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Translational Assessment of Reward and Motivational Deficits in Psychiatric Disorders

Andre Der-Avakian[1], **Samuel A. Barnes**[1], **Athina Markou**[1], and **Diego A. Pizzagalli**[2]

[1]Department of Psychiatry, Health Sciences, University of California San Diego, La Jolla, California, U.S.A.

[2]Department of Psychiatry, Harvard Medical School, Belmont, MA, U.S.A.

Abstract

Deficits in reward and motivation are common symptoms characterizing several psychiatric and neurological disorders. Such deficits may include anhedonia, defined as loss of pleasure, as well as impairments in anticipatory pleasure, reward valuation, motivation/effort, and reward learning. This chapter describes recent advances in the development of behavioral tasks used to assess different aspects of reward processing in both humans and non-human animals. While earlier tasks were generally developed independently with limited cross-species correspondence, a newer generation of translational tasks has emerged that are theoretically and procedurally analogous across species and allow parallel testing, data analyses, and interpretation between human and rodent behaviors. Such enhanced conformity between cross-species tasks will facilitate investigation of the neurobiological mechanisms underlying discrete reward and motivated behaviors and is expected to improve our understanding and treatment of neuropsychiatric disorders characterized by reward and motivation deficits.

1. Introduction

Feeling joy and satisfaction when engaging in social activities or accomplishing a task is an important process that promotes positive reinforcement, ensuring that events that are vital for survival and reproductive success are repeated. Conversely, inability to feel pleasure for normally pleasurable experiences can have severely debilitating effects on many aspects of life, including interpersonal relationships, work, and health. Without pleasure, experiences and activities that promote healthy lifestyles may not be appreciated, engaged in, and repeated.

The term anhedonia was coined by the French psychologist Ribot in the late 19th century to describe his patients, for which “it was impossible to find the least pleasure” (Ribot, 1896). Although the term anhedonia is still widely used more than a century later, the behaviors and

Correspondence to: Athina Markou; Diego A. Pizzagalli.

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neurobiological mechanisms that govern impaired reward processing have since evolved to expand beyond anhedonia. Indeed, pleasure is just one aspect of reward processing that contributes to positive reinforcement. As a result, the term anhedonia does not adequately capture the multi-faceted reward processes that, when disrupted, may each have debilitating effects on daily functioning and health even when other reward constructs remain intact.

Besides anhedonia, or loss of pleasure, deficits in other reward processes could result in behaviors that may be interpreted as loss of pleasure. For example, several reward-related processes precede the point at which an experience or activity could be perceived as pleasurable. Individuals must first: 1) anticipate or predict expected rewards that may occur in the future; 2) determine relative values of different rewards; 3) determine the cost or effort required to obtain different rewards; 4) become motivated to perform the necessary goal-directed actions to obtain worthwhile rewards; and 5) learn from previous experiences in order to repeat pleasurable goal-directed behaviors in the future. Deficits in any of these processes may preclude an individual from engaging in goal-directed actions for rewards, regardless of whether or not the reward is perceived as pleasant once obtained. Furthermore, unless carefully assessed, deficits in any of these processes may be incorrectly interpreted as anhedonia. Because each of these distinct reward processes are subserved by distinct neurobiological mechanisms (Der-Avakian and Markou, 2012), understanding which processes are affected in psychiatric and neurological disorders becomes important for elucidating pathophysiology and potential treatment options. This approach is aligned with the United States National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) initiative, which aims to classify mental disorders based on specific behavioral dimensions, such as reward-related subdomains, that can be linked to specific neurophysiological processes (Insel *et al*, 2010).

2. Deficits of Reward and Motivation in Psychiatric and Neurological Disorders

Several psychiatric and neurological disorders are marked by debilitating symptoms relating to reward and motivational deficits (American Psychiatric Association, 2013; World Health Organization, 1992). Anhedonia has been described in major depressive disorder (MDD; core symptom) (Klein, 1974), bipolar disorder (Leibenluft *et al*, 2003), schizophrenia (Haslam, 1809; Meehl, 1962), substance use disorder (particularly during withdrawal) (reviewed in (Markou *et al*, 1998)), eating disorders (Davis and Woodside, 2002), autism spectrum disorder (Chevallier *et al*, 2012), post-traumatic stress disorder (PTSD) (Nawijn *et al*, 2015), Alzheimer's disease (Starkstein *et al*, 2005), and Parkinson's disease (Isella *et al*, 2003) (see below for some caveats to these examples). Recent interest among clinical researchers has focused on investigating which specific reward processes, beyond anhedonia, are affected in the disorders described above (reviewed in Hyman and Fenton, 2003; Insel *et al*, 2010; Leboyer *et al*, 1998; Meyer-Lindenberg and Weinberger, 2006; Whitton *et al*, 2015). This approach is consistent with research in experimental animals, where broadly defined psychiatric disorders characterized by multiple symptoms cannot be modeled in non-human animals, but rather discrete behavioral processes that are often linked to circumscribed neurobiological mechanisms can be assessed (Geyer and Markou, 2002;

Markou *et al*, 2009). Detailed investigation of the precise reward processes affected in each disorder requires novel clinical assessments that reliably distinguish one reward process from another. To take advantage of basic research in animals that can facilitate treatment development, new clinical behavioral assessments must be carefully designed.

3. Important Considerations for Cross-species Behavioral Assessments

Of the several human and animal behavioral assessments designed to measure different components of reward processing (see below and Barnes *et al*, 2014; Markou *et al*, 2013), most were developed independently between species. Thus, attempts to translate behavior across different species have traditionally been limited by several factors, including limited correspondence between human and animal tasks designed to assess the same construct. To improve correspondence between human and animal procedures and the predictive validity of data derived from animal behavioral procedures for human behaviors, the factors described below should be considered when new tasks are developed for any species.

With regard to clinical assessments, behavior is often measured using self-report questionnaires that are subjective in nature and require verbal communication between the experimenter and participant. For obvious reasons, these types of assessments cannot be implemented in animals. Animals may be observed for changes in non-verbal behavior (e.g., locomotor activity, orofacial responses) or may be trained to perform operant responses. Importantly, behavioral output in animals is generally quantifiable and data collection is (or at least should be) objective. Thus, for any clinical assessment to be successfully back-translated to animals, testing should require no verbal communication. In the examples described in the sections below (also, see Table 1), new clinical assessments that have either been translated from existing animal tasks or back-translated into novel animal tasks utilize a computer-based stimulus-response “game” (Anderson *et al*, 2012; Pizzagalli *et al*, 2005; Treadway *et al*, 2009).

With regard to animal procedures, even though assessments generally meet the criteria above with regard to objectivity and non-verbal communication, behavior is sometimes measured in a manner that cannot be replicated in humans. For example, the forced swim and tail suspension tests commonly used with rodents, which are argued to reflect behavioral despair relating to depression, cannot be readily implemented in humans. Because often the experimenter is forced to interpret the behavior observed in animals in terms relating to human behavior, such an anthropomorphic interpretation can be very misleading and, even worse, has failed to predict treatment efficacy in humans for novel medications (Hyman, 2012; Insel *et al*, 2013; Markou *et al*, 2009; Nestler and Hyman, 2010).

Lastly, with regard to both human and animal tasks, behavioral output should ideally be accompanied by some structural or physiological measure that can be compared between species. While human and animal methods for visualizing neural structure and function each have their respective advantages and limitations, comparison of hypothesized neurobiological mechanisms across species will increase confidence that the similarities in observed behavior are manifested by similar biological mechanisms. Such neurobiological

concordance across species will improve the probability that putative treatments for reward deficits tested in animals will translate to the clinic.

4. Translational Assessments of Reward and Motivation

4.1. Pleasure

To disentangle the subtle differences between pleasure and other reward processes, behavioral procedures are required that can measure aspects of pleasure that are not influenced by factors like motivation and learning. The sections below summarize the procedures commonly used to assess pleasure in humans and animals.

4.1.1. Human Assessments of Pleasure—Commonly used self-report scales that exclusively probe for pleasure deficits include the Snaith-Hamilton Pleasure Scale (SHAPS) (Snaith *et al*, 1995), the Fawcett-Clark Pleasure Scale (Fawcett *et al*, 1983), the Positive and Negative Affect Schedule (PANAS) (Watson *et al*, 1988), and the Revised Chapman Physical Anhedonia Scale (CPAS) (Chapman *et al*, 1976), among others. In addition, a subset of scores from questions relating to anhedonia from the Beck Depression Inventory (BDI) and Hamilton Rating Scale for Depression (HAM-D) may be extracted to distinguish deficits in reward processing from other symptoms of depression, although these subscores have generally not been validated. It should be noted that there are several other self-report measures of pleasure that are not listed here, but are widely used for diagnostic and research purposes.

There are important limitations related to relying on subjective observation or self-report of anhedonia that were described above. Recent adaptations of subjective anhedonia scales have begun to address some of these concerns by parsing reward deficits into discrete reward-related constructs, like consummatory and anticipatory anhedonia (see below). Nonetheless, these new scales remain subjective and require verbal communication, limiting their usefulness as translational measures.

4.1.2. Non-human Animal Assessments of Pleasure—In animals, common procedures used to assess anhedonia include the sucrose consumption and preference tests (Willner, 2005; Willner *et al*, 1987). The sucrose consumption test involves measuring the consumption of a palatable sucrose solution during or after exposure to an anhedonia-producing event. Similarly, the sucrose preference test is used to measure the preference for a sucrose solution when given a choice between the palatable drink and water. Decreased or no preference for the sucrose solution over water is argued to reflect anhedonia. While either test may be conducted without prior food or water restriction that is often used to increase motivation to respond during such tasks, the influence of motivation on these tasks cannot be ruled out. Exposure to various forms of stress, a precipitating factor for several psychiatric disorders, decreased sucrose preference in rodents (Willner *et al*, 1992) and non-human primates (Paul *et al*, 2000). However, the reliability of the sucrose preference test as a measure of anhedonia in animals has been questioned by several researchers who have been unable to replicate decreases in sucrose consumption or preference after chronic mild stress exposure (Forbes *et al*, 1996; Harris *et al*, 1997; Matthews *et al*, 1995; Reid *et al*, 1997).

4.1.3. Convergence of Human and Non-human Animal Assessments of Pleasure—

While the human anhedonia scales cannot be translated into analogous animal tasks, the sucrose preference test has been adapted for use in humans. Interestingly, attempts to translate the animal findings of stress-induced anhedonia to humans have largely resulted in negative results. For example, patients with MDD, schizophrenia, or autism do not show deficits in the hedonic response to sucrose compared to healthy controls (Berlin *et al*, 1998; Damiano *et al*, 2014; Dichter *et al*, 2010). These results from human and animal studies suggest that either: a) the sucrose preference test is not a valid assessment of pleasure; or b) psychiatric disorders such as MDD, schizophrenia, and autism are not associated with deficits in pleasure. Notably, several lines of evidence have begun to confirm the latter point, particularly with regard to schizophrenia (Barch *et al*, 2015; Gard *et al*, 2007; Heerey and Gold, 2007).

4.2. Anticipation

Whereas hedonic, or consummatory, pleasure is defined as pleasure experienced while engaged in a rewarding activity, anticipatory pleasure is pleasure that is experienced at the thought of an event that is expected to occur in the future. Thus, deficits in anticipatory pleasure require the formulation of mental representations of future events. It has been well established that consummatory and anticipatory pleasure are mediated by distinct neural processes (Berridge and Robinson, 2003; Der-Avakian *et al*, 2012; Schultz, 2002). Consummatory pleasure is subserved by opioid and serotonergic mechanisms, while anticipatory pleasure is mediated primarily by dopaminergic mechanisms (Barbano and Cador, 2006, 2007). Thus, it is not surprising that anticipatory pleasure has been linked to motivation, another reward construct mediated by mesolimbic dopamine transmission (see below). For example, in MDD, anticipation for a rewarding event predicted the degree of an individual's motivation to produce goal-directed actions to obtain the rewarding event (Sherdell *et al*, 2012). Importantly, clinical studies have highlighted a dissociation between consummatory and anticipatory pleasure in psychiatric disorders. For example, schizophrenia has been associated with disrupted anticipatory pleasure, but intact consummatory pleasure (Gard *et al*, 2007; Mote *et al*, 2014). Conversely, patients with Parkinson's disease showed deficits in consummatory, but not anticipatory, pleasure (Loas *et al*, 2014). Thus, understanding the precise construct that is affected in different disorders has important implications for treatment development.

4.2.1. Human Assessments of Anticipation—

Clinical assessments that distinguish between consummatory and anticipatory anhedonia have been developed in recent years. The Temporal Experience of Pleasure Scale (TEPS) (Gard *et al*, 2006) is an 18-item self-report measure of trait anticipatory and consummatory pleasure that requires participants to respond using a Likert scale to indicate their agreement with statements that reflect either enjoyment of a reward or enjoyment relating to anticipation of a reward. An example of a statement probing anticipatory pleasure is: "When something exciting is coming up in my life, I really look forward to it." Scores on the anticipatory pleasure-related items of the TEPS positively correlated with scores on the Behavioral Activation Scale (BAS), a measure of motivated behavior (Carver and White, 1994), further confirming the relationship between anticipatory pleasure and motivation (Gard *et al*, 2007).

Similar to the TEPS, the Anticipatory and Consummatory Interpersonal Pleasure Scale (ACIPS) is a 17-item self-report measure specifically designed to assess anticipatory pleasure relating to social-interpersonal interactions as well as consummatory pleasure relating to the experience of pleasure for social-interpersonal interactions when they occurred (Gooding and Pflum, 2014a). The ACIPS also uses a Likert scale that measures level of agreement with statements like: “I look forward to seeing people when I'm on my way to a party or get-together.” Scores on the ACIPS positively correlated with scores on the TEPS, as well as with scores on the BAS, again suggesting that anticipatory pleasure is strongly related to motivated behavior (Gooding *et al*, 2014a; Gooding and Pflum, 2014b).

The TEPS and ACIPS are important tools that have provided new and detailed insights into the disrupted behaviors associated with psychiatric and neurological disorders. The advent of these scales that assess anticipatory pleasure may prompt the development of additional clinical measures that can accurately distinguish consummatory and anticipatory pleasures from motivation, valuation, learning, and so on. Nonetheless, as discussed above, the required verbal communication required to respond to these scales precludes the possibility of developing animal versions of these measures.

4.2.2. Non-human Animal Assessments of Anticipation—Animal behavioral tasks developed to assess anticipatory pleasure generally measure arousal, anticipatory locomotor activity, and approach behavior prior to presentation of an expected reward. The reward is typically presented for several days at the same time of day. After training, anticipatory behavior is assessed on a test day immediately prior to the time of day when the reward is typically presented. Increased locomotor activity has been observed in rodents in anticipation of food (known as food-anticipatory activity) (Mistlberger, 1994), a sweet palatable reward (Hsu *et al*, 2010; Mendoza *et al*, 2005), a sexually receptive female (Mendelson and Pfaus, 1989; Pfaus and Phillips, 1991), or a drug reward (i.e., ethanol) (Buck *et al*, 2014a). While many of the studies on anticipatory pleasure involved rodents, food-anticipatory activity is conserved across species, including honeybees (Moore *et al*, 1989), fish (Weber and Spieler, 1987), birds (Wenger *et al*, 1991), rabbits (Jilge, 1992), and monkeys (Sulzman *et al*, 1977). In rodents, anticipatory activity was disrupted by manipulations known to produce depression-related behaviors in humans, including social stress (Kamal *et al*, 2010; van der Harst *et al*, 2005) and withdrawal from chronic amphetamine treatment (Barr *et al*, 1999a). Moreover, blocking dopamine, but not opioid, signaling disrupted anticipatory behavior in rats (Barbano *et al*, 2006), which is consistent with current knowledge of neurotransmitter systems mediating consummatory (opioid) and anticipatory (dopamine) pleasure (Barbano *et al*, 2007).

Anticipatory pleasure may also be assessed by measuring short, high ultrasonic vocalizations (~50 kHz) in rats, with higher frequency of ultrasonic vocalizations reflecting greater anticipation of an expected reward (Knutson *et al*, 2002). Indeed, increased anticipatory motor behavior was positively correlated with frequency of high ultrasonic vocalizations (Brenes and Schwarting, 2015). High ultrasonic vocalizations were emitted in anticipation of several rewarding stimuli, including food (Buck *et al*, 2014b; Opiol *et al*, 2015), a cocaine or ethanol reward (Buck *et al*, 2014a; Ma *et al*, 2010), and being reunited with a cage mate after a period of social isolation (Willey and Spear, 2012). As with anticipatory activity, blocking

dopamine neurotransmission attenuated high ultrasonic vocalizations in response to food (Buck *et al*, 2014b).

Successive contrast effects reflect adaptations of behavior in response to unexpected changes of an anticipated reward. Positive contrast effects are observed when a greater reward (e.g., 4 food pellets) is unexpectedly obtained compared to an anticipated smaller reward (e.g., 1 food pellet), eliciting a greater behavioral response (e.g., lever pressing) than if the higher value reward was only ever experienced. Conversely, negative contrast effects are observed when a smaller reward is unexpectedly obtained compared to an anticipated greater reward, which typically elicits a greater depression of behavioral responding than if the smaller value reward was only ever experienced. The latter shift (i.e., negative contrast effect) is argued to reflect a state of disappointment that arises from the anticipated reward not being delivered. Successive contrast effects are highly conserved across species, including honeybees (Couvillon and Bitterman, 1984), rats (Barr and Phillips, 2002), dogs (Bentosela *et al*, 2009), and humans (Specht and Twining, 1999). As with anticipatory activity, depression-producing events, like amphetamine withdrawal, exacerbated negative contrast effects in rats (Barr *et al*, 2002), whereas acute amphetamine administration attenuated negative contrast effects (Phelps *et al*, 2015). Moreover, administration of a dopamine D1 receptor antagonist worsened negative contrast effects (Phelps *et al*, 2015), supporting the argument that reward anticipation is mediated by dopaminergic mechanisms. The role of dopamine in successive contrast effects is perhaps not surprising, given that the behavioral procedure may also be argued to reflect positive and negative reward prediction error processing, whereby greater- or lesser-than-expected rewards, respectively, are experienced. Positive and negative reward prediction errors are thought to be mediated by increased and decreased striatal dopamine signaling, respectively (Schultz *et al*, 1997).

4.2.3. Convergence of Human and Non-human Animal Assessments of Anticipation—While both human and animal assessments of anticipatory pleasure have played an important part in our understanding of reward processing in psychiatric and neurological disorders and their underlying neurobiological mechanisms, assessments are limited to the species in which they were developed. As with the assessments of consummatory pleasure reviewed above, the parallel development of objective, non-verbal assessments of anticipatory pleasure across species would benefit translational research efforts aimed at this reward construct. Nonetheless, the convergence of evidence surrounding the role of dopamine in anticipatory pleasure using different human and animal assessments suggests that the different species-specific tasks are tapping into similar behavioral and neurobiological mechanisms.

4.3. Reward Valuation

Reward valuation involves assessment of the relative value of rewards that guide approach and motivated behaviors. For example, rewards of higher value are expected to produce greater anticipation of and motivation to obtain the reward compared to rewards of lower value. Prior experiences allow individuals to create representations of reward value for future stimuli. Thus, reward valuation involves some aspects of pleasure, learning, memory, and decision making. Interestingly, pleasure and valuation have been dissociated in

schizophrenia, with patients showing intact capacity to experience pleasure, but deficits in properly representing the value of future rewards (Gard *et al*, 2007; Gold *et al*, 2008). After reward valuation, effort calculations, based on the work required to obtain the reward, are integrated with value calculations to construct a cost-benefit analysis to determine whether the value of the reward justifies the effort required to obtain it. Accordingly, motivated behavior may be affected by disruptions in reward valuation. Reward valuation is highly conserved across species and has been observed in mice (Crombag *et al*, 2010; Hilario *et al*, 2007), rats (Balleine and Dickinson, 1992), sheep (Catanese *et al*, 2011), monkeys (Burke *et al*, 2014; West *et al*, 2011), and humans (Klossek *et al*, 2008).

4.3.1. Human Assessments of Reward Valuation—Outcome devaluation tasks have been developed for use in humans based on existing non-human animal tasks (see below). An outcome devaluation task is similar to a successive negative contrast task in that lowering the value of an expected outcome results in a decrease in behavior for that outcome. In a typical outcome devaluation task, participants are presented with two different stimuli (e.g., food or money) and perform one of two operant responses to receive either reward. One of the stimuli is then devalued, typically by overexposing the participant to that stimulus. As a result, participants tend to respond more for the stimulus that was not devalued compared to the devalued stimulus. By contrast, impaired outcome devaluation is reflected by a lack of decreased responding for the devalued stimulus.

Several manipulations have been shown to affect outcome devaluation in humans. For example, acute alcohol exposure in healthy individuals disrupted sensitivity to outcome devaluation (i.e., participants did not reduce their responding for the devalued stimulus) (Hogarth *et al*, 2012). fMRI studies revealed that sensitivity to outcome devaluation is associated with activity of the ventromedial prefrontal cortex (de Wit *et al*, 2009; de Wit *et al*, 2012) and orbitofrontal cortex (Valentin *et al*, 2007). Furthermore, consistent with neuroanatomical studies in rodents (see below), patients with Parkinson's disease, which is characterized by dopamine depletion in the dorsal striatum, showed impaired outcome devaluation (de Wit *et al*, 2011), suggesting a corticostriatal mechanism involved in reward valuation.

4.3.2. Non-human Animal Assessments of Reward Valuation—Outcome devaluation in animals is often assessed in an instrumental conditioning task similar to that described above for humans (Adams and Dickinson, 1981). Subjects are presented with two different rewards of different values (e.g., food and sucrose pellets), each requiring a separate behavioral response to obtain the reward (e.g., in rodents, pressing a left vs. right lever for different valued rewards). As in humans, outcome devaluation can be achieved by satiating a subject that responds for a food reward or pairing the reward with a noxious stimulus. After diminishing the value of one of the rewards, the subject is given a choice to respond on either lever and typically chooses to respond more on the lever associated with the non-devalued reward compared to the lever associated with the devalued reward.

Several animal studies using an outcome devaluation task suggest that corticolimbic structures are involved in reward valuation. Lesions of the dorsomedial striatum or administration of a N-methyl-D-aspartate (NMDA) receptor antagonist into this region

blocked the post-conditioning decrease in behavioral responding for a devalued reinforcer in rats, reflecting insensitivity to outcome devaluation (Yin *et al*, 2005a; Yin *et al*, 2005b). This role of the striatum in outcome devaluation is believed to involve the core, but not the shell, of the nucleus accumbens (Corbit *et al*, 2001). In agreement with studies in humans described above, lesions of the medial prefrontal cortex or basolateral amygdala of rats disrupted sensitivity to outcome devaluation (Balleine and Dickinson, 1998; Corbit and Balleine, 2003, 2005; Killcross and Coutureau, 2003). Moreover, smaller orbitofrontal cortex volume was associated with impaired outcome devaluation in monkeys (Burke *et al*, 2014). Overall, these results suggest an involvement of corticolimbic circuits in reward valuation. Interestingly, repeated daily administration of amphetamine, which increases cortical and striatal dopamine signaling, also disrupted sensitivity to outcome devaluation (Nelson and Killcross, 2006).

4.3.3. Convergence of Human and Rodent Assessments of Reward Valuation

—While few examples exist of cross-species parallel comparisons of human and animal reward valuation tasks, results from outcome devaluation tasks are strikingly consistent across species. Perhaps the best example of cross-species correspondence in reward valuation is demonstrated by studies investigating the effects of stress on sensitivity to outcome devaluation. Humans exposed to a socially evaluated cold pressor test (Schwabe and Wolf, 2010) and rats exposed to chronic unpredictable stress, which includes social defeat, forced swim, and restraint (Dias-Ferreira *et al*, 2009), both showed decreased sensitivity to outcome devaluation. In humans, these effect of stress were associated with decreased volume of the medial prefrontal cortex and caudate (Soares *et al*, 2012). Indeed, several lines of evidence from both humans and animals suggest critical involvement of medial prefrontal and orbitofrontal cortices, as well as the striatum, in outcome devaluation (for review, see Balleine and O'Doherty, 2010). Importantly, because the outcome devaluation task was initially developed as an operant task in animals, translation to an analogous human task was possible and produced a framework in which to investigate reward valuation across species.

4.4. Motivation/Effort

Motivation is the incentive or desire to act or accomplish goals. Deficits in motivation may result from deficits in other reward constructs, such as pleasure or anticipation. For example, if an individual is unable to derive pleasure from a normally rewarding activity or from anticipation of that activity, then it is unlikely that the individual will be motivated to pursue that activity (Salamone *et al*, 2009; Sherdell *et al*, 2012). Moreover, deficits in motivation may contribute to the development of other symptoms of psychiatric illness, such as social withdrawal and cognitive impairment (Brebion *et al*, 2009), and can be severely debilitating with regard to functional outcome and reduced quality of life in patients (Barch and Dowd, 2010; Simpson *et al*, 2012).

Recent findings have begun to emerge highlighting the specific role of motivation in psychiatric disorders. For example, although deficits in motivation were recognized nearly a century ago in schizophrenia (Kraepelin, 1921), recent evidence suggests that such deficits are dissociable from consummatory pleasure, which is intact in individuals with

schizophrenia (Barch *et al*, 2015; Gard *et al*, 2007; Heerey *et al*, 2007). Additionally, autism spectrum disorder is associated with anhedonia relating to social, but not other, stimuli (Chevallier *et al*, 2012; Damiano *et al*, 2014), but motivation to complete certain tasks can be greater in autism spectrum disorder compared to healthy controls (Damiano *et al*, 2012).

4.4.1. Human Assessments of Motivation/Effort—As with anticipatory pleasure assessments, clinical self-report questionnaires focused on motivated behavior and drive have emerged over the last two decades. The Behavioral Activation Scale (BAS) is a 13–item Likert-based self-report questionnaire probing aspects of reward relating to "reward responsiveness" (five items), "fun-seeking" (four items), and "drive" (four items) (Carver *et al*, 1994). Low BAS scores have been associated with increased MDD risk, severity of current MDD, and poor outcome with MDD (Kasch *et al*, 2002; McFarland *et al*, 2006; Meyer *et al*, 1999). Similarly, the Motivation and Pleasure Scale – Self Report (MAP-SR) is an 18-item Likert-based self-report questionnaire probing motivation related to social/ interpersonal relationships and recreational/work activities (Llerena *et al*, 2013). In addition, experience-specific motivation scales are available to assess motivational impairment in areas such as academics (the Academic Motivation Scale) (Vallerand *et al*, 1992), athletics (the Sport Motivation Scale) (Pelletier *et al*, 1995), and fitness/health (the Exercise Motivation Scale) (Li, 1999). Again, while attempts to clinically distinguish motivational impairment from other aspects of reward processing are encouraging, these self-report measures offer minimal translational value.

Because several animal procedures exist that measure motivated behavior (see below), recent attempts have been made to adapt those procedures for use in humans in a clinical laboratory setting. For example, using a progressive ratio schedule of reinforcement, operant responding (e.g., lever pressing in rodents) for a food reward is measured as the response requirement to receive each subsequent reward is exponentially increased. Eventually, the subject terminates responding when the effort required to receive a single reward becomes too great, which is interpreted as the subject's maximum level of motivation. The final ratio completed to earn a single reward is termed a breakpoint, with decreased breakpoints reflecting decreased motivation (Hodos, 1961). Human versions of the progressive ratio task have been developed to assess motivated behavior (Roane *et al*, 2001). Similar to rodents, human participants are instructed to perform an operant response (e.g., click a computer mouse or press a key on a keyboard) to earn a reward. Obtaining subsequent rewards then requires exponentially more clicks or key presses. Participants continue to perform the operant response to obtain a reward before ultimately giving up, presumably because the cumulative effort required to obtain the reward eventually outweighs the perceived value of the reward. Importantly, several studies have validated the human procedures, in which more preferred rewards elicited greater breakpoints than less preferred rewards (Glover *et al*, 2008; Penrod *et al*, 2008; Roane *et al*, 2001; Trosclair-Lasserre *et al*, 2008). Most studies utilizing progressive ratio reinforcement schedules in humans have done so using drugs of abuse as reinforcers. As expected, dependent individuals showed high levels of motivation (i.e., breakpoints) for drug administration (Stoops, 2008). Interestingly, using money as a reinforcer, patients with schizophrenia showed decreased breakpoints in a computerized progressive ratio task (Wolf *et al*, 2014).

The effort-related choice tasks represent particularly intriguing examples of translation from rodent to human behavioral testing. In rodents, effort-related choice refers to the choice an animal makes to either exert effort for a high value reward or opt for a low value reward that is freely available (see below) (Salamone *et al*, 1991). The Effort-Expenditure for Rewards Task (EEfRT; Figure 1A) is a computer-based game that was recently developed as a human analogue of the effort-related choice task in rodents (Treadway *et al*, 2009). With EEfRT, participants may choose between performing a hard or easy task (i.e., completed number of key presses within a short or long period of time, respectively). Successful completion of the hard and easy tasks is subsequently rewarded with relatively high and low monetary rewards, respectively, and the probability of receiving a reward varies with each trial and is indicated prior to choosing task difficulty. Given a medium to high probability of receiving a reward, the proportion of choosing the hard task was inversely correlated with self-reported anhedonia (Treadway *et al*, 2009). With regard to psychiatric disorders, patients with MDD were less likely to choose the hard task compared to healthy controls (Treadway *et al*, 2012a), suggesting that willingness to exert effort to obtain rewards is diminished in MDD. Similarly, effort-related choice was disrupted in patients with schizophrenia using EEfRT (Barch *et al*, 2014; Fervaha *et al*, 2013; Treadway *et al*, 2015) as well as other similar computer-based effort-related choice tasks (Gold *et al*, 2013). Interestingly, using EEfRT, adults with autism spectrum disorder were more likely to choose the hard task compared to healthy controls, but were less influenced by reward probabilities, supporting the argument that people with autism spectrum disorder tend to be highly motivated, but only for very selective tasks (Damiano *et al*, 2012).

4.4.2. Non-human Animal Assessments of Motivation/Effort—As described above, progressive ratio tests are often used to assess the motivational properties of natural and drug reinforcers in animals (Hodos, 1961; Hodos and Kalman, 1963). While decreased breakpoints are generally thought to reflect decreased motivation, alternate interpretations must be carefully considered. For example, motor impairment or satiety may impede sustained responding required to achieve high breakpoints. Decreased breakpoints may also reflect intolerance for the progressively increasing time delay between reward presentations. Conversely, increased breakpoints may stem from increased perseverative responding. Additionally, it is difficult to dissociate the hedonic from the motivational aspects of a reinforcer using a progressive ratio task alone. Addressing these caveats will help determine whether altered breakpoints reflect changes in motivation or another factor.

In rodents, several manipulations decrease breakpoints for a reward in a progressive ratio task. Withdrawal from chronic administration of several drugs of abuse, like cocaine (Carroll and Lac, 1987), amphetamine (Barr and Phillips, 1999b; Der-Avakian and Markou, 2010), nicotine (LeSage *et al*, 2006), and morphine (Zhang *et al*, 2007) decreased responding for a sucrose reward on a progressive ratio schedule of reinforcement. Similarly, rhesus monkeys chronically treated with escalating methylphenidate doses showed decreased breakpoints for a food reward (Rodriguez *et al*, 2010). Rats bred for congenital learned helplessness, a genetic animal model of behavioral despair, also showed decreased breakpoints for sucrose (Vollmayr *et al*, 2004). However, not all manipulations typically used to produce depression-like behaviors in non-human animals alter motivated behavior using the progressive ratio

task. For example, chronic mild stress (Barr and Phillips, 1998) and neonatal maternal separation (Shalev and Kafkafi, 2002), two procedures commonly used to model depression-like behavior, failed to alter breakpoints for sucrose in rats.

The effort-related choice task was developed to address some of the limitations of the progressive ratio task described above (Figure 1B) (Salamone *et al*, 1991). This task is similar to the progressive ratio task in that increasing effort is required to obtain a reward. However, an added cost/benefit component is implemented in which the choice of a lesser reward is concurrently offered and can be obtained with little or no effort. With effort requirements being equal, individuals tend to prefer rewards of greater vs. lesser value. However, as the effort required to obtain the greater reward increases, preference eventually shifts towards the lesser reward requiring less effort (Salamone *et al*, 2007; Salamone *et al*, 1997). Thus, the effort-related choice between two different rewards addresses several of the caveats limiting the progressive ratio task described above. Notably, the effort-related choice task allows for a dissociation to be observed between motivation (i.e., exerting effort to obtain the greater reward) and consummatory pleasure (i.e., opting for the freely available lesser reward).

In rats, sucrose pellets or food pellets with high carbohydrate content may be used as a highly palatable reward, whereas standard lab chow is used as the non-preferred reward. The effort required to obtain the highly palatable reward may involve a greater number of lever presses or climbing a larger barrier as compared to obtaining the non-preferred reward (Salamone *et al*, 1994; Salamone *et al*, 1991). Regardless of the details of the procedure used, manipulating dopamine neurotransmission has been consistently shown to shift preference from high cost/high reward choices to low cost/low reward choices. For example, dopamine depletion in the nucleus accumbens or blocking the dopamine D1 or D2 receptor increases preference for freely available lab chow over lever pressing (Salamone *et al*, 1991) or climbing a barrier (Salamone *et al*, 1994; Yohn *et al*, 2015) for a more palatable reward. Similarly, dopamine D2 receptor over-expression in the striatum also increases preference for a low cost/low reward option in an effort-related choice task (Ward *et al*, 2012).

4.4.3. Convergence of Human and Non-human Animal Assessments of Motivation/Effort—Both human and animal versions of the progressive ratio task have been used to investigate the neurobiology of motivated behavior, particularly relating to drug and other addictions, although results have been mixed across species. For example, acute phenylalanine and tyrosine depletion in humans, which acts to decrease dopamine synthesis, decreased breakpoints for alcohol (Barrett *et al*, 2008), tobacco (Venugopalan *et al*, 2011), and money (Cawley *et al*, 2013), suggesting that the increased motivation for these rewards is related to elevated brain dopamine levels. In rats, dopamine depletion produced by 6-OHDA injected directly into the nucleus accumbens decreased breakpoints for a food reward (Aberman *et al*, 1998; Hamill *et al*, 1999), but increased breakpoints for apomorphine (Roberts, 1989), indicating that motivated behavior is mediated by dopamine D1-like and D2-like receptor signaling. Consistent with this view, administration of a dopamine D1-like or D2-like receptor antagonist in rhesus monkeys decreased breakpoints for a food pellet (Von Huben *et al*, 2006).

Not all manipulations have produced congruent results across species. Pretreatment with aripiprazole, a partial agonist at dopamine D2 and serotonin (5-HT) 1A receptors and an antagonist at 5-HT 2A receptors, decreased breakpoints for methamphetamine in recreational users (Stoops *et al*, 2013). Conversely, administration of a 5-HT 2A receptor antagonist failed to alter breakpoints for cocaine, nicotine, or food in rats (Fletcher *et al*, 2002; Fletcher *et al*, 2012). Thus, while the human and animal versions of the progressive ratio task are procedurally similar, parallel cross-species testing using similar manipulations (e.g., global vs. targeted dopamine depletion) and rewards (e.g., drug vs. non-drug reinforcers) will help elucidate the level of congruence between both tasks.

The effort-related choice task in humans (i.e., EEfRT) has only recently been developed, and thus data on congruence with the rodent version of the task is limited, but promising. The findings that effort-related choice is impaired in MDD and schizophrenia (Barch *et al*, 2014; Fervaha *et al*, 2013; Gold *et al*, 2013; Treadway *et al*, 2012a; Treadway *et al*, 2015), psychiatric disorders characterized by disrupted reward-related decision making that is argued to reflect deficits in striatal dopamine transmission, supports rodent studies indicating that effort-related choice is regulated by dopaminergic mechanisms (Salamone *et al*, 1994; Salamone *et al*, 1991). Perhaps even more convincing, acute amphetamine administration, which increases striatal dopamine levels (Kuczenski *et al*, 1991), increased preference for the high cost/high reward choice in both humans (Figure 1C) (Wardle *et al*, 2011) and rats (Figure 1D) (Bardgett *et al*, 2009) in an effort-related choice task. Moreover, willingness to expend effort for larger rewards in humans was positively correlated with increased dopamine in the striatum and ventromedial prefrontal cortex (PFC) in PET imaging studies (Treadway *et al*, 2012b), consistent with the argument for dopamine involvement in effort-related choice.

4.5. Reward Learning

Reward learning is a process by which individuals experience, learn, and repeat goal-directed actions that maximize the probability of receiving future rewards. Similarly, learning can occur to avoid actions that do not result in a reward. Conversely, impaired reward learning results in decisions that are made without regard for reward feedback. Thus, reward learning may involve several other reward processes, including pleasure, motivation, and decision making.

Because of the cognitive aspects associated with reward learning, it is perhaps expected that areas of the prefrontal cortex underlie reward learning. Indeed, increased activity in the dorsal anterior cingulate and orbitofrontal cortices, areas involved in integrating and utilizing reinforcement history to guide behavior, is correlated with elevated reward learning (Frank and Claus, 2006; Santesso *et al*, 2008). Additionally, dopaminergic mechanisms in the striatum are also involved in reward learning (Holroyd and Coles, 2002; Jocham *et al*, 2011, 2014; O'Doherty *et al*, 2004; Santesso *et al*, 2009; Vrieze *et al*, 2013a), suggesting some overlap with mechanisms responsible for anticipatory pleasure and motivation.

4.5.1. Human Assessments of Reward Learning—The Response Bias Probabilistic Reward task (RBPRT) is a laboratory-based task developed initially in humans to objectively

assess normal and disrupted reward responsiveness, defined as the propensity to modulate future behavioral choices based on prior reward experiences (Figure 2A) (Pizzagalli *et al*, 2005; modified after Tripp and Alsop, 1999). The RBPRT combines aspects of a signal-detection task and a probabilistic reward task. In the signal detection component, participants must identify which of two ambiguous stimuli (e.g., a short or long mouth on a schematic face) is presented on a computer screen in order to receive monetary feedback. Unbeknownst to participants, a probabilistic reward component is implemented in the reinforcement schedule, whereby correct identification of one stimulus is reinforced three times more frequently (i.e., rich stimulus) than correct identification of the other stimulus (i.e., lean stimulus). Healthy participants (i.e., without a psychiatric diagnosis) develop a response bias for the rich stimulus, reflecting a shift from accurate responding when either stimulus is presented to increased responding on the key associated with the rich stimulus, regardless of which stimulus was presented. This pattern of change in behavior suggests that reward feedback from the differential reinforcement schedule was effective in modulating subsequent choices, and that healthy participants will tend to bias their responding to try to maximize the rewards received.

Individuals with MDD and bipolar disorder did not develop a response bias for the rich stimulus in the RBPRT (Pizzagalli *et al*, 2008b; Pizzagalli *et al*, 2008c). These individuals instead tended to respond accurately when either rich or lean stimulus was presented, suggesting that the differential reinforcement of the two stimuli was ineffective in promoting a bias for the rich stimulus. Euthymic individuals with remitted depression (Pechtel *et al*, 2013a), individuals without any history of psychiatric illness, but with high trait levels of anhedonia based on a self-report questionnaire (Pizzagalli *et al*, 2005), and healthy individuals exposed to stress, a precipitating factor for several psychiatric disorders (Bogdan and Pizzagalli, 2006; Pizzagalli *et al*, 2007), also showed a blunted response bias compared to controls. Moreover, lower response biases predicted treatment outcome in MDD (Vrieze *et al*, 2013b). Conversely, response bias was not impaired in patients with schizophrenia (Ahnallen *et al*, 2012; Heerey *et al*, 2008).

Another reward learning task, the Probabilistic Stimulus Selection Task (PSST), was developed in humans to assess relative learning associated with positive versus negative reinforcement (Frank *et al*, 2004). In the task, participants are presented with one of three pairs of discrete symbols and instructed to select one of the two stimuli presented in each pair. Correct identification of one stimulus in the pair is rewarded at either an 80%, 70%, or 60% rate (i.e., depending on the pair that is presented). Incorrect identification is rewarded 20%, 30%, and 40% of the time, respectively. Participants train on this procedure until the relative reinforcement probabilities of each pair of stimuli are learned. Participants are then tested by being presented with the stimulus that was reinforced 80% of the time paired with one of the other four stimuli (i.e., stimuli that were reinforced 70%, 60%, 40%, and 30% of the time). Participants are also presented with the stimulus that was reinforced 20% of the time paired with the same four stimuli as above. Greater performance on the pairs that include the 80% reinforced stimulus reflect better learning from positive feedback, whereas greater performance on the pairs that include the 20% reinforced stimulus reflect better learning from negative feedback.

Healthy participants performed equally well when learning from positive and negative feedback using the PSST (Frank *et al*, 2007; Frank *et al*, 2004). However, when exposed to stress (e.g., threat of shock), healthy participants with high physiological and subjective responses to stress showed impairments in learning from positive, but not negative, feedback compared to non-stressed controls (Berghorst *et al*, 2013). Similarly, women with a history of childhood sexual assault were impaired in learning from positive, but not negative, feedback (Pechtel and Pizzagalli, 2013b). Patients with schizophrenia (Waltz *et al*, 2007) or Parkinson's disease (Frank *et al*, 2004) were also impaired in learning from positive, but not negative, feedback. Interestingly, impairment in Parkinson's disease was reversed with dopamine-enhancing medication (Frank *et al*, 2004). Collectively, these findings indicate that pathological or experimental conditions hypothesized to affect dopaminergic neurotransmission have negative effects on the ability to learn from positive feedback.

4.5.2. Non-human Animal Assessments of Reward Learning—The human RBPRT is an example of a clinical behavioral assessment of reward processing that does not rely on subjective self-report of behavior. Accordingly, a rat version of the RBPRT was developed based on the instructions and testing parameters used in the human version to assess reward learning in rats (Figure 2B) (Der-Avakian *et al*, 2013). The rat version of the task is conducted in operant boxes equipped with two levers, a speaker and tone generator, and a food dispenser. Rats are trained to distinguish between two stimuli (e.g., long and short tones) by pressing a lever associated with either stimulus, which results in delivery of a food pellet for some, but not all, correct responses. As in the human task, correct identification of one tone is reinforced three times more frequently (rich) than correct identification of the other tone (lean). Data collected from the RBPRT (i.e., response bias, discriminability, accuracy, and reaction time) are also analyzed identically between humans and rats. Because most of the studies using the rat version of the RBPRT were conducted either in parallel with the human RBPRT or in order replicate previous findings from the human RBPRT, details concerning the results of these studies are described in the next section.

A similar reward bias task was recently developed using ambiguous odor cues (Wang *et al*, 2013) based on a similar task previously developed for use with monkeys (Rorie *et al*, 2010; Samejima *et al*, 2005). In this task, rats respond on either a left or right nose-poke hole in response to one of two odor cues. Each odor is either presented separately or in different mixture combinations (i.e., ambiguous odors). When presented with an ambiguous odor cue, rats tend to be biased toward the nose-poke hole that dispensed a relatively greater reward. This procedure allows for assessment of response vigor as well, whereby time to initiation of subsequent trials is decreased as the net value of rewards is increased. Response vigor (i.e., time to trial initiation) was shown to depend on the dorsomedial striatum (Wang *et al*, 2013).

Like the RBPRT, a rat version of the PSST has been recently developed (Trecker *et al*, 2012). Using touch screen monitors, rats are presented with three pairs of discrete stimuli and trained to select one of the two stimuli in each pair. Correct identification results in delivery of a food pellet on 90%, 80%, and 70% of trials for each pair, whereas incorrect identification results in reward delivery on 10%, 20%, and 30% of trials, respectively. During test trials, rats are presented with either: 1) the stimulus associated with 90% reward paired with one of the other four novel stimuli; or 2) the stimulus associated with 10%

reward paired with one of the other four novel stimuli, in order to assess learning from positive and negative feedback, respectively. Preliminary findings indicate that rats were able to learn the probabilistic contingencies for different stimulus pairs and learned from both positive and negative feedback during test trials. Future studies may explore the roles of stress and dopaminergic transmission in the striatum and prefrontal cortex to determine whether positive feedback learning is impaired, as was observed in humans (see above).

4.5.3. Convergence of Human and Non-human Animal Assessments of Reward Learning—Perhaps because of their novelty, the human reward learning tasks described above have only been modified for use in rats, and parallel data from humans and rats are only available for the RBPRT. As in humans, healthy rats developed a response bias for the rich stimulus, reflected by increasing accuracy for the rich stimulus and decreasing accuracy for the lean stimulus throughout the test session (Der-Avakian *et al*, 2013; Pizzagalli *et al*, 2005). Modulation of reward learning was similar between rats and humans in response to several manipulations. First, an acute, low-dose administration of the dopamine D2/D3 receptor agonist pramipexole blunted response bias in healthy humans (Figure 2C) (Pizzagalli *et al*, 2008a) and rats (Figure 2D) (Der-Avakian *et al*, 2013). The low doses of pramipexole used in both studies, which putatively decrease striatal dopamine levels by means of presynaptic autoreceptor activation, suggest that reward learning can be modulated by altering dopamine neurotransmission in the striatum. Second, and in support of the claim above, acute administration of the psychostimulant nicotine, which acts to increase striatal dopamine levels, increased response bias in humans (Figure 2E) (Barr *et al*, 2008). Similarly, administration of the psychostimulant amphetamine, which also increases striatal dopamine levels, increased response bias in rats (Figure 2F) (Der-Avakian *et al*, 2013). Third, withdrawal from chronic nicotine exposure blunted response bias in humans (Figure 2G) and rats (Figure 2H) (Pergadia *et al*, 2014). In rats, re-exposure to acute nicotine after withdrawal dose-dependently increased response bias, suggesting a mechanism by which nicotine-induced enhancement of reward learning in abstinent smokers may contribute to relapse to smoking.

5. Conclusions and Future Considerations

Identifying and treating reward deficits in psychiatric and neurological disorders has become increasingly important given not only the pervasiveness of the deficits across several disorders, but also our increasing understanding of the precise reward processes that are involved, like pleasure, anticipation, valuation, motivation, and reward learning. In order to understand the neurobiological mechanisms underlying these distinctive reward processes that will ultimately facilitate discovery of treatment targets, animal procedures are necessary that may be readily translated into analogous human tasks. Similarly, novel human tasks that do not already have a non-human analogue should be designed to assess behavior objectively using non-verbal communication. Ideally, moving forward, animal and human behavioral assessments that are developed in parallel will ensure that task parameters and psychometric properties are as analogous as possible.

Furthermore, many of the investigations probing the neurobiological mechanisms underlying different reward processes involved procedures that are not directly comparable across

species. For example, human studies often relied on functional magnetic resonance imaging (fMRI) and electroencephalography (EEG), whereas non-human animal studies typically used brain lesion, intracranial microinjection, and gene knock-out techniques. While inferences may be made about similarities in brain function tied to behavior between humans and animals using different techniques, ideally, similar approaches to measuring brain function in different species would help strengthen and validate observed similarities in behavior. For example, recent advances in human electrophysiological techniques and animal brain imaging techniques now allow for such parallel cross-species comparisons. Such an approach would not only facilitate discovery of novel neurobiological mechanisms subserving different reward processes, but, importantly, would help determine whether the reward behavior, or disruptions in reward behavior, being assessed are mediated by similar neurobiological mechanisms across different species.

A limitation of the procedures described above is that as reward processes become more narrowly defined, tasks designed to assess aspects of those reward constructs tend to become more complicated. The level of task complication may not be problematic for assessments in humans, where detailed verbal instructions may be given to study participants. However, verbal instructions must be translated to training protocols for animal tasks that may require several weeks or months to train for the most complicated tasks. Such high levels of sophistication are necessary if tasks are required to probe increasingly discrete aspects of the reward spectrum that are not confounded by other behavioral factors. Moreover, enhancing the specificity of the reward construct being assessed improves the likelihood of discovering more focused, discrete neurobiological mechanisms that underlie a given reward process.

Ultimately, the value of this approach is in being able to use animal procedures to make specific testable hypotheses regarding novel treatment strategies that have a high degree of successfully translating to the clinic. It is anticipated that this new approach in cross-species translational research will lead to the development of safe and effective medications for the treatment of reward deficits in psychiatric and neurological disorders that have thus far eluded researchers.

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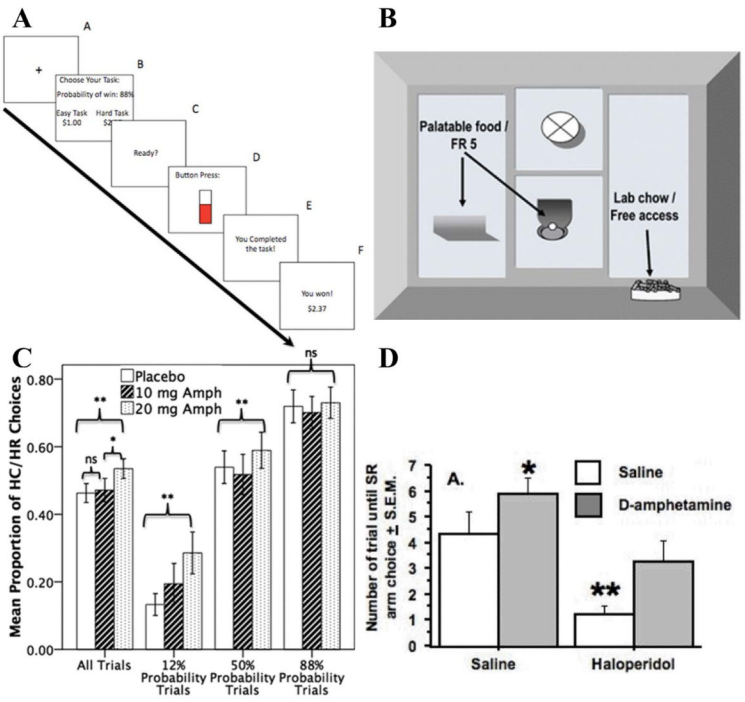

Figure 1.

Schematics of the human (A; EEfRT) and rat (B) effort-related choice tasks used to assess motivated behavior. The psychostimulant amphetamine (Amph) increased preference for the high cost/high reward (HC/HR) choice over the low cost/low reward option in humans (C) and rats (D). [FR5: fixed ratio 5 reinforcement schedule; SR: small reward] (Figures were reproduced with persmissions from Bardgett *et al*, 2009; Salamone *et al*, 2007; Treadway *et al*, 2009; Wardle *et al*, 2011)

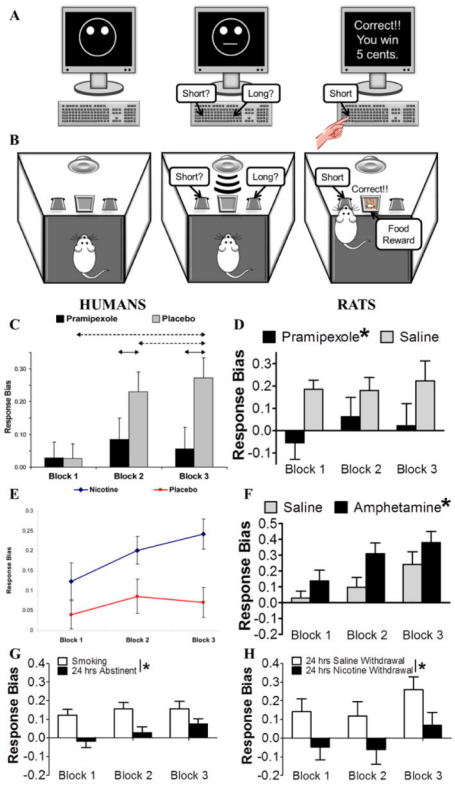

Figure 2.

Schematics of human (A) and rat (B) versions of the Response Bias Probabilistic Reward Task used to assess reward learning. The dopamine D2/D3 receptor agonist pramipexole blunted response bias in humans (C) and rats (D). The psychostimulants nicotine and amphetamine increased response bias in humans (E) and rats (F), respectively. Withdrawal from chronic nicotine exposure blunted response bias in humans (G) and rats (H). Altogether, these data suggest a high level of concordance between the human and rat versions of this reward learning task. (Figures were reproduced with permissions from Barr *et al*, 2008; Der-Avakian *et al*, 2013; Pergadia *et al*, 2014; Pizzagalli *et al*, 2008a)

Table 1

Correspondence between human and non-human animal assessments of reward processes and associated neurobiological mechanisms

Reward Processes	Human Assessments	Non-human Animal Assessments	Correspondence	Neurobiological Mechanisms
Consummatory Pleasure	Self-report (e.g., SHAPS, CPAS)		Poor To Mid	Nucleus accumbens Ventral pallidum Orbitofrontal cortex Opioids Endocannabinoids
	Sucrose preference	Sucrose consumption and preference		
Anticipatory Pleasure	Self-report (e.g., TEPS, ACIPS)		Poor	Anterior cingulate cortex Orbitofrontal cortex Medial prefrontal cortex Basal ganglia Dopamine
		Arousal, anticipatory locomotion, approach behaviors		
		Ultrasonic vocalizations		
		Successive contrast effects		
Reward Valuation	Outcome devaluation task	Outcome devaluation task	High	Medial prefrontal cortex Dorsal striatum Nucleus accumbens Basolateral amygdala Orbitofrontal cortex Dopamine, Glutamate
Motivation	Self-report (e.g., BAS, MAP-SR)		Mid to High	Ventral tegmental area Nucleus accumbens Medial prefrontal cortex Anterior cingulate cortex Lateral hypothalamus Dopamine Glutamate
	Progressive ratio task	Progressive ratio task		
	EEfRT	Effort-related choice tasks		
Reward Learning	RBPRT	RBPRT	High	Anterior cingulate cortex Orbitofrontal cortex Striatum Dorsal striatum Dopamine
	PSST	PSST		