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The genetic basis of delay discounting and its genetic relationship to alcohol dependence

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Abstract

Delay discounting is steeper for individuals who drink heavily or are alcohol dependent, but the reasons for this are unclear. Given the substantial genetic component for alcohol dependence it is not unreasonable to ask whether discounting and alcohol dependence have a genetic relationship. For there to be a genetic relationship, delay discounting must have a genetic component (heritability). A review of the human and animal literature suggests that this is the case. Other literature examining whether discounting is a correlated phenotype in individuals who are genetically predisposed to drink (family history positive individuals and selected lines of rats and mice) is mixed, suggesting that networks of genes are critical for the relationship to be seen. The identities of the genes in this network are not yet known, but research examining polymorphisms associated with differences in discounting is beginning to address this issue.

Keywords

Alcohol dependence; Genetics; Delay Discounting; Rat; Mouse; Human

Introduction to the delay discounting phenotype

Delay discounting occurs when a reward is available following a delay and its subjective value is lower than when the reward is available sooner (e.g., Ainslie, 1974). This phenomenon has been observed in an array of species (mice: e.g., Mitchell et al., 2006; rats: e.g., Bradshaw & Szabadi, 1992; pigeons: e.g., Rachlin & Green, 1972; humans: e.g., Rodriguez & Logue, 1988; monkeys: e.g., Tobin et al., 1996) using a variety of different techniques (see recent review by Madden & Johnson, 2010). These techniques usually involve examining choices between a smaller, immediate reward and a larger, more delayed reward to yield one of two measures: (1) a percent preference measure for the larger reward, or if a titration procedure is used (2) an indifference point at which the subjective values of the smaller, immediate and larger, delayed reward. By varying the delay to the larger reward, a series of indifference points/choice percentages can be obtained and the alteration in subjective value of the larger, later reward as a function of delay can be quantified (the “discounting function” and “area under the curve” of the discounting function).

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In studies using nonhuman animals, food rewards are commonly used; requiring subjects to be food-restricted prior to performing the task. Delays to the larger food reward are in the order of seconds. In studies using humans, monetary rewards are usual, although other commodities, including food, have been examined. Delays range from seconds (Reynolds & Schiffbauer, 2004) to years (e.g., Green, et al., 1994). Unique to studies using human subjects, rewards and delays may be real or hypothetical. Similar data appear to be obtained with real and hypothetical rewards (e.g., Bickel, et al., 2009; Madden, et al., 2004), but systematic comparisons have not been performed for discount curves generated using experiential and hypothetical delays.

The form of the discounting function derived from animal and human studies is described equally well by the same mathematical formulae, and the type of choice (small, immediate reward versus larger, later reward) required in delay discounting problems is ostensibly the same. However, it is not clear that the underlying processes that generate discounting behavior in animals and humans are equivalent; the effects on discounting of varying the magnitude of the delayed reward differ between animal and human subjects (e.g., Jimura et al., 2009) and the acute effects of drugs of abuse on discounting also differ markedly (see de Wit & Mitchell, 2010 for review). Thus, though some features of performance may be associated with similar neuroanatomical processes and shared genotypic characteristics in animal and human subjects, other features almost certainly are associated with different processes and characteristics. Thus, it is advisable to keep this latter possibility in mind when using animal models to identify genotypic associations with specific delay discounting phenotypes in humans.

In studies using human subjects, monetary rewards are the most frequently used, but as noted earlier, studies have examined other commodities. Some research suggests a significant correlation between measures of discounting independent of the commodity being discounted, which suggests the contribution of a common delay-related component to the behavior. For example, Odum and Rainaud (2003; Table 2) present data for 20 individuals performing three types of discounting task: immediate vs delayed money, immediate alcohol vs delayed alcohol and immediate food vs delayed food. Based on these data, we can calculate correlation coefficients between discounting measures for each type of reward. These correlations are highly significant ($r_{\$,\text{alcohol}} = 0.68$, $r_{\$,\text{food}} = 0.63$, $r_{\text{alcohol},\text{food}} = 0.90$). Others have also reported significant correlations, although not as large (e.g., Tsukayama & Duckworth, 2010). These data support the idea that there are core processes involved in discounting that are commodity-independent. The existence of core processes is an important prerequisite for arguing that links between delay discounting phenotypes and other behaviors of interest reflect a shared biological basis, as will be done in later sections of this review.

Behavioral relationship of delay discounting to alcohol dependence

While interesting from a basic science perspective because of the information it provides about reward valuation processes, interest in delay discounting has been augmented recently due to an apparent relationship between discounting and substance dependence disorders, including alcohol dependence. Numerous studies have reported that individuals who are dependent on alcohol devalue delayed monetary rewards to a larger degree than people who are not, that is, they have steeper delay discounting functions (see recent reviews by Lejuez et al., 2010; Perry & Carroll, 2008; Reynolds, 2006; Yi et al., 2010). One explanation for this higher level of discounting in dependent individuals is that substance dependence in general, and alcohol use in particular, can be conceptualized as a choice between an immediate or rapid-onset pleasurable experience (including removal of withdrawal symptoms) versus the later benefits of increased health due to abstinence. Because

discounting studies have focused on delayed monetary rewards, rather than immediate pleasure and later health, this explanation of the steep discounting functions relies on there being a commodity-independent delay-related component to delay discounting, such as that suggested by the data provided earlier. Commodity-independent discounting also suggests that procedures that alter discounting of one commodity might carry over to discounting of other commodities. This, in turn, implies that identifying procedures that reduce delay discounting for monetary rewards might be useful to reduce discounting of the delayed health benefits of alcohol abstinence and, thereby, be useful for treating alcohol dependence, or other forms of substance dependence. However, research is currently unavailable to examine whether this is indeed the case.

The conceptualization of drug use as a choice between immediate alcohol-associated pleasure versus delayed health benefits is not perfect for several reasons. First, the later health benefits are not assured, in that the individual might not be healthy later due to contracting an disease unrelated to alcohol consumption, which introduces a probabilistic element to the delay discounting scenario. Second, the choice of abstinence might be associated with an unpleasant detoxification experience before health can be enjoyed later. Third, choosing to drink alcohol may be associated with unpleasant consequences as well as positive ones, including somewhat delayed consequences such as hangover. Research examining delay discounting and alcohol dependence does not ordinarily utilize such complex models. However, incorporating negative features of the choice situation may reveal important individual differences due to the lack of a strong relationship between discounting positive and negative outcomes within individuals (Mitchell & Wilson, 2010). Additional research is needed to determine whether the use of more complex discounting scenarios strengthens the observed relationship between discounting measures and measures of alcohol dependence and recovery.

Although a well-established relationship, the physiological mechanisms underlying the relationship between delay discounting and alcohol dependence are unclear. Further, it is unknown what the relationship of delay discounting is to other features of alcohol use known to be related to the development of dependence: initiation of alcohol use, maintenance of regular use and escalation to problematic levels of use (see Carroll et al., 2010 for a review of animal literature relating discounting to these features of cocaine use). Existing research indicates that these features of alcohol use involve distinct genetic, neurobiological and environmental factors (e.g., Kendler, et al., 2008; also see Witt, 2010 for recent review). It is plausible, but as yet unexplored, that delay discounting has different genetic relationships to different stages of alcohol use predating alcohol dependence. However, researchers have focused on simpler models linking discounting and substance abuse (e.g., Mitchell, 2004; Perry & Carroll, 2008). Two models are depicted in Figure 1a and 1b. In Model 1, heightened discounting is associated with some mechanism that results in heightened alcohol drinking and the development of dependence (Figure 1a). At a neural level, the mechanism may involve slight differences in the structure or functioning of neural structures implicated in reward valuation, but the mechanism can be conceptualized at different levels. For example, discounting of delayed rewards might be altered by a difference in activity of receptor systems in the nucleus accumbens (Acheson et al., 2006; Cardinal et al., 2001; also see Basar et al., 2010 for review), which is an area known to be critical in the reinforcing effects of alcohol (e.g., Doyon et al., 2003; Koob, 2000). In Model 2, higher levels of alcohol exposure in alcohol dependent individuals are associated in some way with heightened discounting (Figure 1b). Again this could be a direct neural effect in which alcohol alters the brain in some way, for example, reducing gray matter volume in frontal areas (Chanraud et al., 2007), which are implicated in choosing between different rewards. Alternatively, the mechanism might be conceptualized as altering cognitive

processes like working memory, which is implicated in delay discounting (e.g., Bobova et al., 2009; Hinson et al., 2003).

The directionality of Models 1 and 2 becomes less important if delay discounting and alcohol dependence are instead viewed as products of some underlying event (Figure 1c) that alters activity in the brain in a way that alters the value of rewards (relative value of immediate vs delayed rewards but also the relative value of alcohol consumption vs abstinence). This event might be environmentally-driven, e.g., initiation of a stressful situation like job loss. Alternatively, the event might be an effect of the immediate reward experience on the brain, for example, winning a prize for some sporting behavior. Other types of events are also possible, but all are assumed by the model to affect choices in a delay discounting task or alcohol drinking through changes in neural processing. Further, effects of these environmentally-driven or behaviorally-initiated events on the brain at a molecular level are generated by mechanisms related to the individual's genotype. This may involve differences in the way that the genes within specific neural structures are expressed thereby generating proteins or differences in the action of pre-existing proteins that regulate neurotransmission and composition (e.g., Clarke et al., 2008; also see review by Hariri, 2009 for examples and expansion of this argument).

Because of the underlying importance of an individual's genotype on brain function, including its potential impact on delay discounting and alcohol dependence, the remainder of this review focuses on the data indicating that genotype plays a role in delay discounting, and that there is a genetic relationship between delay discounting and alcohol dependence.

Considerations when assessing the genetic component to delay discounting

To determine whether a behavioral phenotype, like high levels of delay discounting, has a genetic component there are several approaches. One approach examines whether the behavior of interest has a genetic component. That is, using twin studies or family association studies to determine whether the behavior of interest is more likely to occur in genetically-related individuals than in unrelated individuals. Another approach examines whether specific genes can be identified that contribute significantly to the behavior of interest. That is, genome wide association studies (GWAS) or functional polymorphism studies to determine whether genes of polymorphisms at specific locations are more common in individuals engaging in the behavior of interest than individuals not exhibiting the behavior.

Independent of the type of approach, the confidence placed in the results is influenced by both the ability to quantify the behavioral phenotype as well as information about the stability of the phenotype under specific, repeatable conditions. With respect to quantification, measures of performance on the various delay discounting tasks potentially provide a quantitative measure of the delay discounting phenotype. Researchers argue about the analytical methods used to quantify the extent to which discounting occurs (e.g., use of the quasi-hyperbolic or hyperbolic equations to fit the indifference points, use of area under the discounting curve, etc.), but the key consideration is that tasks exist that yield concordant measures of some latent variable associated with the extent of discounting. While there are studies indicating some level of concordance between measures obtained from different tasks for human subjects (Reynolds, 2006; Reynolds et al., 2008), as well as measures used with nonhuman subjects (Green et al., 2007), this literature is sparse and additional research is needed.

In addition to the need to be able to confidently quantify the extent to which discounting occurs, being able to delineate the processes responsible for choices in a delay discounting task is useful. This is especially true when a phenotype such as heightened delay discounting can occur through the action of different processes, which may be associated with different genetic mechanisms. As noted earlier, delay discounting is a complex behavior, influenced by various factors like motivation (e.g., MacKillop et al., 2010) and working memory (e.g., Hinson, et al, 2003). Further, heightened levels of discounting can occur due to a differential sensitivity to temporal “costs” of the delayed reward or sensitivity to the magnitude of the sooner or delayed rewards (see Locey & Dallery, 2009 and Da Costa Araujo et al., 2010 for examples of rodent studies separating these factors; comparable studies with human subjects are unavailable). It is entirely reasonable that different networks of genes influence these sensitivity processes while simultaneously generating the same behavioral phenotype of heightened delay discounting. Potentially, this scenario could result in underestimations of the genetic contribution to the phenotype.

A final consideration when assessing whether delay discounting has a heritable component is the replicability of measures of delay discounting. Like the delineation of processes contributing to discounting, replicability is also a relatively unexplored topic, though potentially very important. Only if the measure shows some degree of test-retest reliability can confidence be placed in its ability to assess the latent construct. While requiring some degree of stability, it is unclear what duration of stability is critical in the measure because geneticists appreciate that developmental alterations occur due to alterations in the value of rewards, alterations in the neural structures associated with decision making and time horizons. In addition, it is recognized that short-term perturbations in delay discounting may occur due to emotional or motivational factors. However, theoretically, these should be associated with specific commodities only rather than the commodity-independent processes involved in delay discounting. This is consistent with the observation that discounting of delayed money was increased relative to the value of immediate cigarettes when smokers were nicotine deprived, while discounting delayed and immediate money was unaffected (Mitchell 2004). Data suggest that some measures of discounting in humans, where the delayed and immediate commodities are the same, are stable over 12 months (Kirby, 2009). However, stability data for individual nonhuman animals are unavailable, and additional research on reliability of individual differences in discounting is required.

Data indicating delay discounting has a genetic component (heritability)

Given the research gaps noted in the preceding section it is unsurprising that few studies have examined the heritability of delay discounting. In humans, only a single study was found. Anokhin et al. (2010) examined concordance between 744 pairs of twins aged 12 or 14 years old using a simple discounting measure that required each member of a twin pair to choose between receiving a \$7 bonus at the end of the experiment or having \$10 mailed to them (estimated delay to receipt = 7 days). Interestingly, 35% of 12-year old twins selected the immediate reward, whereas only 27.5% of the older twins selected the immediate reward; a reduction that is consistent with the idea that adolescents value delayed rewards more as they mature (Scheres et al., 2006; Steinberg et al., 2009). Tetrachoric correlations, which assess the relationship between normally distributed variables that are dichotomous (twin number [1 or 2] and choice [immediate or delayed]), were used to analyze the data. Results indicated that correlations between immediate or delayed choice within monozygotic twin pairs of each gender were substantially higher than correlations for dizygotic twin pairs, indicating the presence of a genetic contribution. For the 12-year olds, heritability coefficients were 0.37 and 0.38 for males and females respectively, and for 14-year olds they were 0.45 and 0.80 for males and females, respectively.

These values are somewhat similar to those reported by Wilhelm & Mitchell (2009) in a study that examined performance of six inbred strains of male rats (Copenhagen, Noble, Brown Norway, Lewis, Wistar Furth and Fischer). They compared behavior on a delay discounting task examining preference for sucrose solution available immediately or a larger amount available after delays of 0, 2, 4, 8, 16 seconds, with delay varied between sessions (adjusting amount task: Richards et al., 1997). Copenhagen and Noble strains devalued the delayed sucrose substantially less than the Wistar and Fischer strains, with Brown Norway and Lewis rats discounting at intermediate levels. Heritability was calculated to be 0.40. The use of inbred strains, such as in that study, is critical when examining heritability because each member of the inbred strain is assumed to be homozygous for the same allele at all genetic loci, so genetically identical. Thus any strain difference reflects the effect of genotype, with the numbers of animals/strain merely determining the level of confidence that can be placed on the value of the estimate of the strain mean.

Three other studies have compared delay discounting in Lewis and Fischer inbred rat strains (Anderson & Diller, 2010; Anderson & Woolverton, 2005; Madden et al., 2008). In all of these studies the Lewis strain discounted delayed rewards significantly more steeply than the Fischer strain, while no significant differences between the two strains were observed in the Wilhelm & Mitchell (2009) study. However, there are several differences between the studies that might account for the lack of concordant results, and the 2-strain comparisons should not in any case be interpreted as demonstrating a genetic correlation (see Kosten & Ambrosio, 2002 for a review of the numerous physiological differences between Lewis and Fischer 344 strains). First, Wilhelm & Mitchell obtained their animals from a different vendor than the other three studies (Charles River versus Harlan). This is a concern because research has demonstrated that behavioral differences can be observed for rats of the same strain obtained from different vendors (e.g., Balcells-Olivero et al., 1998; Paré & Kluczynski, 1997). The fact that Charles River has two inbred strains of the Fischer 344 type (F344/DuCrI and F344/NCrI) available while Harlan has only one, underscores this issue and indicates the need for authors to provide the genetic designations for their study subjects in publications. A second issue that could contribute to differences between the studies relates to an issue noted earlier: the internal validity of different delay discounting measures. That is, these studies used different procedures to assess delay discounting. Wilhelm & Mitchell used the adjusting amount procedure (Richards et al., 1997) while the other studies used the within-session procedure (Evenden & Ryan, 1999). These two procedures differ in a number of aspects including the delays and reward sizes used, and the psychophysical basis on which preference is calculated (indifference points derived using the methods of limits and percent choice derived from the method of constant stimuli; Stevens, 1975). Unfortunately, there are no published studies that directly compare the adjusting amount and within-session procedures, so it is impossible to know the degree to which they yield equivalent results.

Using a within-session procedure, Isles et al. (2004) examined delay discounting in just four inbred strains of mice (C57BL/6J, 129/Sv, CBA/Ca, BALB/C). Notice: typical studies use 8–20 inbred strains because heritability is determined by the significance of the relationship between the behavior of interest and strain identity, and the fewer the strains, the larger the test statistic must be for the relationship to be viewed as statistically significant (see Crabbe, 1999 and Crabbe et al., 1990 for discussion of the advantages and disadvantages of this method of heritability assessment). In the Isles et al. study, the 129 and CBA strains chose the larger sucrose solution reward over the smaller reward on more trials than the C57s and BALB strains when both small and large rewards were available immediately. While it is not surprising that the larger reward was selected, it is of potential interest that there were strain differences in choice when there was no delay. Moreover, increasing the delay to the large reward did not interact with this initial strain difference (heritability coefficient for

discounting = 0.16). These data highlight one of the complexities of examining delay discounting in nonhuman animal models: when strain differences are preserved over delays, it is difficult to know that delay discounting differs between the strains rather than there just being a choice bias (Wilhelm & Mitchell, 2010). One other study with mice has reported differences between two inbred strains in delay discounting paradigm assessed using the adjusting amount procedure (C57BL/6J and DBA/2J: Helms et al., 2006). While this result is consistent with there being a genotypic difference that contributes to heritability, as noted earlier, the use of two strains is not sufficient to assess heritability coefficients with any confidence. Thus, additional work is required to determine whether there is a heritable component to delay discounting in mice.

Use of selected lines to demonstrate genetic contribution to delay discounting

When evidence suggests that a trait is heritable it may be feasible to create lines of mice or rats that are selected for that trait. This has proved to be a useful tool in understanding alcohol and substance dependence because, like inbred strains, it permits the examination of correlated traits. These are physiological or behavioral phenotypes that appear genetically related to the selected characteristic that may serve as markers of the characteristic and suggest interventions. For example, Bell et al. (2006) review the extensive literature examining correlated traits found in the alcohol-preferring, P and alcohol-non-preferring, NP, rats, which were bred over numerous generations to drink 5 g ethanol/kg/day and <1 g/kg/day respectively. In addition to showing behavioral characteristics reminiscent of the difference between alcoholics and non-alcoholics such as high novelty seeking behavior and a more substantial physiological response to initial ethanol exposure than ethanol-naïve animals, several specific neurochemical phenotypes are associated with the P and NP animals. Such differences may be instrumental in developing treatments for reducing alcohol consumption in these genetically-predisposed animals.

Creating selected lines is a straight forward, but time consuming process (see Crabbe et al., 2009 for very clear description of the procedures to be followed when selecting for high or low blood ethanol levels following access to alcohol during the dark phase of the light-dark cycle). While it is exciting to imagine creating selected lines for high or low levels of delay discounting, this has not yet occurred. Interesting research from Dr Marilyn Carroll's lab has reported behaviors that differ between groups of animals selected for high or low levels of delay discounting (Anker et al., 2009). However, this research does not address whether there is a shared genetic basis to these behaviors.

The creation of selected lines for high and low delay discounting may be a very difficult task even though, as described earlier in this review, there are data suggesting that delay discounting is heritable. From a practical standpoint, part of the reason for the difficulty is the number of animals required to create selected lines. Founder populations usually include at least 25 pairs of animals to ensure that a wide range of behavior is generated on which to base the selection. Subsequent generations usually involve 40–50 pairs of animals (20–25/line) to ensure that individuals with common grandparents will not be mated. A second difficulty is that training and attaining stable responding in mice on a discounting task requires a substantial amount of time (e.g., Helms et al., 2006 reported requiring approximately 60 sessions to generate discounting curves in C57BL/6J and DBA/2J mice). A final and more complex, theoretical issue is the idea that multiple processes are inherent in generating discounting functions, e.g., timing (al-Zahrani, et al., 1996; Ho et al., 2002), sensitivity to the reinforcer size (Da Costa Araujo et al., 2010; Locey & Dallery, 2009), ability to perform the task including remembering the values of choice alternatives over trials (Rachlin, 2006; but also Dellu-Hagedorn, 2006). Research examining the heritability

of these putative processes that underlie discounting is unavailable, nor is their discrete contribution to delay discounting known. Thus, while we have evidence suggesting that delay discounting is heritable we do not know whether the observed heritability reflects the heritability of a single process or multiple processes.

Shared genetic relationship between alcohol dependence and delay discounting

In contrast to the small literature examining heritability of delay discounting, a plethora of data indicate that alcohol dependence is heritable: twin studies, family association studies, and some work has been done to identify the genes and the gene networks (see recent reviews by Ducci & Goldman, 2008; Gelernter & Kranzler, 2009; Khokhar et al., 2010). Further, it has been shown, primarily using animal models, that there are a number of genetically-correlated traits that accompany excessive drinking. The question addressed in this section is whether heightened delay discounting is one of these traits, which would indicate that there are genes common to both excessive drinking and to heightened delay discounting, or whether the co-occurrence of these two phenotypes is due to some other, not necessarily genetic, mechanism.

As noted at the outset of this review, there appears to be a strong relationship between alcohol consumption and discounting (Field et al., 2007; JM Mitchell et al., 2005; Petry, 2001; Vuchinich & Simpson, 1998) but this does not provide information about any potential genetic relationship. As noted earlier, selected line studies can address whether a high level of delay discounting is a correlated trait by examining discounting with ethanol-naïve rats and mice genetically selected for high or low levels of alcohol consumption. Only a few studies have been published examining this question, and the data from them is mixed. In the earliest study, Wilhelm et al. (2007) examined ethanol-naïve male and female mice from the fourth generation of two lines selected to consume high or low amounts of 10% ethanol-containing solution (STDRHI2 and STDRLO2) derived from a C57BL/6J × DBA/2J cross. While both lines exhibited steep delay discounting, there was no line difference in delay discounting assessed using an adjusting amount procedure, suggesting that genetic propensity to consume alcohol was not genetically associated with discounting. In contrast, Oberlin & Grahame (2009) also used the adjusting amount procedure but with ethanol-naïve male and female mice selected to consume high or low amounts of 10% ethanol (HAP2 and LAP2), derived from HS/Ibg mice, a cross of eight inbred strains. They reported that the line selected for high consumption discounted delayed sucrose solution rewards more than the low line. A similar result to that obtained by Oberlin & Grahame was reported by Wilhelm & Mitchell (2008) using the adjusting amount procedure and assessing discounting in rats selected to drink either high amounts of 10% ethanol or low amounts (HAD1, HAD2 and LAD1, LAD2). The strength of this result is enhanced by the inclusion of two lines, “replicates”, which were independently derived from different foundation animals at the same time. Based on these few studies it appears that heightened delay discounting may be a correlated trait but that the background strains from which the selected lines are derived are critical to whether the selection of genes implicated in alcohol consumption includes genes associated with discounting.

With humans, we can examine whether a family history of alcoholism is associated with higher levels of delay discounting, because such a history is usually interpreted as indicating a genetic propensity to consume alcohol. Three studies with humans have been reported in the literature. An early study by Petry et al. (2002) examined 58 males and females who had a paternal family history of alcoholism (father was diagnosed as alcohol dependent with approximately 35% of individuals having another other first-degree relative and 16% having a second-degree relative diagnosed) and 64 males and females who had no such paternal

family history. Family history negative females had low levels of delay discounting compared with family history positive females, but no family-history effect was observed for males. That is, males and family history positive females had similar levels of discounting, which were higher than the family history negative females. Groups exhibited similar levels of alcohol drinking and use of other substances, though data were not subdivided by gender. In the same year, Crean et al. (2002) found comparable results to Petry et al. when they examined 20 males with paternal family histories of alcoholism (father met 2 or more of the 4 criteria for DSM-IV alcohol dependence) and 20 males who had no first degree relatives diagnosed with alcohol dependence. There was no significant difference between males who were paternal family history positive or negative for alcohol dependence. In a third study, Herting et al. (2010) compared 15 male and female family history positive adolescents (one or both parents or at least two second-degree relatives) and 18 males and female family history negative adolescents. While the article reports a slight trend for family history positive individuals to devalue delayed rewards to a greater degree, no reliable differences in behavior were reported though slight differences in brain structure were identified. The study was not sufficiently powered to make an examination of gender differences worthwhile.

Thus, while delay discounting does appear to have a heritable basis, both the animal and human studies have had some difficulties conclusively demonstrating that heightened delay discounting is a genetically-correlated trait with alcohol dependence, that is, that common genes are involved in discounting behavior and excessive alcohol drinking. The animal data suggest that the genetic relationship may be present in some selected lines but the underlying network of other selected genes is critical to the expression of this relationship. The human data suggest a limited genetic relationship, but are difficult to interpret because family history positive or negative status is usually determined through verbal reports. Use of self-report is required because genetic markers to verify individuals at risk are currently unavailable. However, the reliance on such data for categorization of subjects does open the research to interpretational problems. A related interpretational issue arises from subject selection: while it is preferable to select individuals who are alcohol-naïve so that differences in discounting cannot be attributed to any differences in use, it is unclear whether they have inherited the excessive-alcohol-use genotype prior to participants actually exhibiting heightened alcohol use phenotype. On balance, these animal and human studies suggest that any genetic link between alcohol dependence and delay discounting is somewhat tenuous and additional research is required to delineate the conditions under which there is a relationship and when there is not.

Genes associated with delay discounting

The studies reviewed indicate that there is a heritable basis for delay discounting and suggest that there may be genes that both influence delay discounting *and* are associated with developing alcohol dependence. However, these studies do not provide any information about the identity of the genes that are involved. Four studies using human subjects have attempted to do this and no animal studies. This section reviews those studies.

All studies have focused on genes associated with dopamine, a neurotransmitter which has been implicated in reward valuation and anticipation of reward (e.g., Schultz, 2010; but also Salamone et al., 2009). Given research suggesting the important role of dopamine in delay discounting, especially D2 subtype receptors (e.g., Floresco et al., 2007; Wade et al., 2000), this focus on genes associated with dopamine synthesis, signaling and metabolism seems reasonable.

In an early study, Eisenberg et al. (2007) examined 195 individuals with the A1/A1, A1/A2 or A2/A2 polymorphisms of the dopamine receptor (DR) D2 receptor gene TaqI A combined with either a large or small number of variable number of tandem repeats (VNTR) in the DRD4 allele. While these genes are thought to regulate dopamine binding in the striatum and other studies have linked them to risk-taking, psychopathology and addiction, it is currently unclear what the precise effects of these polymorphisms and their interactions are on dopamine signaling. Individuals with at least one A1 allele of the TaqI A gene discounted more steeply than individuals without and this effect was exacerbated if the participant had a large VNTR value. However, the study did not shed light on any of the alterations in dopamine signaling that might be associated with these group differences. More recently, White et al. (2009) examined another gene associated with dopamine binding to the D2 receptor. Subjects were either homozygous for the CC variant of the C957T gene, which is associated with the lowest levels of D2 receptor binding in the striatum, or possessed the CT or TT polymorphisms. Choice of the immediate alternative did not differ between groups showing the different polymorphisms, although other work has suggested that the CC polymorphism is associated with poorer working memory and executive function, as reviewed by White et al. As this group did not examine any genes associated with DRD4, as was done in the earlier study, it may be that the negative results reflect the absence of polymorphisms at additional loci.

Using a somewhat different approach to studies focused only on identifying which genetic polymorphisms are associated with steeper delay discounting, Boettinger et al. (2007) examined choice between smaller, sooner and larger, later rewards while alcohol dependent and control participants underwent functional magnetic resonance imaging (fMRI). After controlling for alcohol dependence, the data indicated that a higher proportion of immediate alternatives were selected by individuals who were homozygous for the Val158Val polymorphism of the COMT gene. This gene is critical in the rate of metabolism of dopamine and the Val/Val polymorphism is associated with a faster rate of metabolism than other polymorphisms, consistent with dopamine having a role in discounting. Interestingly, during the delay discounting procedure the brain activation patterns were mediated by the genotype of the participant. A similar imaging genetics approach was used by Hariri et al. (2009) which reported that the amount of neural activity in the ventral striatum was negatively correlated with delay discounting only in carriers of the A/A or A/C polymorphisms of a gene associated with signaling in the endocannabinoid system (FAAH C385A), while there was no relationship in CC carriers. The precise link between this system and dopamine signaling is not entirely clear at this time, but this polymorphism was one of a number examined and the only one to show a neural activation $\times$ genotype interaction. While the idea of genotype moderating the relationship between neural activity and delay discounting is reasonable, without a priori hypotheses about the neurochemical impact of these difference polymorphisms, the mechanistic role of the genotypic differences on delay discounting cannot be fully appreciated.

Conclusions

Few studies have been conducted to examine the heritability of delay discounting and whether some of the same genes relate choices of immediate rewards in a discounting paradigm to choices to self-administer alcohol. Part of the reason for this may be the different backgrounds of individuals conducting much of the basic research examining delay discounting and those focused on genetics, including the genetics of alcohol dependence. Another factor might be difficulties associated with assessing delay discounting in a manner compatible with genetic analyses. First, operant research with mice, the main species used to examine alcohol-related genotypes is difficult and time consuming. Second, rat models of alcohol drinking that are easier to work with in behavioral assays, are not as well-developed

as the mouse models. Third, the genetics of alcohol drinking in humans has not developed sufficiently to permit sophisticated alcohol genotypes to be identified and their behavioral phenotype characterized. However, research does suggest that there is a genetic component to delay discounting, which may have genetic elements in common with alcohol dependence, but the genes and their networks are as yet undetermined and a substantial amount of work in this area remains to be completed.

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Figure 1. Three models to describe the relationship between delay discounting and alcohol dependence

A: high levels of delay discounting are associated with, and possibly cause, higher levels of alcohol drinking.

B. High levels of alcohol levels are associated with, and possibly cause, higher levels of delay discounting.

C. Delay discounting and alcohol consumption are both consequences of neural activity, which the model shows as being influenced directly by altering the brain structurally or functionally, or indirectly by altering the environment that the organism is in gene expression or existing RNA products.