme, researchers often lump people diagnosed with alcohol use disorder together, ignoring research indicating that there are phenotypic and genotypic differences between those with family histories of alcohol problems and those without (e.g., compare Czapla et al., 2017, and Kareken et al., 2013). In contrast, the splitting approach identifies phenotypic differences between healthy controls and a specific SUD or subset of individuals within that SUD, and is unconcerned about whether that phenotype is observed in other SUDs. From a gene discovery perspective, splitting approaches will be more likely to identify genes associated with phenotype linked to a single particular SUD, such as CYP2A6 which appears to have a role only in nicotine metabolism relevant to SUDs. With lumping approaches, it will be more difficult to identify genes that have more subtle or substance specific roles, but genes with relatively larger effect sizes or more general roles in SUD ("transdisease phenotypes"), should be more easily identified.

The Research Domain Criteria (RDoC) initiative from the National Institutes of Health Institute of Mental Health [NIMH] (NIMH, n.d.) supports the search for "transdisease" phenotypes that encompass not only different SUDs but also other psychiatric disorders such as depression and schizophrenia. For transdisease phenotypes already identified, e.g., novelty seeking (Wingo, Nesil, Choi, & Li, 2016), there are data indicating a strong heritable component. Phenotypes having such genetic components, coupled with being continuous, quantifiable measures linked to a

psychopathology like SUD, are referred to as endophenotypes (Gottesman & Gould, 2003). Another term, "intermediate phenotype," was originally developed to label biological traits or processes linked to disorders like SUDs, without meeting all of the criteria used to classify a phenotype as an endophenotype, but more recently it has been used as a synonym for endophenotype (MacKillop & Munafò, 2013) and both terms will be used interchangeably in this article. As noted earlier, novelty seeking can be classified as a transdisease endophenotype, but a number of research papers have suggested that another is "delay discounting" (Bickel & Mueller, 2009; Bickel, Jarmolowicz, Mueller, Koffarnus, & Gatchalian, 2012; Volkow & Baler, 2015). The remainder of this article reviews the evidence used to conclude that delay discounting is an endophenotype, its association with SUD and, finally, discusses progress and limitations associated with understanding the associations between delay discounting and other phenotypes linked with SUD.

Delay Discounting as an Endophenotype

There are clear data indicating that delay discounting is heritable. In humans, Anokhin and colleagues (Anokhin, Golosheykin, Grant, & Heath, 2011; Anokhin, Grant, Mulligan, & Heath, 2015) reported correlations of the range 0.5–0.6 in monozygotic twins compared to 0.1–0.3 in dizygotic twins, using the classical twin study approach of comparing the level of association for indices of delay discounting between twin pairs. These correlations indicate a genetic contribution (G) to the delay discounting performance of approximately 0.6 (60%), derived from the difference between the monozygotic versus dizygotic twin correlations. These heritability coefficients are consistent with data from studies examining differences in delay discounting between pairs of inbred rat strains, which are assumed to arise from differences in genotype because individuals within each inbred strain have identical genotypes (e.g., Anderson & Woolverton, 2005: Lewis and Fischer 344 inbred rat strains obtained from Harlan, Indianapolis IN; Stein, Pinkston, Brewer, Francisco, & Madden, 2012: Lewis and Fischer 344 inbred rat strains obtained from an unspecified source unspecified); though it should be noted that estimates of heritability cannot be calculated with any confidence when only two inbred strains are examined. More compelling, several studies exist in which delay discounting was examined in multiple inbred mouse and rat strains; these studies have suggested a heritability coefficient of about 0.5 (Garcia & Kirkpatrick, 2013; Isles, Humby, Walters, & Wilkinson, 2004; Richards et al., 2013; Wilhelm & Mitchell, 2009). In addition to the similarity to the estimates derived from the human studies, these rodent data are made more persuasive because they were obtained using different rodent species, strains, and procedures to quantify delay discounting. All of which increases confidence in the conclusion that delay discounting is strongly heritable in rodents and people alike.

Using a similar logic to that applied to SUD earlier in this article, after accepting the evidence that delay discounting is heritable, a next logical step is to identify the specific genes that contribute to the delay discounting phenotype. Complications arise in doing this because, like SUD, delay discounting is a complex phenotype, implying the action of multiple genes. Currently gene discovery strategies for SUD center on identifying genes associated with specific behavioral components that contribute to a SUD being

observed, such as sensitivity to drug-associated cues. A similar strategy for delay discounting will require better delineations of component processes of delay discounting, because each process might be associated with distinct genotypes. To illustrate the types of processes that might be involved, imagine an individual exhibiting higher levels of delayed reward discounting, as demonstrated by a greater likelihood of choosing a smaller, sooner reward over a larger, later reward. This choice pattern might be attributable to the action and interaction of any of the following independent, component processes.

Reward Size Related

1. Higher motivation for the smaller, sooner reward; possibly exacerbated if the smaller, sooner reward is present at the time of the choice or by the physiological state of the individual.
2. Lower sensitivity to differences in reward size between the smaller, sooner and larger, later rewards, which may reduce the relative attractiveness of the later reward.

Reward Delay Related

3. Higher sensitivity to the length of the delay associated with the larger reward, possibly due to differences in temporal processing.
4. Higher levels of aversion to the prospect of waiting for reward, independent of the length of the delay period.
5. Higher levels of discomfort associated with any uncertainty associated with delivery of the reward in the future.

Integration of Alternatives

6. Low integration of valuation information for the smaller, sooner, and larger, later rewards resulting in a reliance on any preexisting bias, presumably toward the smaller, sooner reward.

It should be noted that these processes are assumed. Researchers do not ordinarily assess components of delay discounting and, for some processes, assessment tools are lacking or are underdeveloped. However, it is strongly recommended that this should be a focus of future research because the independent contributions of these processes may be responsible for trait-like individual differences in delay discounting, and they may be differentially affected by manipulations aimed at altering delay discounting (see research by Kim Kirkpatrick's group for a notable exception to this neglect, e.g., Marshall, Smith, & Kirkpatrick, 2014). Because these data are lacking, the individual differences in the delay discounting phenotype are discussed during the remainder of this article as if they arise through the action of a single process.

The strategy used by most studies to examine the genetic basis of the delay discounting phenotype has been to identify candidate genes in humans, selected

because of their links to neuropharmacological processes known to affect delay discounting. Examining individuals with polymorphisms in catechol-ortho-methyl-transferase (COMT) provides an example of this approach. COMT enzymes are critical in metabolizing dopamine. This neurotransmitter is known to play a role in delay discounting in prefrontal regions of the brain such that increased dopamine is associated with more delay discounting (e.g., Gianotti, Figner, Ebstein, & Knoch, 2012; Paloyelis, Asherson, Mehta, Faraone, & Kuntsi, 2010), although the exact mechanism by which this occurs is not entirely known. The efficacy with which COMT acts is determined by the presence of G [guanine] and A [adenine] in the codon in the COMT gene; G codes for valine amino acid whereas A codes for methionine amino acid, which is associated with less efficient metabolism of dopamine resulting in increased dopamine availability. Accordingly, it is not surprising that MacKillop et al. (2015) reported that individuals with two copies of the gene coding for adenine nucleobases (A/A) exhibited higher discounting than those with the adenine/guanine (A/G) or guanine/guanine (G/G) polymorphisms (also Smith & Boettiger, 2012). Polymorphisms in other genes have been identified using a similar strategy drawing on knowledge about the genetic bases of the dopamine and other neurotransmitter systems (e.g., Eisenberg et al., 2007; but also see Hart, de Wit, & Palmer, 2013, for a study indicating that these studies may have replication issues).

Candidate gene studies in rodents are surprisingly lacking. One reason for this lack is that traditionally mouse models have been used to examine the role of genetics in SUD behaviors. However, relatively few research groups have examined delay discounting in mouse models (e.g., Nautiyal et al., 2017), perhaps because of the difficulties associated with producing stable delay discounting in mice or the long duration of required training (see Mitchell, 2014, for a protocol describing mouse discounting procedures and troubleshooting tips). One notable exception is Nick Grahame (e.g., O'Tousa, Matson, & Grahame, 2013; Oberlin & Grahame, 2009). However, the Grahame lab has not focused on identifying candidate genes associated with delay discounting, but rather has confirmed that different genotypes, related to ethanol use, exhibit differences in delay discounting. A second reason for the lack of candidate gene studies in rodents is that, although researchers using rats have produced stable delay discounting without problems, these teams have focused on identifying the neuroanatomical and neuropharmacological correlates of the behavior rather than on identifying the specific genes underlying the delay discounting phenotype (e.g., Frost & McNaughton, 2017).

Although not an issue until a body of literature is created, caution should be exerted when comparing identified genes in rodents to those derived from human candidate gene studies and when interpreting G x E interactions. There are two sources for this recommendation of interpretational hesitancy: procedural differences between studies using different species that might affect some of the putative component processes of delay discounting and not others, as might the radically different environments in which humans and rodents are studied. With respect to the procedural differences, for example, in human or rodents for whom high delay discounting is driven by differences in sensitivity to delay (reward delay processing), candidate gene studies might identify

similar gene targets despite different delay lengths in the experimental procedures (days and months for people, seconds for rodents). However, for individuals in whom sensitivity to differences in reward size (reward size processing) is the key driver of high delay discounting, use of hypothetical rewards in humans and real rewards in rodents might cause different genes to be identified even though both species' discounting is driven by the same basic process. This is speculation but without additional research examining the component processes of delay discounting, interpretation of any differences in identified genes will be difficult. With respect to the environmental contribution to delay discounting behavior, for example, the richness of human versus rodent environments may create contrasts that qualitatively and quantitatively effect reward processing in rodents and people. However, without the first steps in which common genes are identified, evaluating species-specific or process-specific nuances is not feasible.

Extending the earlier candidate gene studies, and in a collaboration with 23andMe (https://www.23andme.com/), Sanchez-Roige et al. (2018) reported the results of a genome-wide association study (GWAS) for delay discounting in people. Although there were some genes that approached the conventional statistical threshold for GWAS studies of 5×10^{-8}, only GPM6B, a glycoprotein widely expressed in the brain and associated with cellular housekeeping and membrane trafficking, was significantly associated with delay discounting. Genes identified though candidate gene studies, such as COMT mentioned earlier, did not pass the statistical threshold. The reason for this discordance is not immediately clear and raises concerns about both procedures for gene discovery. A number of limitations and caveats associated with each method are well recognized. In candidate gene studies, for example, the biological rationale for the choice of gene examined is often unclear because, as noted earlier, there are complex, unidentified steps intervening between gene transcription and behavioral outcomes. Further, even when a reasonable gene candidate is selected based on biology, the frequency of the different polymorphisms in the population may result in the study being underpowered and the critical genes being unidentified in the analysis. In GWAS, a source of dissatisfaction is that when significant gene variants are identified, like GPM6B, they usually have only small associations with the heritable trait of interest. There has been a growing interest in complementary approaches. Thus, Boyle, Li, and Pritchard (2017) argued that complex traits, such as delay discounting, are most likely attributable to small coding variations within networks of genes spread across the genome, the "omnigenic model." Such a perspective would suggest that specific genes might be identified as important in GWAS or candidate gene studies but the key factor is how those genes function within the network of other genes. This conceptualization is similar to the view in neuroscience that while specific regions are important, e.g., the nucleus accumbens core in delay discounting (e.g., Cardinal, Pennicott, Sugathapala, Robbins, & Everitt, 2001), but the activity–inactivity correlations (functional connectivity) with other regions is also critical (e.g., Costa Dias et al., 2015). Several future research directions are thus warranted to understand delay discounting as an endophenotype: research confirming the role of GPM6

B, additional GWASs replicating these findings and exploring connections to genes identified through candidate gene approaches, as well as studies examining the genetics underlying processes contributing to delay discounting.

Associations between SUDs and Delay Discounting Phenotypes

Behavioral data linking delay discounting and SUDs appear unassailable and have been comprehensively reviewed in a number of articles and meta-analyses (e.g., Amlung, Vedelago, Acker, Balodis, & MacKillop, 2016). These reviews indicate several truisms. First, individuals who have been diagnosed with a SUD, or who use a substance recreationally, exhibit higher levels of discounting than those who have no such diagnosis. Second, this relationship is observed across numerous substances: opiates and opioids, methamphetamine, cocaine, nicotine, and alcohol, though data for marijuana are inconclusive (Strickland, Feinstein, Lacy, & Smith, 2016; VanderBroek, Acker, Palmer, de Wit, & MacKillop, 2016). Third, higher levels of delay discounting have been associated with earlier ages of substance use (e.g., Audrain-McGovern et al., 2009, for tobacco use; but also see Isen, Sparks, & Iacono, 2014) and a higher likelihood of relapse during cessation attempts (e.g., Sheffer et al., 2014). Referring back to the discussion of lumping and splitting, these results, and the association of high levels of delay discounting with other psychopathologies like schizophrenia and depression (e.g., Ahn et al., 2011), are the basis on which researchers have suggested that delay discounting can be thought of as a transdisease phenotype.

The association between higher levels of delay discounting and a higher likelihood of a SUD diagnosis appears highly consistent between numerous research groups, as indicated by the meta-analyses mentioned earlier. However, it should be noted that most of the studies were performed using quasi-experimental methods; that is, comparing individuals diagnosed with the SUD of interest or not (e.g., Hoffman et al., 2006: comparing methamphetamine dependent users and healthy controls). Such studies often have fewer than 50 participants in each diagnostic group (see review by Gowin, Sloan, Ramchandani, Paulus, & Lane, 2018, Table 1). This limits the statistical power available if investigators try to identify contributing variables or interactions with sociological, psychological, and biological factors that might contribute to the linkage between delay discounting and SUDs. Most prior studies have augmented their sensitivity to SUD diagnosis by equating groups on intellectual function, income, and other variables known to influence both delay discounting and SUD. However, this research strategy, although useful, does reduce the ability to detect interactions and mediational relationships amongst SUDs, delay discounting, and these other variables by restricting the ranges of variables like intellectual function and income. These limited-N, matched designs also reduce the ability to determine if there are discontinuous functional relationships between delay discounting and psychopathology, that is, relationships in which, beyond a specific threshold ("tipping point"), levels of delay discounting become pathological. To examine such nuances and interactions, data sets with hundreds of individuals and scalar or ordinal measures of SUDs are required. Only under these conditions can Bayesian and other statistical modeling techniques can be used (Chávez, Villalobos, Baroja, & Bouzas, 2017; Vincent, 2016).

Smaller samples, however, can play a useful role for more targeted studies of links between delay discounting and SUD-related phenotypes. Unfortunately, few experimental studies exist. One exception is a study reported by Mitchell, Reeves, Li, and Phillips (2006), who observed that mice that showed higher levels of drug-naïve delay discounting for sucrose rewards also exhibited less locomotor activity following their initial exposure to ethanol. This result is consistent with a body of research in humans indicating that less physiological response to alcohol is a risk factor for future problematic alcohol use (Schuckit et al., 2011). In a second example, Weafer, Burkhardt, and de Wit (2014) observed that adults with higher levels of discounting reported greater levels of liking for solutions that were sweeter; a heritable preference associated with an increased propensity to drink alcohol (e.g., Kampov-Polevoy, Tsoi, Zvartau, Neznanov, & Khalitov, 2001). Unfortunately these types of study linking delay discounting to phenotypes that have established relationships to SUD trajectories are rare; addressing this knowledge gap could provide information useful to understanding links between delay discounting and SUD phenotypes. It does not however, speak to possible shared genes unless those SUD phenotypes are *intermediate* phenotypes. Thus, examining relationships among delay discounting, intermediate phenotypes, and SUD trajectories should be a high research priority.

Conclusions

The behavioral association between SUD and high levels of delay discounting is clear. The contribution of genes to SUDs including alcoholism is well-accepted, and data were presented here supporting the view that delay discounting is also heritable. Data from inbred strains of rodent are compelling, and data from human twin studies support the same conclusion. However, identifying a heritable phenotype does not provide information about which genes, or how many genes, are involved, nor information about their interactions or interactions with environmental conditions. Further, it is not an automatic consequence of both behaviors being heritable that there are *common* genes for SUDs and delay discounting. Determining if there are indeed common genes is difficult. Several factors that contributed to this difficulty were discussed including the complexity of SUDs and delay discounting behaviors and the existence of multiple factors that influence these behaviors, each of which may have specific genes associated with it. One research approach, advocated in this article, is one in which high levels of delay discounting (or contributory processes) are related to processes known to influence behavioral phenotypes associated with SUDs, rather than the presence of absence of a SUD diagnosis. These studies could suggest mechanisms by which SUDs and delay discounting might be linked phenotypically. By identifying these linkages, it is hoped that genetic bases of these common characteristics can be identified. These studies may also suggest excellent places to intervene to reduce substance use and increase relative preference for the larger, later reward. Indeed, ongoing initiatives by the National Institute for Drug Abuse (NIDA) and the National Institute for Alcoholism and Alcohol Abuse (NIAAA) seek to identify genes associated with these processes.

Acknowledgements

SHM was supported by National Institutes of Health awards P60 AA010760 and U01 DA046077.

References

Ahn, W. Y., Rass, O., Fridberg, D. J., Bishara, A. J., Forsyth, J. K., Breier, A., et al. (2011). Temporal discounting of rewards in patients with bipolar disorder and schizophrenia. *Journal of Abnormal Psychology, 120*(4), 911–921. https://doi.org/10.1037/a0023333.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing. Retrieved from https://www.psychiatry.org/patients-families/addiction/what-is-addiction

Amlung, M., Vedelago, L., Acker, J., Balodis, I., & MacKillop, J. (2016). Steep delay discounting and addictive behavior: A meta-analysis of continuous associations. *Addiction, 112*(1), 51–62. https://doi.org/10.1111/add.13535.

Anderson, K. G., & Woolverton, W. L. (2005). Effects of clomipramine on self-control choice in Lewis and Fischer 344 rats. *Pharmacology Biochemistry & Behavior, 80*(3), 387–393. https://doi.org/10.1016/j.pbb.2004.11.015.

Anokhin, A. P., Golosheykin, S., Grant, J. D., & Heath, A. C. (2011). Heritability of delay discounting in adolescence: a longitudinal twin study. *Behavior Genetics, 41*, 175–183. https://doi.org/10.1007/s10519-010-9384-7.

Anokhin, A. P., Grant, J. D., Mulligan, R. C., & Heath, A. C. (2015). The genetics of impulsivity: evidence for the heritability of delay discounting. *Biological Psychiatry, 77*, 887–894. https://doi.org/10.1016/j.biopsych.2014.10.022.

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

Barkley-Levenson, A. M., & Crabbe, J. C. (2014). High drinking in the dark mice: a genetic model of drinking to intoxication. *Alcohol, 48*, 217–223. https://doi.org/10.1016/j.alcohol.2013.10.007.

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

Bickel, W. K., & Mueller, E. T. (2009). Toward the study of trans-disease processes: A novel approach with special reference to the study of co-morbidity. *Journal of Dual Diagnosis, 5*, 131–138. https://doi.org/10.1080/15504260902869147.

Billieux, J., Schimmentic, A., Khazaal, Y., Mauragea, P., & Heerena, A. (2015). Are we overpathologizing everyday life? A tenable blueprint for behavioral addiction research. *Journal of Behavioral Addictions, 4*, 119–123. https://doi.org/10.1556/2006.4.2015.009.

Boyle, E. A., Li, Y. I., & Pritchard, J. K. (2017). An expanded view of complex traits: From polygenic to omnigenic. *Cell, 169*, 1177–1186. https://doi.org/10.1016/j.cell.2017.05.038.

Byun, S., Ruffini, C., Mills, J. E., Douglas, A. C., Niang, M., Stepchenkova, S., et al. (2009). Internet addiction: Metasynthesis of 1996–2006 quantitative research. *CyberPsychology & Behavior, 12*, 203–207. https://doi.org/10.1089/cpb.2008.0102.

Cardinal, R. N., Pennicott, D. R., Sugathapala, C. L., Robbins, T. W., & Everitt, B. J. (2001). Impulsive choice induced in rats by lesions of the nucleus accumbens core. *Science, 292*, 2499–2501. https://doi.org/10.1126/science.1060818.

Carey, C. E., Agrawal, A., Bucholz, K. K., Hartz, S. M., Lynskey, M. T., Nelson, E. C., et al. (2016). Associations between polygenic risk for psychiatric disorders and substance involvement. *Frontiers in Genetics, 7*, 149. https://doi.org/10.3389/fgene.2016.00149.

Chartier, K. G., Karriker-Jaffe, J. J., Cummings, C. R., & Kendler, K. S. (2017). Review: Environmental influences on alcohol use: Informing research on the joint effects of genes and the environment in diverse U.S. populations. *American Journal on Addictions, 26*(5), 446–460. https://doi.org/10.1111/ajad.12478.

Chávez, M. E., Villalobos, E., Baroja, J. L., & Bouzas, A. (2017). Hierarchical Bayesian modeling of intertemporal choice. *Judgment & Decision Making, 12*, 19–28.

Chen, H., Hiler, K. A., Tolley, E. A., Matta, S. G., & Sharp, B. M. (2012). Genetic factors control nicotine self-administration in isogenic adolescent rat strains. *PLoS One, 7*, e44234. https://doi.org/10.1371/journal.pone.0044234.

Chenoweth, M. J., & Tyndale, R. F. (2013). Nicotine metabolism as an intermediate phenotype. In J. MacKillop & M. R. Munafò (Eds.), *Genetic influences on addiction: An intermediate phenotype approach* (pp. 65–95). Cambridge: MIT Press.

Costa Dias, T. G., Iyer, S. P., Carpenter, S. D., Cary, R. P., Wilson, V. B., Mitchell, S. H., et al. (2015). Characterizing heterogeneity in children with and without ADHD based on reward system connectivity. *Developmental Cognitive Neuroscience, 11*, 155–174. https://doi.org/10.1016/j.dcn.2014.12.005.

Czapla, M., Baeuchl, C., Simon, J. J., Richter, B., Kluge, M., Friederich, H. C., et al. (2017). Do alcohol-dependent patients show different neural activation during response inhibition than healthy controls in an alcohol-related fMRI go/no-go-task? *Psychopharmacology, 234*, 1001–1015. https://doi.org/10.1007/s00213-017-4541-9.

Eastwood, E. C., Barkley-Levenson, A. M., & Phillips, T. J. (2014). Methamphetamine drinking microstructure in mice bred to drink high or low amounts of methamphetamine. *Behavioural Brain Research, 272*, 111–120. https://doi.org/10.1016/j.bbr.2014.06.035.

Eisenberg, D. T., MacKillop, J., Modi, M., Beauchemin, J., Dang, D., Lisman, S. A., et al. (2007). Examining impulsivity as an endophenotype using a behavioral approach: A DRD2 TaqI A and DRD4 48-bp VNTR association study. *Behavioral & Brain Functions, 3*:2. https://doi.org/10.1186/1744-9081-3-2.

Everitt, B. J., & Robbins, T. W. (2005). Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. *Nature Neuroscience, 8*(11), 1481–1489. https://doi.org/10.1038/nn1579.

Frost, R., & McNaughton, N. (2017). The neural basis of delay discounting: A review and preliminary model. *Neuroscience & Biobehavioral Reviews, 79*, 48–65. https://doi.org/10.1016/j.neubiorev.2017.04.022.

Garcia, A., & Kirkpatrick, K. (2013). Impulsive choice behavior in four strains of rats: evaluation of possible models of Attention-Deficit/Hyperactivity Disorder. *Behavioural Brain Research, 238*, 10–22. https://doi.org/10.1016/j.bbr.2012.10.017.

Gianotti, L. R., Figner, B., Ebstein, R. P., & Knoch, D. (2012). Why some people discount more than others: Baseline activation in the dorsal PFC mediates the link between COMT genotype and impatient choice. *Frontiers in Neuroscience, 6*:54. https://doi.org/10.3389/fnins.2012.00054.

Gottesman, I. I., & Gould, T. D. (2003). The endophenotype concept in psychiatry: etymology and strategic intentions. *American Journal of Psychiatry, 160*(4), 636–645. https://doi.org/10.1176/appi.ajp.160.4.636.

Gowin, J. L., Sloan, M. E., Ramchandani, V. A., Paulus, M. P., & Lane, S. D. (2018). Differences in decision-making as a function of drug of choice. *Pharmacology, Biochemistry & Behavior, 164*, 118–124. https://doi.org/10.1016/j.pbb.2017.09.007.

Hart, A. B., de Wit, H., & Palmer, A. A. (2013). Candidate gene studies of a promising intermediate phenotype: Failure to replicate. *Neuropsychopharmacology, 38*(5), 802–816. https://doi.org/10.1038/npp.2012.245.

Hoffman, W. F., Moore, M., Templin, R., McFarland, B., Hitzemann, R. J., & Mitchell, S. H. (2006). Neuropsychological function and delay discounting in methamphetamine-dependent individuals. *Psychopharmacology, 188*, 162–170. https://doi.org/10.1007/s00213-006-0494-0.

Hopfer, C. J., Stallings, M. C., Hewitt, J. K., & Crowley, T. J. (2003). Family transmission of marijuana use, abuse, and dependence. *Journal of the American Academy of Child & Adolescent Psychiatry, 42*, 834–841. https://doi.org/10.1097/01.CHI.0000046874.56865.85.

Isen, J. D., Sparks, J. C., & Iacono, W. G. (2014). Predictive validity of delay discounting behavior in adolescence: A longitudinal twin study. *Experimental & Clinical Psychopharmacology, 22*, 434–443. https://doi.org/10.1037/a0037340.

Isles, A. R., Humby, T., Walters, E., & Wilkinson, L. S. (2004). Common genetic effects on variation in impulsivity and activity in mice. *Journal of Neuroscience, 24*, 6733–6740. https://doi.org/10.1523/JNEUROSCI.1650-04.2004.

Kampov-Polevoy, A. B., Tsoi, M. V., Zvartau, E. E., Neznanov, N. G., & Khalitov, E. (2001). Sweet liking and family history of alcoholism in hospitalized alcoholic and non-alcoholic patients. *Alcohol & Alcoholism, 36*(2), 65–70. https://doi.org/10.1093/alcalc/36.2.165.

Kareken, D. A., Dzemidzic, M., Wetherill, L., Eiler, W., II, Oberlin, B. G., Harezlak, J., et al. (2013). Family history of alcoholism interacts with alcohol to affect brain regions involved in behavioral inhibition. *Psychopharmacology, 228*, 335–345. https://doi.org/10.1007/s00213-013-3038-4.

Kendler, K. S., Prescott, C. A., Myers, J., & Neale, M. C. (2003). The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. *Archives of General Psychiatry, 60*, 929–937. https://doi.org/10.1001/archpsyc.60.9.929.

MacKillop, J., Gray, J. C., Bidwell, L. C., Bickel, W. K., Sheffer, C. E., & McGeary, J. E. (2015). Genetic influences on delay discounting in smokers: Examination of a priori candidates and exploration of dopamine-related haplotypes. *Psychopharmacology, 232*(20), 3731–3739. https://doi.org/10.1007/s00213-015-4029-4.

MacKillop, J., & Munafò, M. R. (2013). An intermediate phenotype approach to addiction genetics. In J. MacKillop & M. R. Munafò (Eds.), *Genetic influences on addiction: An intermediate phenotype approach* (pp. 1–18). Cambridge MA: MIT Press.

Marshall, A. T., Smith, A. P., & Kirkpatrick, K. (2014). Mechanisms of impulsive choice: I. Individual differences in interval timing and reward processing. *Journal of the Experimental Analysis of Behavior, 102*(1), 86–101. https://doi.org/10.1002/jeab.88.

Mitchell, S. H. (2014). Assessing delay discounting in mice. *Current Protocols in Neuroscience, 66*(8.30), 1–12. https://doi.org/10.1002/0471142301.ns0830s66.

Mitchell, S. H., Reeves, J. M., Li, N., & Phillips, T. J. (2006). Delay discounting predicts behavioral sensitization to ethanol in outbred WSC mice. *Alcoholism: Clinical & Experimental Research, 30*(3), 429–437. https://doi.org/10.1111/j.1530-0277.2006.00047.x.

Morrow, J. D., & Flagel, S. B. (2016). Neuroscience of resilience and vulnerability for addiction medicine: From genes to behavior. *Progress in Brain Research, 223*, 3–18. https://doi.org/10.1016/bs.pbr.2015.09.004.

Nautiyal, K. M., Wall, M. M., Wang, S., Magalong, V. M., Ahmari, S. E., Balsam, P. D., et al. (2017). Genetic and modeling approaches reveal distinct components of impulsive behavior. *Neuropsychopharmacology, 42*(6), 1182–1191. https://doi.org/10.1038/npp.2016.277.

Nolan, B. V., Taylor, S. L., Liguori, A., & Feldman, S. R. (2009). Tanning as an addictive behavior: A literature review. *Photodermatology, Photoimmunology & Photomedicine, 25*, 12–19. https://doi.org/10.1111/j.1600-0781.2009.00392.x.

Oberlin, B. G., & Grahame, N. J. (2009). High-alcohol preferring mice are more impulsive than low-alcohol preferring mice as measured in the delay discounting task. *Alcoholism: Clinical & Experimental Research, 33*, 1–10. https://doi.org/10.1111/j.1530-0277.2009.00955.x.

O'Tousa, D. S., Matson, L. M., & Grahame, N. J. (2013). Effects of intoxicating free-choice alcohol consumption during adolescence on drinking and impulsivity during adulthood in selectively bred high-alcohol preferring mice. *Alcoholism, Clinical & Experimental Research, 37*, 141–149. https://doi.org/10.1111/j.1530-0277.2012.01857.x.

Paloyelis, Y., Asherson, P., Mehta, M. A., Faraone, S. V., & Kuntsi, J. (2010). DAT1 and COMT effects on delay discounting and trait impulsivity in male adolescents with Attention Deficit/Hyperactivity Disorder and healthy controls. *Neuropsychopharmacology, 5*(12), 2414–2426. https://doi.org/10.1038/npp.2010.124.

Reed, D. D., Kaplan, B. A., Becirevic, A., Roma, P. G., & Hursh, S. R. (2016). Toward quantifying the abuse liability of ultraviolet tanning: A behavioral economic approach to tanning addiction. *Journal of the Experimental Analysis of Behavior, 106*, 93–106. https://doi.org/10.1002/jeab.216.

Reginsson, G. W., Ingason, A., Euesden, J., Bjornsdottir, G., Olafsson, S., Sigurdsson, E., et al. (2018). Polygenic risk scores for schizophrenia and bipolar disorder associate with addiction. *Addiction Biology, 23*, 485–492. https://doi.org/10.1111/adb.12496.

Richards, J. B., Lloyd, D. R., Kuehlewind, B., Militello, L., Paredez, M., Solberg Woods, L., & Palmer, A. A. (2013). Strong genetic influences on measures of behavioral-regulation among inbred rat strains. *Genes, Brain & Behavior, 12*, 490–502. https://doi.org/10.1111/gbb.12050.

Sanchez-Roige, S., Fontanillas, P., Elson, S. L., Pandit, A., Schmidt, E. M., Foerster, J. R., et al. (2018). Genome-wide association study of delay discounting in 23,217 adult research participants of European ancestry. *Nature Neuroscience, 21*(1), 16–18. https://doi.org/10.1038/s41593-017-0032-x.

Schuckit, M. A., Smith, T. L., Trim, R. S., Allen, R. C., Fukukura, T., Knight, E. E., et al. (2011). A prospective evaluation of how a low level of response to alcohol predicts later heavy drinking and alcohol problems. *American Journal of Drug & Alcohol Abuse, 37*(6), 479–486. https://doi.org/10.3109/00952990.2011.598590.

Sheffer, C. E., Christensen, D. R., Landes, R., Carter, L. P., Jackson, L., & Bickel, W. K. (2014). Delay discounting rates: A strong prognostic indicator of smoking relapse. *Addictive Behaviors, 39*(11), 1682–1689. https://doi.org/10.1016/j.addbeh.2014.04.019.

Smith, C. T., & Boettiger, C. A. (2012). Age modulates the effect of COMT genotype on delay discounting behavior. *Psychopharmacology, 222*, 609–617. https://doi.org/10.1007/s00213-012-2653-9.

Stein, J. S., Pinkston, J. W., Brewer, A. T., Francisco, M. T., & Madden, G. J. (2012). Delay discounting in Lewis and Fischer 344 rats: steady-state and rapid-determination adjusting-amount procedures. *Journal of the Experimental Analysis of Behavior, 97*(3), 305–321. https://doi.org/10.1901/jeab.2012.97-305.

Strickland, J. C., Feinstein, M. A., Lacy, R. T., & Smith, M. A. (2016). The effects of physical activity on impulsive choice: Influence of sensitivity to reinforcement amount and delay. *Behavioural Processes, 126*, 36–45. https://doi.org/10.1016/j.beproc.2016.03.002.

VanderBroek, L., Acker, J., Palmer, A. A., de Wit, H., & MacKillop, J. (2016). Interrelationships among parental family history of substance misuse, delay discounting, and personal substance use. *Psychopharmacology, 233*(1), 39–48. https://doi.org/10.1007/s00213-015-4074-z.

Vincent, B. T. (2016). Hierarchical Bayesian estimation and hypothesis testing for delay discounting tasks. *Behavior Research Methods, 48*(4), 1608–1620. https://doi.org/10.3758/s13428-015-0672-2.

Volkow, N. D., & Baler, R. D. (2015). NOW vs LATER brain circuits: Implications for obesity and addiction. *Trends in Neurosciences, 38*, 345–352. https://doi.org/10.1016/j.tins.2015.04.002.

Walters, G. D. (2002). The heritability of alcohol abuse and dependence: a meta-analysis of behavior genetic research. *American Journal of Drug & Alcohol Abuse, 28*(3), 557–584. https://doi.org/10.1081/ADA-120006742.

Weafer, J., Burkhardt, A., & de Wit, H. (2014). Sweet taste liking is associated with impulsive behaviors in humans. *Frontiers in Behavioral Neuroscience, 8*, 228. https://doi.org/10.3389/fnbeh.2014.00228.

Wilhelm, C. J., & Mitchell, S. H. (2009). Strain differences in delay discounting using inbred rats. *Genes Brain and Behavior, 8*(4), 426-434. https://doi.org/10.1111/j.1601-183X.2009.00484.x.

Wingo, T., Nesil, T., Choi, J. S., & Li, M. D. (2016). Novelty seeking and drug addiction in humans and animals: From behavior to molecules. *Journal of Neuroimmune Pharmacology, 11*, 456–470. https://doi.org/10.1007/s11481-015.

Zou, Z., Wang, H., d'Oleire Uquillas, F., Wang, X., Ding, J., & Chen, H. (2017). Definition of substance and non-substance addiction. *Advances in Experimental Medicine & Biology, 1010*, 21–41. https://doi.org/10.1007/978-981-10-5562-1_2.