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Therapeutic Opportunities for Self-Control Repair in Addiction and Related Disorders: Change and the Limits of Change in Trans-Disease Processes

Warren K. Bickel, Ph.D., Amanda J. Quisenberry, Ph.D., Lara Moody, B.S., and A. George Wilson, Ph.D.

Virginia Tech Carilion Research Institute, Roanoke, VA

Abstract

Contemporary neuro-economic approaches hypothesize that self-control failure results from drugs annexing normal learning mechanisms that produce pathological reward processing and distort decision-making as a result from the dysregulation of two valuation systems. An emphasis on processes shared across different diseases and disorders is at odds with the contemporary approach that assumes unique disease etiologies and treatments. Studying trans-disease processes can identify mechanisms that operate in multiple disease states and ascertain if factors that influence processes in one disease state may be applicable to all disease states. In this paper we review the dual model of self-control failure, the Competing Neurobehavioral Decision Systems approach, the relationship of delay discounting to the relative control of these two systems, and evidence that the executive system can be strengthened. Future research that could result in more potent interventions for executive system improvement and potential constraints on the repair of self-control failure are discussed.

Keywords

rate dependence; delay discounting; working memory training; addiction; trans-disease processes; competing neurobehavioral decision systems

Self-control failure presents an important challenge to U.S. and global public health. For example, a recent Institute of Medicine report (2013) compared the health among those in the U.S. to 16 peer countries and drew conclusions that informed the subtitle of that report, “Shorter Lives, Poorer Health.” The individual behaviors contributing to the excess mortality identified in that report included tobacco use, diet and physical inactivity, alcohol and other drug use, and sexual practices. A similar set of behaviors has been identified as major contributors to global mortality.

To date, most interventions directed at stopping or improving these behaviors have shown therapeutic efficacy relative to control treatments, but arguably those results are less effective than would be preferred. For example, treatments for tobacco cessation are

relatively well developed and available (e.g., nicotine replacement therapy, cognitive behavioral therapy [CBT], non-nicotine medications). They improve rates of successful quit attempts relative to control treatments. However, the efficacy of these treatments leaves considerable room for improvement. For example, Cochrane Collaboration (Cahill, Stevens, Perera, & Lancaster, 2013) reviewed several treatments for smoking cessation and reports a 2- to 3-fold improvement compared to control conditions. Thus, the reviewed treatments may produce up to a 30% success rate, given that many of the control treatments have a success rate of approximately 10%. Therefore, even with these efficacious treatments, any given quit attempt will likely fail. Similar outcomes are evident with treatments for other behaviors, suggesting that existing treatments although efficacious are not yet robust. Perhaps more successful treatments may result from an improved understanding of these challenging behaviors and by examining processes that are shared across them.

An emphasis on processes shared across different diseases and disorders is at odds with the contemporary approach to addressing these challenging behaviors (see Bickel & Mueller, 2009, for a review). The contemporary approach assumes that each disease or disorder is unique, has its own etiology, and, therefore, requires its own unique treatment. Such an approach is evident in disease-specific scientific societies, scholarly journals, and in the very organization of the National Institutes of Health. Within this context and informed by the highly successful scientific program of reductionism, scientists seek to repair these disorders by specializing in a small component part of the disorders. This along with the increasing rates of publication and the corresponding need of scientists to stay current in their respective research area may collectively contribute to both the development of scientific silos and the failure to notice potential commonalities across disorders.

An alternative approach, relevant to these challenging behaviors, is what we refer to as the study of trans-disease processes (Bickel, Jarmolowicz, Mueller, Koffarnus, & Gatchalian, 2012a; Bickel & Mueller, 2009). The goal of the study of trans-disease processes is to identify processes that operate in more than one disease state and ascertain if the factors that influence or ameliorate that process in one disease state may, in principle, be applicable to all disease states that share that process (Bickel, et al., 2012a). Self-control failure is such a trans-disease process that is operative across the various challenging health behaviors referred to above. Self-control, or the ability to forgo immediate rewards in preference for delayed rewards, has been widely linked to several negative health outcomes where a lack of self-control or, stated differently, excessive impulsivity leads to maladaptive and unhealthy behaviors including tobacco use (Bickel, Odum, & Madden, 1999), substance dependence (Bickel et al., 2007), pathological gambling (Alessi & Petry, 2003; MacKillop, Anderson, Castelda, Mattson, & Donovan, 2006a, 2006b; Petry, 2001), overeating (Epstein, Salvy, Carr, Dearing, & Bickel, 2010), and risky sexual practices (CDC, 2008; Reimers, Maylor, Stewart, & Chater, 2009). Although in the field of addiction “failure” often means relapse, slips in cessation, and giving into the temptations, here it refers to choices for immediate over delayed rewards (e.g. employment, improvements in health, improved social relationships) indicative of dysfunctional neuronal processes.

Contemporary neuro-economic approaches consider self-control failure to result from drug commandeering normal learning mechanisms that, in turn, produce dysfunctional reward

processing (Bickel, Yi, Mueller, Jones, & Christensen, 2010). These impaired valuations distort decision making by (1) overvaluing immediate drug-associated stimuli and (2) undervaluing longer-term rewards. This distortion is recognized to result from the dysregulation of two valuation systems. Immediate reward valuation is associated with relatively greater activation of the limbic and paralimbic neural network, referred to as the impulsive decision system, while the valuation of future rewards is associated with relatively greater control by the frontal cortices, referred to as the executive decision system. This model, although largely consistent with a wide variety of dual system approaches, is different in that it suggests that less relative control by the executive decision system is a reason for self-control failure. Importantly, this approach provides a novel target for intervention in the field of addiction and other disorders such as obesity.

The purpose of this paper is to review (1) the dual model of self-control failure, referred to as the Competing Neurobehavioral Decision System approach, (2) a measure that summarizes the relative control of these two systems in an individual, (3) recent work, based on neural plasticity, showing that aspects of the executive system can be strengthened via training and, in turn, improve measures of self-control, (4) opportunities for possible future research that could result in more potent or implementable interventions for executive decision system improvement, and (5) potential constraints on the repair of self-control failure and the consequences for treatment.

The Competing Neurobehavioral Decision System

Self-control, as discussed above, can be conceptualized as resulting from the interaction of a dual system of decision-making. Dual decision systems have been discussed in the decision science literature under many names and variations over the past several decades (for a review of dual process models, see Evans & Stanovich, 2013). To name a few, Metcalfe and Mischel (1999) posit cold and hot systems, Bechara (2005) proposes a reflective and impulsive system, and Jentsch and Taylor (1999) illustrates an inhibitory control and impulsive system. As applied to addiction, the models authored by Bechara (2005) and Jentsch and Taylor (1999) posit dual decision systems that both describe the evolutionarily older impulsive system, which disproportionately values immediate reinforcers and within addiction literature is associated with increased cue reactivity and drug-seeking behaviors. Building on the work of the two models discussed above, we have proposed the Competing Neurobehavioral Decision System approach; that is, a dual decision model that reflects the relative balance between the impulsive decision system and the executive decision system (Bickel, et al., 2007).

The impulsive decision system, as noted earlier, is embodied in the limbic and paralimbic regions of the brain which are rich in dopaminergic innervation (Winstanley, Theobald, Cardinal, & Robbins, 2004), and is sensitive to deprivation states, reactive to cue-induced craving (Childress et al., 1999), drives drug-seeking behaviors (Gloria et al., 2009), and works toward establishing short-term wants and needs. The executive decision system, composed of the prefrontal and parietal cortices, is involved in assigning value to future events, modulating behavior during temporally distant decisions, and largely implicated in

successful self-control (Bickel, Jarmolowicz, Mueller, Gatchalian, & McClure, 2012b; Luhmann, Chun, Yi, Lee, & Wang, 2008; McClure, Laibson, Loewenstein, & Cohen, 2004).

For normal functioning individuals, the Competing Neurobehavioral Decision System approach states that the dual system should function in regulatory balance, characterized by flexibility in different situations. When in regulatory balance, the dual decision system is not strongly under the influence of either short or long term reinforcers, but rather can respond adaptively in favor of either the short or long term depending upon circumstance and/or need (Bickel, et al., 2007). Behaviorally, shorter-term valuation may predominate when facing a threatening situation, such as being confronted with a thief carrying a weapon. Alternatively, longer-term valuation may predominate when making decisions about retirement. Flexibility between short-term and long-term valuation is a key feature of the system such that normal functioning individuals, in principle, can exhibit a broad range of valuations and can be more or less self-controlled. Indeed, much of the work on self-control depletion shows momentary change toward the impulsive range of decision-making resulting from task effort immediately preceding measurement of self-control (for review, see Baumeister, Vohs, & Tice, 2007).

Behavioral evidence of flexible regulatory balance of the Competing Neurobehavioral Decision System is also implicated in brain imaging and modulation studies. Neurally, functional magnetic resonance imaging (fMRI) studies show selective activation of limbic brain regions when individuals choose immediately available rewards and prefrontal region activation during choices for delayed or self-controlled options (McClure, Ericson, Laibson, Loewenstein, & Cohen, 2007; McClure, et al., 2004). Additionally, evidence comes from the transcranial magnetic stimulation (TMS) literature where stimulation of the dorsal lateral prefrontal cortex, part of the executive decision system, leads to either increases or decreases in self-control (Cho et al., 2010; Figner et al., 2010; Genovese, Lazar, & Nichols, 2002). Together, TMS and fMRI evidence supports two neural systems working together in regulatory balance among normal functioning individuals. However, for the purposes of this paper these individuals are not our primary concern.

Our primary concern is a substantial and sustained dysregulation between the impulsive and executive decision systems demonstrated in various disease states. For example, in a study comparing heroin-dependent and matched controls that were asked to think about the future, controls referred to an average time horizon of 4.7 years, while heroin-dependent individuals referred to an average time horizon of 9.0 days (Petry, Bickel, & Arnett, 1998). Consistent with this behavioral observation, individuals with addiction have reduced gray matter volume in prefrontal cortical areas associated with the executive decision system while showing no reduction in limbic areas associated with the impulsive system (Bjork, Momenan, & Hommer, 2009; Lyoo et al., 2006). In sum, dysregulation of the executive component of the decision system resulting in greater relative control of the impulsive decision system has been demonstrated across a variety of disease states.

Regulatory imbalance of the impulsive and executive decision systems can lead to two types of suboptimal decision-making, both of which are linked to negative health behaviors (Bickel et al., 2012b). Individuals with a strong impulsive decision system, our primary

concern in this paper, are at greater risk for several health challenging behaviors such as tobacco use (Bickel, et al., 1999; Dinn, Aycicegi, & Harris, 2004; Razani, Boone, Lesser, & Weiss, 2004), substance dependence (Bechara & Damasio, 2002; Bickel, et al., 2007; Verdejo-Garcia, Bechara, Recknor, & Perez-Garcia, 2006), pathological gambling (Alessi & Petry, 2003; Brand et al., 2005; Cavedini, Riboldi, Keller, D'Annuncci, & Bellodi, 2002; Goudriaan, Oosterlaan, de Beurs, & van den Brink, 2006; Mackillop, et al., 2006a; Petry, 2001), risky sexual practices (Reimers, et al., 2009), overeating and obesity (Cserjesi, Luminet, Poncelet, & Lenard, 2009; Epstein, et al., 2010). At the other end of the spectrum, individuals with disproportionately greater executive functioning compared to relatively lower impulsivity are also at risk for specific types of pathology. The propensity to exert excessive self-control is a hallmark of disorders such as anorexia (Cavedini et al., 2004; Cavedini et al., 2006) and obsessive compulsive personality disorder (Pinto, Steinglass, Greene, Weber, & Simpson, 2014).

Delay Discounting: A Trans-Disease Process Measuring the Dual System

The relative balance of impulsivity and self-control can be measured by the rate at which one discounts future reinforcement. Temporal, or delay, discounting refers to the reduced or discounted value of a reinforcer as a function of its delay (Mazur, 1987). The process of delay discounting is intuitive in that most individuals would rather receive \$100 today over \$100 in a month. The choice of the more immediate monetary amount indicates that the later amount is not worth as much; that is, the later amount is discounted. During the delay discounting task, the participant is asked to choose between a hypothetical smaller-sooner amount of money or a hypothetical larger-later amount of money. The amount of money available now is adjusted until it is subjectively equivalent to the constant delayed amount, which is referred to as the indifference point. These indifference points are gathered at a wide range of timeframes to obtain a discounting function. The delay discounting function can be quantified when the indifference points are fitted to the following equation:

$$V=A/(1+kD) \quad (\text{Eq. 1})$$

where V is the subjective value of the objective monetary amount A, to be delivered after some delay, D (Mazur, 1987). The free parameter k describes the slope of the hyperbolic function and is used as an index of the extent to which participants discount the value of future rewards (see Figure 1, described in more detail below). Taken together, higher k values indicate a tendency to devalue future rewards at a higher rate and this, in turn, suggests greater impulsivity. While there are other equations used to approximate the rate of delay discounting (McKerchar et al., 2009; Yi, Landes, & Bickel, 2009) Eq. 1 denoted above is the most commonly used model of addicted individuals as evidenced by its use in approximately 70% of studies (MacKillop et al., 2011). Note, that delay discounting can be used with a wide variety of commodities, including, but not limited to drugs, food, and health.

Based on the work of McClure and others, delay discounting was shown to characterize the relative balance of the Competing Neurobehavioral Decision System. Excessive delay discounting illustrates greater relative control of the impulsive over the executive decision

system, while limited delay discounting illustrates greater relative control of the executive over the impulsive decision system (McClure, et al., 2004).

Consequently, excessive discounting of future rewards indicates the dysregulation between the dual systems. Such dysregulation, or excessive discounting, has been robustly observed in substance dependence (Bickel, et al., 1999; MacKillop, et al., 2006b; Reimers, et al., 2009), so much so, that nearly every substance of abuse is associated with increased delay discounting. For example, in one of the early studies of delay discounting, heroin-dependent individuals and matched control participants discounted a hypothetical \$1000. The results from this study are illustrated in Figure 1 and show that heroin addicts discount the future significantly more than controls. Additionally, negative health behaviors (i.e., pathological gambling, overeating and obesity, and risky sexual behavior) are also associated with excessive discounting of future rewards when compared to a community sample (Bickel et al., 2011; Camchong et al., 2011; Monterosso et al., 2007). The increase in the maladaptive choice to forgo long term benefits and instead opt for short term gratification is indeed a common thread across the aforementioned negative health behaviors is consistent with a trans-disease process (Bickel et al., 2012a). Indeed, if delay discounting is an underlying construct, then efficacious treatments for one negative health behavior should be useful for another.

Increasing the Relative Control by the Executive Decision System

Therapies specifically designed to increase the influence of the executive decision system within the field of addiction are largely nascent. Here we primarily discuss the emerging research on working memory training to improve self-control. We then discuss two other approaches, episodic future thinking, and TMS, that may render working memory training a more potent or implementable intervention. The present limitations and future directions of research into the efficacy of these three therapies will then be discussed.

Working Memory Training

Working memory refers to the temporary storage of a finite amount of information that allows one to (1) form a representation of the current environment, (2) manipulate this information to solve immediate problems, and (3) achieve current goals (Baddeley, 1986). Working memory is one of the executive functions (Miyake et al., 2000) and is believed to be a major determinant of one's general fluid intelligence (Unsworth, Fukuda, Awh, & Vogel, 2014; Unsworth & Spillers, 2010), likewise this ability correlates with self-control (Hinson, Jameson, & Whitney, 2003; Shamosh et al., 2008).

Working memory training is the process of having a participant complete blocks (usually between 4 to 8) of working memory tasks during sessions that occur several times a week (Klingberg, 2010). First reported in children with attention deficit hyperactivity disorder (Kerns, Eso, & Thomson, 1999), this mode of training is often computerized, as training is most effective when task difficulty is constantly adjusted so that each task taxes the individual at the limit, or above the limit, of their abilities (Gibson et al., 2013). In some cases (e.g., individuals with brain injury, Bjorkdahl, Akerlund, Svensson, & Esbjornsson,

2014; ADHD, Klingberg, 2010) engaging in this training produces enhancements in working or months (Holmes, Gathercole, & Dunning, 2009) after training cessation.

The mechanism by which working memory training results in changes in executive function is currently unknown (Shipstead, Redick, & Engle, 2012). Consistent with research on neural plasticity, working memory training has been shown to change neural structure and function. Cortical changes in white and gray matter densities in areas involved in working memory performance have been observed (Buschkuhl, Jaeggi, & Jonides, 2012; Takeuchi et al., 2010). Likewise prefrontal cortex activity increases as a function of training exposure (Olesen, Westerberg, & Klingberg, 2004), however frontal cortex activity was shown to increase after early training sessions, followed by a decrease in activity after later training sessions (Klingberg, 2010), a pattern which may reflect the transition of an unlearned, novel skill to a learned, behavioral repertoire (Bickel et. al., 2012a).

Germane to drug addiction, the degree of improvement in working memory ability (specifically, updating of information) in normal functioning individuals after five weeks of training was associated with increased striatal activity (Backman & Nyberg, 2013; Dahlin, Neely, Larsson, Backman, & Nyberg, 2008) and dopamine release in the striatum (Backman et al., 2011) on similar transfer tasks. Likewise, an increased density of dopamine (type 1) receptors in the pre-frontal cortex has been observed after working memory training (McNab et al., 2009). This is important because substance dependent individuals demonstrate deficiencies in dopamine concentration and functionality in both of these brain regions (See Volkow, Fowler, Wang, Baler, & Telang, 2009; Volkow et al., 2008, for reviews) as well as individuals suffering from obesity (Volkow, et al., 2008; Wang et al., 2001) (specifically, dopamine type 2 receptors: see Volkow, et al., 2008; Wang, et al., 2001). Indeed, working-memory training appears to modify multiple brain areas (e.g., the prefrontal cortex and striatum) that do not function optimally among substance dependent and obese individuals.

Working memory training effects on negative health behaviors—In the first extension of working memory training to drug dependent adult participants, Bickel, Yi, Landes, Hill & Baxter (2011) tested in treatment stimulant users pre- and post-working memory training intervention on a series of tasks including delay discounting, a frontal lobe functionality questionnaire, response inhibition, and a letter sequencing test. Participants were enrolled into either the experimental or control condition and matched on several demographic and behavioral features. Control participants were yoked to a participant in the experimental condition. In the experimental condition, participants completed a series of four working memory training tasks, whereas the control participants received a battery of computerized tasks modified to provide the correct answers; that is, working memory ability was not taxed. After receiving training (between 4-15 sessions for all participants) the degree of delay discounting of several monetary amounts significantly decreased for the experimental participants relative to controls. No other significant differences were observed between these groups. This result was the first to show that the self-control abilities of former stimulant users could be improved using working memory training. Note, this study examined the effects of working memory on delay discounting but did not employ measures of clinical outcome.

Several studies have examined the clinical effects of working memory training among problem drinkers (see Bates, Buckman, & Nguyen, 2013, for a review). For example, a recent study where problem drinkers experienced 28 sessions of internet-based working memory training; in the experimental condition the task difficulty was adjusted so that the participants were tested at the limit of their capabilities, whereas difficulty in the control condition was not adjusted and remained at the easiest level throughout training. Participants who received the experimental conditions demonstrated an increase in working memory capacity relative to control participants, and in conjunction with this, weekly consumption of alcoholic drinks was significantly less in the experimental group both after training and one week after training cessation (Houben, Wiers, & Jansen, 2011).

Working memory training has also been investigated in other disorders associated with excessive discounting. Specifically, it was investigated as an adjunctive treatment program designed to decrease obesity in children. Forty-four overweight children were randomly separated into two groups: one group received a highly successful 3 month cognitive behavioral therapy regimen alone, whereas the other group received this same therapy as well as a game-based training program that taxed working memory four times a week for six weeks. While no significant difference in weight loss (measured via body mass index) was obtained between the two group at the end of treatment (both groups had lost weight throughout the course of the treatment), children who also experienced working memory training re-gained significantly less weight 8 weeks after leaving the program, however, after 12 weeks there was no significant difference in current body mass index between the two groups (Verbeken, Braet, Goossens, & van der Oord, 2013). The above study suggests the possibility that working memory training can contribute to the continuation of treatment outcomes. Perhaps if participants were provided a booster working memory sessions during the follow-up period, then the treatment effects may have been extended further post-treatment.

Combined these results, provide initial support for working memory training as a potentially effective treatment for those disorders associated with excessive discounting. Participants who received this treatment showed self-control repair (as indicated by changes in delay discounting), decreased alcohol consumption, and experienced greater sustained success in maintaining weight loss. If similar therapeutic outcomes were obtained with other groups who exhibit excessive discounting, then working memory training could be considered a trans-disease therapeutic intervention.

Limitations—As mentioned above, the exact mechanism behind working memory training enhancement in self-control is unknown. Relatedly, the most efficacious amount of training (in terms of minutes, number of tasks, number of session per week, and number of weeks) needed to instill improvements in self-control has yet to be identified (Wiers, Gladwin, Hofmann, Salemink, & Ridderinkhof, 2013). Further, the effect of this intervention on self-control has been shown to be temporary, but the time limit before a participant's behavior returns to baseline levels varies widely across studies – some have identified this limit as being either weeks (Shipstead, Hicks, & Engle, 2012) or months (Holmes, et al., 2009). Likewise whether booster training sessions could be used to maintain the benefits remains to be determined as well as, when and how often these booster sessions should be

administered. Working memory training has also been shown to cause different effects in diffuse brain regions (e.g., prefrontal cortex and striatum) and behaviors. While initial evidence suggests negative side effects are unlikely, unintended consequences of this training may yet be observed.

Potential Means to Augment Working Memory Training Efficacy

Evidence suggests that working memory training is beneficial, however, in several studies the frequency and duration of training can be challenging. Methods that could decrease the amount of training necessary to achieve an effect or that might contribute sustained improvements would be useful to identify. Such outcomes could be possible by examining the interaction of working memory training with other interventions that also operate via the executive decision system. Below we describe two such techniques, episodic future thinking and TMS, briefly explain (1) the changes in neural activation produced by these methods, (2) positive effects that have had on individuals with addiction or an impulsive behavior disorder (e.g., obesity), and (3) suggest ways these interventions can be used in conjunction with working memory training in future self-control studies.

Episodic Future Thinking

Episodic future thinking, or mental time travel, is the act of projecting a representation of oneself into a plausible future scenario (Atance & O'Neill, 2001; Sullivan, Riccio, & Castillo, 2009). Engaging in this action appears to create a more elaborate representation of the event (Boyer, 2008), as individuals who engage in episodic future thinking have been shown to discount delayed rewards less (see Koffarnus, Jarmolowicz, Mueller, & Bickel, 2013, for a review). The role of episodic future thinking in decision-making has been investigated among a community sample by Peters & Buchel (2010). In this study, delay discounting was dependent on how vividly one envisioned future episodes. In a follow-up study by Lin & Epstein (2014) rates of delay discounting decreased when the participants were reminded of future episodes they previously described. The magnitude of change was correlated with working memory capacity. Extension of this observation to obese individuals demonstrated that cues of future vivid episodes decreased delay discounting (Daniel, Stanton, & Epstein, 2013a). When these same cues were played during a free access to food session, participants consumed fewer calories relative to the control condition (Daniel, Stanton, & Epstein, 2013b).

The above findings suggest that both creating a future episode and being prompted by a previously formed episode result in a temporary increase in self-control. As this effect is likely transitory, the best application of this procedure as an aid to individuals with self-control deficits would be its use in conjunction with working memory training. Perhaps reviewing cues of previously formed future episodes following working memory training sessions would have additive or supra-additive effects on exercising or improving executive function.

Transcranial Magnetic Stimulation

TMS is a procedure where a magnetic field is created above neuronal tissue, causing the voltage-gated ion channels in neurons to open and initiate action potentials (Barker, Jalinous, & Freeston, 1985). Increased long-term potentiation and neuronal plasticity between areas receiving certain types of stimulation and connected brain tissues has been observed (see Sandrini, Umiltà, & Rusconi, 2011, for a review). While the exact mechanism of action of these changes is unknown, the therapeutic potential of TMS continues to be explored.

Therapeutic application of repetitive TMS (a rapid sequence of magnetic pulses) has been used to alleviate symptoms of drug-resistant depression (see Fitzgerald & Daskalakis, 2013, for a review), chronic migraine headaches (Misra, Kalita, & Bhoi, 2013) and is currently being explored as a potential treatment for diseases such as Parkinson's, post-traumatic stress disorder, and chronic pain (see Horvath, Perez, Forrow, Fregni, & Pascual-Leone, 2011, for a review). A number of studies have also found that delay discounting, can be modulated by administering repetitive TMS to the left dorsal lateral prefrontal cortex (Figner, et al., 2010; Hare, Hakimi, & Rangel, 2014; Hayashi, Ko, Strafella, & Dagher, 2013). As a result, repetitive TMS is being explored as an intervention for individuals suffering from impulsive behavioral disorders such as drug addiction.

Initial findings suggest that TMS is a potential therapeutic target for self-control deficits, and an aid for individuals entering drug addiction recovery (see Barr et al., 2011, for a review). To date, only one study has investigated the effects of TMS on both drug use and self-control. Stimulation of the left dorsal lateral prefrontal cortex in non- and current-cigarettes smokers resulted in decreased discounting for monetary gains, but not monetary losses in both groups (Sheffer et al., 2013). In this study, however, TMS caused no change in smoking status.

Several studies have found that the effect of TMS on the motor cortex is more robust if the muscle is activated when stimulation is applied (Agostino et al., 2007; Kim, Park, Ko, Jang, & Lee, 2004; Reis et al., 2008; Yoo et al., 2008). Whether a similar effect will occur in other brain areas, such as the prefrontal cortex, remains to be determined. If this phenomenon is relevant to other brain areas than the effect of TMS on self-control may be additive or supra-additive effects if delivered concurrently with working memory training. Therefore, administration of TMS during working memory training (at a high-frequency specifically, as this form of stimulation increases neuronal excitability; Maeda, Keenan, Tormos, Topka, & Pascual-Leone, 2000) may improve self-control through a synergistic effect of both interventions.

Both episodic future thinking and TMS have been shown to be promising aids in addiction recovery and self-control improvement. However, more research and systematic replications in other self-controlled impaired groups will be necessary to determine the efficacy of these interventions alone or in combination with working memory training.

Constraints on Self-Control Repair and the Consequences for Treatment

When groups who excessively discount the future are compared to controls, often two overlapping distributions are obtained. For example, Figure 2 represents the correlations of future and past \$1000 delay discounting conditions for smokers and controls (Bickel, Yi, Kowal, & Gatchalian, 2008). Discounting of past and future rewards is symmetrical, and in this study, smokers discounted the past and future more than controls. Examination of Figure 2 shows several smokers who do not excessively discount delayed rewards (see arrows in Figure 2) and indeed their discount rate is near the extreme end of little discounting among the control participants. If a treatment that improves delay discounting, such as working memory training, is given to such a heterogeneous group, then the question is whether those participants who discount little will show change in delay discounting rates. Indeed, perhaps the greatest change will occur among those who discount the most and the extent of change will be less as the discounting approximates control values. If a limitation on change exists such as what we outlined here, then that change may exhibit a quantitative signature.

One well-known quantitative signature of change has been identified and employed in the field of behavioral pharmacology (Koffarnus & Katz, 2011). This quantitative signature, rate dependence, refers to an inverse relationship between baseline rates of responding pre- and post-intervention (Witkin & Katz, 1990). That is, the magnitude and directional effects of an intervention are dependent upon the level or rate of behavior at baseline immediately prior to the intervention (Bickel, Landes, Kurth-Nelson, & Redish, 2014). Rate dependence has been found with drug and non-drug interventions in clinical and preclinical studies (Bickel, Higgins, Kirby, & Johnson, 1988; Diamond & Lee, 2011; Koffarnus, et al., 2013). Indeed, rate dependence has been implicated as the mechanism by which stimulants treat symptoms of attention deficit hyperactivity disorder (Swanson, Baler, & Volkow, 2011) and as a predictor of executive function training efficacy in children (Diamond & Lee, 2011). Importantly and related to the present paper, Diamond and Lee (2011) noted that the children with the greatest deficit in executive function showed the greatest improvement, although the quantitative signature of these changes was not described by them.

Evidence of this quantitative signature of change was found in a recent paper utilizing the delay discounting assay in substance-dependent participants. Those with high rates of baseline discounting were most likely to respond to highly efficacious treatment options (Bickel, et al., 2014). Six intervention studies with 222 total participants were evaluated in this paper. This study found that those with the highest pre-intervention rates were the individuals with the largest change following treatment. Figure 3 depicts the proportion of discount rate change relative to baseline discounting rate in each of the studies analyzed. Rate dependent change after treatment is distinct in studies A – D, however the results from study D are due to regression to the mean. Of the six studies analyzed in Bickel, et. al. (2014), biological treatment outcome measures were obtained in four. Evaluation of the urinalysis revealed the fewest number of positive urine tests was evident in the two studies where rate dependence was observed. Note that baseline delay discounting rate in these two studies were not predictive of therapeutic outcome, rather discounting was changed. Although, biological measures of drug use were not obtained, the experimental group in the

working memory training study showed rate dependent changes in delay discounting while the control group did not show rate-dependent effects. Given that working memory training produced rate dependent effects similar to the highly efficacious treatments then working memory training may produce therapeutic effects consistent with highly efficacious treatments. Moreover, the observed rate dependent effects may indicate that efficacious treatments render the two systems of the Competing Neurobehavioral Decision System into regulatory balance.

The rate dependent effects of highly efficacious treatment is in contrast to the results from studies with moderately effective treatments (e.g. group cognitive behavioral therapy) where baseline rate of delay discounting is predictive of therapeutic outcome for individuals with the highest discounting rates who go on to have poorer therapeutic outcomes (MacKillop & Kahler, 2009; Sheffer et al., 2012; Stanger et al., 2012; Yoon et al., 2007). For example, in a treatment study for overweight children, those who initially discounted future rewards more steeply were those that did not lose weight after an environmental enrichment intervention that included access to many non-food alternative reinforcers (Best et al., 2012). Thus, rate dependence may be a marker of high efficacy treatments and delay discounting may be a predictor of a patient's therapeutic outcome in moderately efficacious treatments.

Collectively, these studies may suggest two orderly relationships between delay discounting and therapeutic efficacy: (1) for moderately efficacious treatments for which baseline delay discounting is predictive of therapeutic outcome, and (2) for highly efficacious treatments for which delay discounting changes inversely to the baseline delay discounting rate. Moreover, these relationships may provide novel opportunities to enhance the efficacy of moderately effective treatment by using patient treatment matching of adjunctive treatments. After baseline delay discounting rates are determined, those likely to have a poor treatment outcome can be identified. A treatment plan can be implemented with a supplemental intervention, such as working memory training, perhaps in conjunction episodic future thinking, or TMS. If adjunctive treatment repairs self-control (i.e., decreases discount rate), then the change in delay discounting rate will be predictive of positive therapeutic outcome. If this strategy proves effective, this signature of change could enable an improvement in the outcome of moderately efficacious treatments without the costs of providing highly efficacious treatments to all patients.

Conclusions

As reviewed above, self-control can be improved by a variety of interventions. An important next step in this line of research is to determine how to maintain those changes in self-control; that is, momentary improvements in self-control are unlikely to have clinical significance. Perhaps, the best way to approach this issue is to adopt the notion developed by Muraven and Baumeister (2000) that self-control functions like a muscle. In that case, we can conceptualize working memory training, for example, as building self-control capacity. However, if working memory abilities, like muscles, are not regularly exercised, then that capacity will begin to atrophy. This was evident in the trial, mentioned above, where obese adolescents received working memory training in addition to a weight-loss intervention (Verbeken, Braet, Goossens, & van der Oord, 2013). They were able to sustain their weight

loss at the first follow-up to a significantly greater extent than a control group that received the same weight loss intervention without working memory training, but not at the subsequent follow-up.

This finding suggests the importance of a future study examining how to sustain self-control improvements. This could be addressed by providing a relevant group with working memory training as part of a treatment intervention (e.g., cognitive behavior therapy) where at the end of the intervention participants would be randomized into two groups. One group would receive booster sessions of working memory training at regular intervals and the other would receive an appropriate control. Such a study would demonstrate whether booster sessions are necessary for sustained improvement in self-control. Once the technology for engendering the maintenance of self-control improvements are determined, then many of the research and clinical questions raised above could be answered.

This review suggests the challenge, the need, the opportunity, the direction, and the constraints involved in the repair of self-control failure evident across multiple negative health behaviors. The challenge is to address the global contribution of self-control failure to excess morbidity and mortality. The need is demonstrated by the poor efficacy of contemporary treatments for disorders associated with self-control failure. The opportunity is to employ recent advances in the conceptual understanding of the decision systems underlying self-control failure in addiction and related negative health disorders. The directions are to utilize the recognition of executive dysfunction in self-control failure as a basis for development of therapeutic interventions such as working memory training alone or together with episodic future thinking or TMS. The constraint is the level of self-control dysfunction, which modulates its repair based on the interaction of both baseline levels of delay discounting and treatment efficacy. Collectively, this series of observations and experimental results may facilitate advances in the treatment of self-control failure, a trans-disease process evident in a broad array of negative health behaviors.

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Figure 1.

Reprinted from Madden et al. (1997). Mean indifference points between large delayed and small immediate monetary rewards in opioid-dependent and control individuals. The closer the function to the x-axis, the greater the discounting rate.

Figure 2.

Reprinted from Bickel et al. (2008). Scatter plots with linear regression lines of future and past \$1000 gains (top) and losses (bottom). Open circles with dashed lines represent smokers and solid circles and lines represent nonsmokers. Arrows indicate smokers with low discounting rates comparable to controls.

Figure 3.

Reprinted from Bickel et al. (2014). Individual change in discounting plotted by baseline discounting rate. Rate dependence is demonstrated in plots A, B, and C. The similar pattern in plot D was due to regression toward the mean.