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SI:APPLICATIONS OF QUANTITATIVE METHODS

Toward a Quantification of Anhedonia: Unified Matching Law and Signal Detection for Clinical Assessment and Drug Development

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Abstract

Anhedonia, the loss of pleasure from previously rewarding activities, is a core symptom of several neuropsychiatric conditions, including major depressive disorder (MDD). Despite its transdiagnostic relevance, no effective therapeutics exist to treat anhedonia. This is due, in part, to inconsistent assays across clinical populations and laboratory animals, which hamper treatment development. To bridge this gap, recent work has capitalized on two long-standing research domains dedicated to quantifying responsivity to antecedents and consequences across species: the generalized matching law and signal detection theory. This review traces the integration of these quantitative frameworks, which yielded two empirically derived metrics: response bias (log *b*) and task discriminability (log *d*). These metrics serve as primary dependent variables in the Probabilistic Reward Task (PRT). In this computerized task, subjects make visual discriminations and probabilistic contingencies are arranged such that correct responses to one alternative are rewarded more often (rich) than correct responses to the other (lean). Under these conditions, healthy participants consistently develop a response bias in favor of the rich alternative, whereas participants with MDD exhibit blunted biases, which correlate with current and predict future anhedonia. Given the correspondence between anhedonic phenotypes and response bias, the PRT has been reverse-translated for rodents and nonhuman primates. Orderly log *b* and log *d* values have been observed across diverse clinical populations and laboratory animals. In addition, pharmacological challenges have produced similar outcomes across species. Taken together, this quantitative framework offers a highly translational approach to assaying reward

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responsiveness to accelerate treatment development for neuropsychiatric disorders involving anhedonia.

Keywords anhedonia · generalized matching law · signal detection theory · quantitative models · translational research · drug development

Anhedonia: Statement of Problem

Anhedonia, the loss of pleasure or lack of reactivity to previously rewarding activities, is an endophenotype and core facet of major depressive disorder (MDD; American Psychiatric Association, 2013; Whitton et al., 2015; World Health Organization, 1992). Anhedonia constitutes reduced positive affect and engagement with the environment, which can predict the prognosis of depression (Gabbay et al., 2015; Klein, 1974; Spijker et al., 2001; Wardenaar et al., 2012). Although often associated with MDD, anhedonia has also been implicated in a variety of other neuropsychiatric conditions. For example, bipolar disorder is marked by alterations in manic and depressive phases that exhibit, respectively, hyperhedonia and anhedonia and includes altered reward processing in response to changing or intermittent reward (Hasler et al., 2006; Leibenluft et al., 2003; Pizzagalli, Goetz, et al., 2008b). Anhedonia has also been shown to be a reliable behavioral marker of schizophrenia and is strongly interrelated with other negative affective symptoms (Horan et al., 2006; Meehl, 1962, 1975). In addition, findings from studies of post-traumatic stress disorder suggest that reward deficit is a key feature insomuch as patients exhibit reduced approach and hedonic responses to appetitive stimuli compared to healthy control subjects (Nawijn et al., 2015). Finally, reward deficits have been implicated in substance use disorders, especially during periods of drug withdrawal and abstinence (Markou et al., 1998).

Despite the transdiagnostic relevance of anhedonic phenotypes, there are no available medications to treat anhedonia approved by the Food and Drug Administration. Critically, when asked, patients ascribe restoration of positive mood, rather than decreases in depressed mood, as reflecting recovery (Zimmerman et al., 2012). In this regard, front-line antidepressants such as selective serotonin reuptake inhibitors (SSRIs) are typically ineffective in the restoration of hedonic tone (Admon & Pizzagalli, 2015; Calabrese et al., 2014). This is problematic because anhedonia robustly predicts worse outcomes to pharmacological treatment of depression (Uher et al., 2012), higher suicide risk (Ballard et al., 2017; Bonanni et al., 2019), and disease chronicity, that is, a persisting diagnosis of MDD from 8 weeks (Vrieze et al., 2013) to 10 years (Moos & Cronkite, 1999). Thus, there is a clear and urgent need for novel treatment strategies to restore positive mood in anhedonic patients.

Traditional Assessments of Anhedonia

Two reasons that contribute to this gap in anhedonic treatments described above are (1) a lack of precise and objective assessments and (2) the use of substantially different assays across species. With respect to the first point, clinical assessment of anhedonia

traditionally has relied on self-report questionnaires such as the Snaith-Hamilton Pleasure Scale (SHAPS; Snaith et al., 1995), Chapman Physical and Social Anhedonia Scales (CPAS/CSAS; Chapman et al., 1976), and Fawcett-Clark Pleasure Capacity Scale (FCPCS; Fawcett et al., 1983), as well as more modern scales such as the Dimensional Anhedonia Rating Scale (DARS; Rizvi et al., 2015) and Temporal Experience of Pleasure Scale (TEPS; Gard et al., 2006). However, these instruments subsume multidimensional aspects (e.g., motivational and consummatory behavior) into the umbrella term of anhedonia, which is imprecise and has shown poor reliability, especially in MDD, which has high heterogeneity (Rizvi et al., 2016). And it is important to note that these instruments rarely map onto modern conceptualizations of reward processing, which have identified distinct subdomains of reward learning (e.g., Research Domain Criteria [RDoC] Positive Valence Systems; see Insel et al., 2010; and, for a recent example, Khazanov et al., 2020).

With respect to the second point, although there are several commonly employed animal models of anhedonia that are designed to assay key features of the endophenotype (reviewed in Scheggi et al., 2018), they depart significantly from diagnostic instruments used in the clinic. For example, the sucrose preference test examines a laboratory animal's consummatory response for a sweetened solution versus water (Willner et al., 1987). The forced swim task is also a common animal model designed to assay depressive-like behavior and despair and is quantified by examining the proportion of time engaging in escape-related behaviors relative to immobility (Porsolt et al., 1977). In another experimental approach, intracranial self-stimulation (ICSS), animals can respond to self-stimulate specific reward regions in the brain, and previous studies have observed increases in stimulation threshold during putative anhedonic conditions (Zacharko & Anisman, 1991). Although these animal models have for decades generated highly interesting data and have played an important role in drug development for mood disorders, interpretive caution is required, especially given the difficulty in conducting parallel studies in human subjects. Moreover, when functional task analogs have been examined, for example, in sweetened food preference studies, it has been repeatedly documented that individuals with mood disorders do not differ from healthy control subjects in their preference for sweet solutions (e.g., Amsterdam et al., 1987; Berlin et al., 1998; Dichter et al., 2010; Kazes et al., 1994).

Unified Quantification of Reward Responsiveness

Mitigating the cross-species discrepancies described above is likely necessary in the pursuit toward quantifying reward responsiveness to allow for objective characterizations of anhedonia (Der-Avakian et al., 2016). In turn, coordinated alignment of tasks in humans and laboratory animals could accelerate the development of innovative treatment strategies and pharmacotherapies by better predicting clinical outcomes (Silverman et al., 2020). This section traces the integration of two well-established research domains, the generalized matching law and signal detection theory, which yielded analytical tools to objectively quantify reward responsiveness across diverse clinical populations and species.

The Matching Law

One powerful approach to characterizing responsivity to reward in both humans and laboratory animals is the matching law. This paradigm can be traced back to a highly active research domain in the 1940s and 1950s investigating how the delivery of reward can generate and maintain behavior via exposure to various schedules of reinforcement (typified in Ferster & Skinner, 1957). These early efforts gave rise to subsequent investigations of how responding is allocated when more than one alternative is available. In a seminal study, Herrnstein (1961) examined such concurrent choice arrangements using pigeons trained to peck on two response keys that were each programmed with an independent schedule of reinforcement. When the concurrent schedules were the same, subjects allocated their responses equally between the two alternatives. However, when the reinforcement schedules differed, subjects allocated their responses proportionally more toward the alternative with a richer schedule of reinforcement. After examining response allocation between the two operanda, which were programmed with a variety of balanced and imbalanced reinforcement schedules, an orderly relationship was observed between the relative response rate on each alternative and the relative reinforcement rate each alternative yielded. Herrnstein (1961) expressed this relationship using the following equation:

$$\frac{B_1}{B_1 + B_2} = \frac{r_1}{r_1 + r_2} \tag{1}$$

where B_1 and B_2 denote responses made on the two alternatives, and r_1 and r_2 denote the reinforcement provided by those options. This equation, termed the *matching law*, analyzes the relative distribution of responses across alternatives as a function of the relative reinforcement obtained. For example, if r_1 produces three times as many reinforcers relative to r_2, the matching law predicts three times as many B_1 responses relative to B_2.

Although early studies reported orderly matching across several experimental preparations (e.g., Herrnstein, 1970; Reynolds, 1963; Shimp & Wheatley, 1971), other studies observed systematic deviations from the matching equation described above (e.g., Baum & Rachlin, 1969; Myers & Myers, 1977; Nevin, 1971; Staddon, 1968; reviewed in McDowell, 2005). One such deviation involves a subject's *sensitivity* to reinforcement, that is, the amount of change in response allocation associated with each change in relative reinforcement rate. Two common sensitivity profiles observed are overmatching and undermatching. *Overmatching* occurs when responses are allocated disproportionally more toward the richer reinforcement alternative. Conversely, *undermatching* occurs when responses are allocated disproportionally more toward the leaner reinforcement alternative. A second systematic deviation that is commonly observed is *inherent bias*, that is, preference for a particular response alternative that is not accounted for by the programmed reinforcement contingencies but rather is inherent in the subject or recording equipment (e.g., subject handedness, differences in operanda force requirements). To account for these deviations from strict matching as defined in Eq. 1, Baum

(1974) introduced the *generalized matching law*, which included two additional parameters, expressed as:

$$\frac{B_1}{B_2} = c\left(\frac{r_1}{r_2}\right)^a \tag{2}$$

where a denotes sensitivity of behavior to imbalanced schedules of reinforcement and c denotes inherent bias for a particular alternative. If strict matching is observed, a and c values equal 1, reducing Eq. 2 to Eq. 1. In addition, Eq. 2 can be expressed in logarithmic form to transform curvilinear functions into linear functions, a common strategy in many scientific fields to allow for easier interpretation of the data. The generalized matching law with logarithmic transforms is expressed as:

$$\log\left(\frac{B_1}{B_2}\right) = a\log\left(\frac{r_1}{r_2}\right) + \log c. \tag{3}$$

Plotted graphically, strict matching would generate a line with a slope of 1 (Fig. 1A), where a unit increase in the ratio of reinforcement corresponds to a unit increase in the

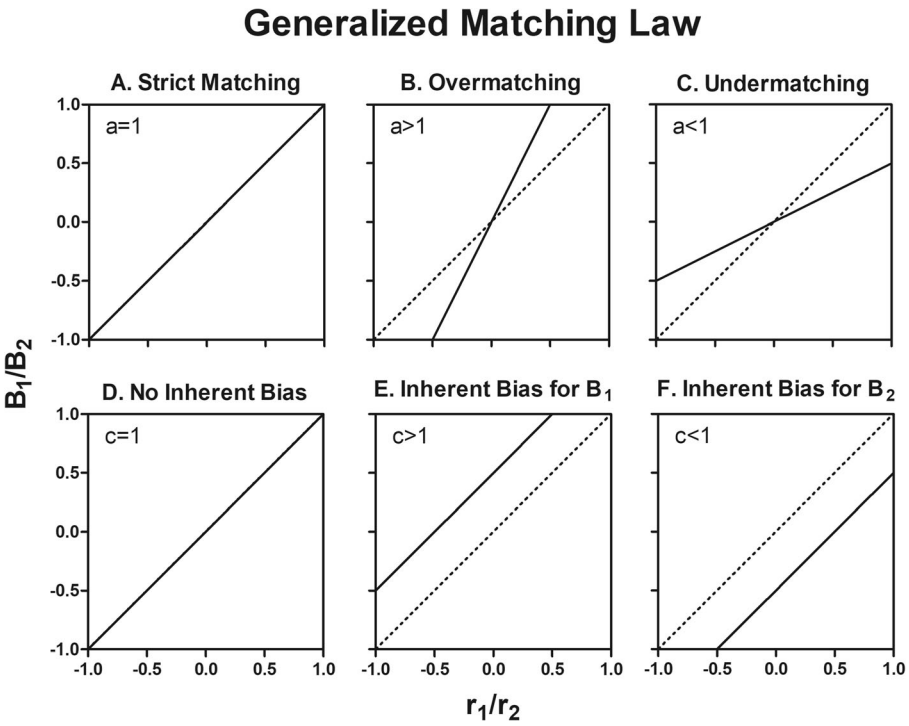

Fig. 1 Idealized data representing the ratio of responding (ordinate) as a function of the reinforcement obtained on the two alternatives (abscissa). The dotted line represents strict matching and the solid line represents possible variations in sensitivity (top panel) and inherent bias (bottom panel). Figure adapted from Reed and Kaplan (2011)

relative rate of responding. Values of a greater or less than 1 define the slope of the function and indicate, respectively, overmatching (Fig. 1B) or undermatching (Fig. 1C). Values of c greater or less than 1 denote y-intercept values above or below 0 and indicate, respectively, an inherent bias for the response alternative associated with B_1 (Fig. 1E) or B_2 (Fig. 1F).

It is important to note that although the matching law equations described above were initially devised to characterize how reward modulates response allocation in pigeons, they have also proven to be highly effective in accounting for responding under symmetrical and asymmetrical choice conditions in subsequent controlled laboratory investigations of rodents, monkeys, and humans (e.g., Belke & Belliveau, 2001; Corrado et al., 2005; Ecott & Critchfield, 2004; Elsmore & McBride, 1994; Kangas et al., 2009; Lau & Glimcher, 2005; reviewed in Davison & McCarthy, 2017). Furthermore, although procedural variables need to be carefully considered when extending the matching framework to human subjects (e.g., Kollins et al., 1997; Pierce & Epling, 1983; Simon & Baum, 2017; Takahashi & Iwamoto, 1986), these equations have been shown to account for how reward can modulate choice and decision making outside of the laboratory, including complex phenomena such as social interactions in adults (e.g., Borrero et al., 2007; Conger & Killeen, 1974; Pierce et al., 1981), alcohol consumption in adults (Oscar-Berman et al., 1980), problem behavior in children (e.g., Borrero et al., 2010), completion of academic tasks in educational settings (e.g., Billington & DiTommaso, 2003; Mace et al., 1996; Neef et al., 1992), and elite athletic performance in professional and collegiate sports (e.g., Cox et al., 2017; Reed et al., 2006; Seniuk et al., 2020; Vollmer & Bourret, 2000).

Signal Detection Theory

Another long-standing research domain concerned with examining fundamental relations between reward and behavior in humans and laboratory animals is signal detection theory (Gescheider, 2013; Green & Swets, 1966; Stevens, 1957). Although the matching law and signal detection theory developed by and large independently, they have parallel objectives and shared aims. Whereas the matching law examines the distribution of behavior as a function of reward obtained across alternatives, signal detection theory examines behavior as a function of the discriminability of controlling antecedent stimuli by quantifying the relationship between stimulus properties and the perceptual outcomes they produce. Central to signal detection theory specifically, and psychophysics more generally, is the concept of a *sensory threshold*, where the intensity of a stimulus exceeds some sufficient value and is perceived by a subject. The minimum detectable level of intensity along some physical dimension is the *absolute threshold*, and the minimum detectable difference of intensity between two stimuli is the *difference threshold*.

A standard paradigm to measure both absolute and difference thresholds is the yes–no signal detection task. To determine absolute thresholds, subjects indicate that a signal was presented or, alternatively, that it was not presented. Four stimulus–response events are measured in terms of the presence or absence of the stimulus and the subject's response to it. These events can be represented in the matrix presented in Fig. 2 where w represents the number of correct responses when the signal was present (*hits*), x represents the number of incorrect responses when the signal was present

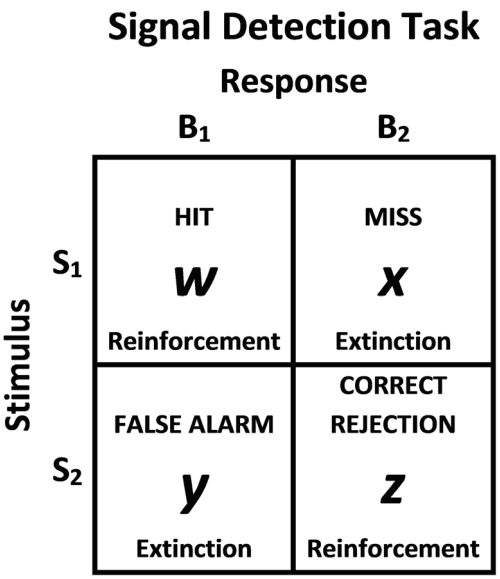

Fig. 2 The four stimulus and response events in the yes–no signal detection task, where B_1 and B_2 denote responses with respect to the stimuli S_1 and S_2. *w* and *z* represent, respectively, the number of hits and correct rejections of S_1 resulting in reinforcement. *x* and *y* represent, respectively, the number of misses and false alarms resulting in extinction. Figure adapted from McCarthy (1983)

(*misses*), *y* represents the number of incorrect responses when the signal was absent (*false alarms*), and *z* represents the number of correct responses when the signal was absent (*correct rejections*). Likewise, to determine difference thresholds, stimulus–response events are examined by assessing responding (B_1 and B_2) in the presence of one of two different stimuli that vary in intensity (S_1 and S_2).

In signal detection theory, the basic measure of stimulus discriminability, *d'* (pronounced *d-prime*), is calculated by examining the difference in hit rates and false alarms in standard-deviation units, thus providing a measure of the tendency to respond effectively in the presence *and* absence of a stimulus (Green & Swets, 1966). Specifically, *d'* is expressed as:

$$d' = \mathrm{z}(w) - \mathrm{z}(y) \tag{4}$$

where z*(w)* and z*(y)* are the z-score transformations of the hit and false-alarm rates, respectively. A *psychometric function* can be derived by plotting *d'* values obtained as a function of varied stimulus intensities. For example, a *d'* value of 0 indicates that the rate of hits and false alarms were the same and is interpreted as no perceived difference between the stimuli. Conversely, a *d'* value of 1 indicates a hit proportion of 1 and false alarm proportion of 0 and reflects perfect discrimination between the stimuli.

A considerable amount of work in psychophysics has been dedicated to understanding the shape of the psychometric function across stimulus modalities. In addition, like the generalized matching law, applications of signal detection theory not only effectively describe sensory thresholds in laboratory settings but also complex decision-making processes in real world situations. For example, signal detection theory has

proven to be highly successful in accounting for phenomena such as false identification rates in eyewitness testimony (e.g., Clark, 2012), detection of pain across diverse clinical conditions (e.g., Allan & Siegel, 2002; Clark, 1969; Cohen et al., 1983; Kemperman et al., 1997; Yang et al., 1985), detection of prohibited items in X-ray baggage screening (e.g., Sterchi et al., 2019), and detection of the presence or absence of an illness in diagnostic testing (e.g., McFall & Treat, 1999).

Integration of Generalized Matching and Signal Detection

As summarized above, both the generalized matching law and signal detection theory account for fundamental, but relatively distinct, aspects of reward and behavior in humans and laboratory animals. That is, the generalized matching law is designed to account for how behavior is allocated across response alternatives as a function of the relative reward associated with the alternatives. In contrast, signal detection theory is designed to account for how behavior is allocated across response alternatives as a function of stimulus intensities and resultant perceptual information that allow for effective responding. Put another way, the generalized matching law emphasizes controlling variables of behavior via examination of their *consequences*, whereas signal detection theory emphasizes controlling variables of behavior via examination of their *antecedents*. Although these two parallel research domains developed by and large independently, effective behavior is often a product of sensitivity to both antecedents *and* consequences. As such, there is obvious value in a quantitative framework that can simultaneously account for both and also allow for examination of how their components contribute independently. In the context of the present review, although assessment of reward responsiveness is most relevant to characterizing anhedonia, it is also critically important to quantify a subject's discriminative ability (Kangas et al., 2011) and determine if it contributes to blunted reactivity to appetitive consequences. An assay able to isolate differences in reward responsiveness—independent of any perceptual dysfunction that may accompany a given neuropsychiatric condition—would allow for a powerful examination of selectivity in the anhedonic phenotype and guide subsequent evaluation of candidate treatment options.

In order to examine both reward responsiveness and discriminative ability, generalized matching and signal detection were first integrated in a seminal paper by Davison and Tustin (1978) using two equations to represent responding in the presence of each of the two stimuli. During S_1 presentations, this relationship is expressed as:

$$\log\left(\frac{B_w}{B_x}\right) = a\log\left(\frac{r_w}{r_z}\right) + \log c + \log d \tag{5}$$

and during S_2 presentations as:

$$\log\left(\frac{B_y}{B_z}\right) = a\log\left(\frac{r_w}{r_z}\right) + \log c - \log d. \tag{6}$$

Log d is analogous to the signal detection measure d' and represents the control of behavior caused by the discriminability of the two stimuli (S_1 and S_2). The better a subject can discriminate between the two stimuli, the more hits (w) and correct

rejections (z) will accrue and thus increase the B_w/B_x ratio in Eq. 5 and reduce the B_y/B_z ratio in Eq. 6. Because the numerators in Eqs. 5 and 6 are B_1 responses, log d is positive in Eq. 5 and negative in Eq. 6 when discriminability is high.

Independent point estimates of stimulus discriminability (log d) and response bias (log b) can be derived from Eq. 5 and Eq. 6. To find log d, Eq. 6 is subtracted from Eq. 5 to remove reinforcement effects, expressed as:

$$\log\left(\frac{(B_w)*(B_z)}{(B_x)*(B_y)}\right) = 2\log d. \tag{7}$$

Rearranging algebraically then gives:

$$\log d = \frac{1}{2}\log\left(\frac{(B_w)*(B_z)}{(B_x)*(B_y)}\right). \tag{8}$$

As the two stimuli become more discriminable, hits (w) and correct rejections (z) increase the numerator and log d becomes larger.

To find response bias, Eq. 5 is added to Eq. 6 to remove stimulus discriminability effects, expressed as:

$$\log\left(\frac{(B_w)*(B_y)}{(B_x)*(B_z)}\right) = 2\,a\log\left(\frac{B_w}{B_z}\right) + 2\log c. \tag{9}$$

The left side of Eq. 9 is the measure of response bias and the right side is the generalized matching equation. In the generalized matching law, a subject's inherent bias (c) and sensitivity to reward (a) are assumed to be the same whether in the presence of S_1 or S_2. Therefore, eliminating those variables and rearranging algebraically yields:

$$\log b = \frac{1}{2}\log\left(\frac{(B_w)*(B_y)}{(B_x)*(B_z)}\right). \tag{10}$$

Thus, a response bias in favor of S_1 is reflected by a larger number of B_1 hits in the presence of S_1 (w) and B_1 false alarms in the presence of S_2 (y) that grow the numerator and yield a positive log b value. A response bias in favor of S_2 is reflected by a larger number of B_2 misses in the presence of S_1 (x) and B_2 correct rejections in the presence of S_2 (z) that grow the denominator and yield a negative log b value.

Like the matching-law and signal-detection studies highlighted above, applications of these integrated equations have also been used outside of the laboratory to help characterize phenomena in real world settings. For example, these metrics have accounted for phenomena in individuals suffering from hypoxia induced by high elevation aircraft ascent (McCarthy & Miller, 2016) and in individuals subjected to injury leading to concussion (McCarthy, 1991). In addition, refinement and expansion of integrated generalized-matching and signal-detection frameworks have continued by Davison and colleagues (e.g., Davison & Nevin, 1999; Davison, 2018), as well as other laboratories (e.g., Hutsell & Jacobs, 2012; Shahan & Podlesnik, 2006; White & Wixted, 1999).

Probabilistic Reward Task

Characterizing a subject's responsiveness to reward via their response allocation across alternatives provides a quantitative assay in which reward deficit profiles can be objectively defined in laboratory settings. In turn, these performance outcomes offer an operational understanding of certain aspects of anhedonia and facilitate the identification of novel therapeutic approaches. This interpretive system also comports well with contemporary RDoC taxonomies for examining reward learning within the context of Positive Valence Systems (Insel et al., 2010). A prominent example of this approach is the Probabilistic Reward Task (PRT), which has recently been chosen as a recommended task for the reward learning subdomain in the latest revision of the RDoC matrix (National Institute of Mental Health [NIMH], 2016). The PRT is a computerized task expressly designed to quantify reward responsiveness (i.e., a subject's ability to modulate behavior as a function of reinforcement history) using the integrated matching-law and signal-detection equations described above. Initially designed to examine reward responsiveness in children with attention deficit hyperactivity disorder (Tripp & Alsop, 1999), the PRT was modified by Pizzagalli et al. (2005) to serve as an assessment of anhedonic phenotypes in human subjects with a variety of mood disorders, including MDD. In the prototypical computerized task, human subjects are instructed to discriminate between two briefly presented (100 ms) mouths on cartoon faces that vary slightly in length (13 mm or 11.5 mm) by pressing one of two response keys associated with the long or short line (see Fig. 3, top panels). Unbeknownst to the subjects, 3:1 probabilistic contingencies are arranged so that 60% of correct responses on one alternative are rewarded (e.g., long line: rich alternative) and 20% of correct responses on the other alternative are rewarded (e.g., short line: lean alternative). Correct responses during trial types scheduled for reward result in delivery of points exchangeable for money followed by a brief timeout whereas correct responses during trial types not scheduled for reward have consequences identical to incorrect responses (i.e., a brief timeout without points). The implementation of probabilistic contingencies yields two primary dependent measures: task discriminability and response bias, which can be quantified, respectively, by using variants of the log d (Eq. 8) and log b (Eq. 10) measures. Substituting terms in the Fig. 2 matrix with the number of correct and incorrect responses obtained during rich and lean stimulus trial types, task discriminability is calculated using the following modified log d equation:

$$\log d = \frac{1}{2}\log\left(\frac{(Rich_{Correct}+0.5)*(Lean_{Correct}+0.5)}{(Rich_{Incorrect}+0.5)*(Lean_{Incorrect}+0.5)}\right). \tag{11}$$

High discriminability values are point estimates produced by high numbers of correct responses for both rich and lean trials. Likewise, response bias is calculated using the following modified log b equation:

$$\log b = \frac{1}{2}\log\left(\frac{(Rich_{Correct}+0.5)*(Lean_{Incorrect}+0.5)}{(Rich_{Incorrect}+0.5)*(Lean_{Correct}+0.5)}\right). \tag{12}$$

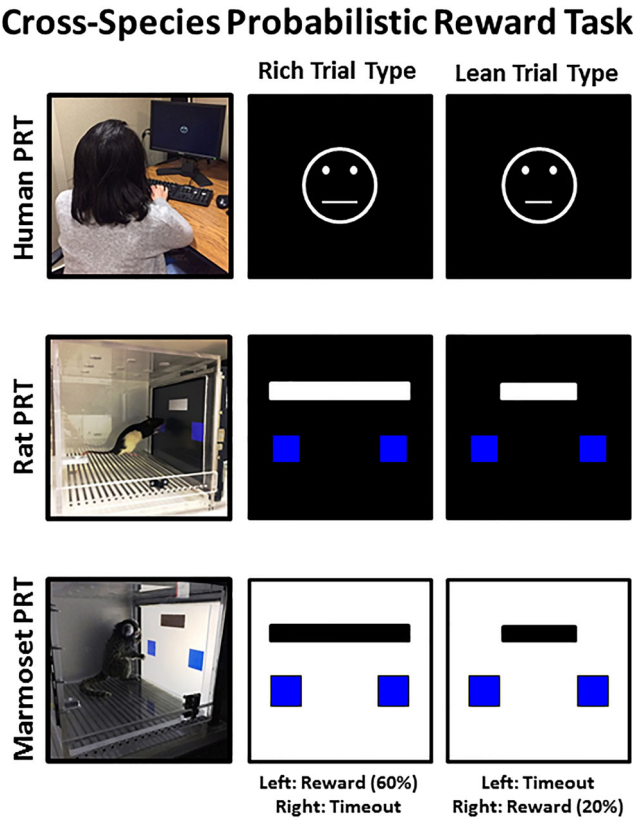

Fig. 3 Photographs and task schematics for the human (top; Pizzagalli et al., 2005), rat (middle; Kangas et al., 2020), and marmoset (bottom; Wooldridge et al., 2021) PRT

High bias values are point estimates produced by high numbers of correct responses for rich trials and incorrect responses for lean trials. It is a common practice to add 0.5 to all parameters in Eqs. 11 and 12 to avoid instances where no errors are made on a given trial type, which would make log transforms impossible (Brown & White, 2005; Hautus, 1995).

Probabilistic Reward Task: Human Subjects

Numerous studies have empirically validated the PRT as an objective and quantitative assessment of reward responsiveness in humans. As predicted by integrated matching law and signal detection theory, healthy subjects consistently develop a response bias in favor of the rich alternative and do so without disruption in overall task discriminability (e.g., Pizzagalli et al., 2005). It is important to note, however, that subjects with anhedonia reliably exhibit a blunted or reduced response bias, compared to healthy control subjects (e.g., Vrieze et al., 2013). Moreover, blunted response bias has been repeatedly documented to correlate with current, and predict future, anhedonia in MDD and other mood disorders. For example, whereas anhedonia is central to the definition of MDD, pervasive anhedonia is particularly characteristic to melancholic depression,

which has been proposed as a distinct subtype of MDD (Parker et al., 2010; Taylor & Fink, 2008; reviewed in Harald & Gordon, 2012). Indeed, in studies examining PRT performance, blunted reward responsiveness corresponded well to depressive subtypes in melancholic and non-melancholic patients (Fletcher et al., 2015). That is, patients with melancholic MDD consistently showed little to no response bias for the rich alternative whereas patients with non-melancholic MDD developed a response bias that approximated performance of healthy control subjects but required extended exposure to the asymmetrical rich/lean conditions before doing so. It is critical to note that subjects in all groups exhibited similar levels of stimulus discriminability as quantified using log *d* measures, thus confirming that blunting of reward responsiveness was not due to general deficits in task performance.

Blunted reward responsiveness in PRT performance has also been observed in studies of other mood disorders in which anhedonia is implicated. For example, patients with bipolar disorder exhibited a delayed acquisition of response bias across trials and an overall reduction compared to healthy control subjects and did so even during euthymic states (i.e., during relatively stable mood states in between manic and depressive episodes; Pizzagalli, Goetz, et al., 2008b). Moreover, patients with bipolar disorder tended to misclassify the rich stimulus when the immediately preceding trial was a rewarded lean stimulus or a nonrewarded rich stimulus, suggesting a dysfunctional integration of reward learning over time.

Anhedonia is also implicated in substance use disorders, which is thought to be most pronounced during drug withdrawal (Hatzigiakoumis et al., 2011; Markou et al., 1998). Consistent with this notion, studies of heavy smokers who abstained from nicotine for 24 hr revealed significant reductions in PRT response bias compared to values observed in the same subjects during conditions of unrestricted access to cigarettes (Pergadia et al., 2014). Thus, the PRT has been examined as one component of a larger appraisal of therapeutic outcomes for substance use disorders. For example, reward responsiveness was evaluated using the PRT in adolescent patients with co-occurring depressive and substance use disorders, first upon admission and again following discharge from a residential treatment program (Boger et al., 2014). Results documented significant increases in PRT response bias at discharge relative to levels observed at admission. Moreover, patients reported increased recognition of their drug problem and an improved motivation to change drug use, as measured by the Stages of Change Readiness and Treatment Eagerness Personal Drug Use and Personal Drinking (SOCRATES) questionnaire.

In addition to a detailed account of behavioral outcomes associated with anhedonic phenotypes, enhancing treatment strategies will benefit from an understanding of neural mechanisms associated with reward responsiveness. Studies examining brain activity using imaging techniques have reported localization of function and neurochemical signaling that corresponds to behavioral outcomes of the PRT. For example, Santesso et al. (2008) used event-related potentials (ERP) to measure the feedback-related negativity (FRN), a negative electrical signal deflection that follows receipt of feedback. Less negative amplitudes are typically observed following reward delivery (also referred to as feedback-related positivity [FRP]), whereas larger amplitudes are typically observed following outcomes worse than expected (Gehring & Willoughby, 2002; Müller et al., 2005). FRNs are thought to originate from the dorsal anterior cingulate cortex (dACC) and reflect reward-related dopamine signal transmission

(Holroyd & Coles, 2002). And, indeed, these PRT studies have confirmed that participants with large response biases generated smaller FRNs following rich reward feedback, relative to participants with a blunted response bias, who showed development of more negative FRNs. Similar FRN findings have also been produced using laboratory-based acute stressors (Bogdan & Pizzagalli, 2006). For example, female participants who completed the PRT during stress conditions in which presession instructions indicated that response-independent shock would be delivered, generated blunted response biases that correlated with smaller and delayed FRPs compared to no-stress conditions (Bogdan et al., 2011). Moreover, subsequent studies in individuals with remitted MDD replicated these outcomes, including blunted FRPs to reward feedback and reduced activation of the dACC, suggesting that impaired reward learning can persist well into remission (Whitton et al., 2016).

Consistent with these electrophysiological findings, pharmacological studies have also implicated disruptions in dopaminergic signaling as a source of impaired reward responsiveness in the PRT. In particular, drugs known to modulate dopamine can decrease or increase response bias accordingly. For example, relative to placebo, blunted response biases have been observed following administration of a low dose of the dopamine D_2-family agonist pramipexole, putatively due to presynaptic autoreceptor activation leading to reduced phasic dopaminergic signaling (Pizzagalli, Evins, et al., 2008a). On the other hand, kappa opioid receptor (KOR) antagonists have been shown to increase dopamine release in the canonical neural reward circuit projecting from the ventral tegmental area of the midbrain to the nucleus accumbens of the basal forebrain (Carlezon et al., 2009; Van't Veer & Carlezon, 2013). Treatment with the high-affinity and selective KOR antagonist JNJ-67953964 (Aticaprant) was recently documented to increase response biases in participants reporting anhedonia, putatively via normalization of dopamine signaling (Pizzagalli et al., 2020) during a double-blind placebo-controlled randomized clinical trial (Krystal et al., 2020). Preclinical drug screening efforts of this sort using the PRT is one such example in which this methodology can accelerate medication development. Indeed, the aforementioned study was selected by the NIMH's Fast-Fail Trials initiative to rapidly test and discover potentially effective psychiatric medications.

Probabilistic Reward Task: Laboratory Animals

The apparent correspondence between decreased reward responsiveness assayed by the PRT and anhedonia in affective disorders has led researchers to reverse-translate the task for laboratory animals, with the expectation that this methodology might help bridge the preclinical gap between therapeutic discovery and treatment (Der-Avakian & Pizzagalli, 2018). An initial effort yielded a PRT analog designed for rodents in which rats were trained to discriminate between two auditory tones varying in duration (Der-Avakian et al., 2013). Subsequent test sessions programmed with 3:1 probabilistic contingencies produced response biases to the rich alternative similar to biases observed in previous PRT studies with human subjects, without disruption in task discriminability. Furthermore, pharmacological task sensitivity was confirmed by administration of low doses of pramipexole and resultant decreases in response bias in rats, an effect which, as discussed above, was also reported in human participants (Pizzagalli, Evins, et al., 2008a). In subsequent studies, task sensitivity to social stress

was documented, with rats exposed to social defeat exhibiting a blunted response bias relative to nonstressed controls (Der-Avakian et al., 2017). The effects of drug treatment and social stress were recently independently replicated by Lamontagne et al. (2018), highlighting important reproducibility in the auditory rodent PRT across laboratories.

Although the auditory rodent PRT is functionally analogous to the human task, the stimulus modality differs across species (humans, visual; rodents, auditory). Therefore, another variant of the PRT was recently developed that employs visual stimuli with formal similarity to the human task (Kangas et al., 2020; Fig. 3, middle panels). Using a touchscreen-based apparatus (Kangas & Bergman, 2017), rats were trained to discriminate between two lines varying in length. To optimize task variables, parametric manipulations were conducted. First, although 3:1 probabilistic contingencies are standard in human PRT studies to assist performance comparisons across diverse clinical populations, response bias and stimulus discriminability were examined in rats under a range of asymmetrical rich:lean probabilistic contingencies (i.e., 4:1, 3:1, and 2:1). Next, response bias and stimulus discriminability were examined using a variety of line length stimuli under a 3:1 reinforcement ratio. Results revealed an orderly relationship in response bias as a function of the asymmetry in probabilistic reward, whereas discriminability remained intact. Parametric studies of line–length stimuli revealed no systematic changes in response bias, but produced an orderly relationship in discriminability as a function of the line–length differential. Furthermore, pharmacological sensitivity in the touchscreen-based rodent PRT was confirmed by showing that drugs known to enhance hedonic tone, such as d-amphetamine (McIntyre et al., 2017; Wise, 2008) and the fast-acting antidepressant scopolamine (Dulawa & Janowsky, 2019; Jaffe et al., 2013), produced dose-related increases in response bias. On the other hand, administration of drugs that have well-known euphoriant effects but no known antidepressant effects, such as oxycodone, did not modify reward responsiveness as assayed by the PRT.

The touchscreen-based PRT designed for rodents has also recently been modified for the marmoset (Wooldridge et al., 2021; Fig. 3, bottom panels). Advances in precision gene editing (e.g., CRISPR-Cas9), paired with the marmoset's comparatively high reproductive rate relative to other nonhuman primates, have facilitated the creation of a number of transgenic lines making the marmoset a valuable neuroscience model of considerable interest and translational value (Kishi et al., 2014; Okano et al., 2016; Sasaki et al., 2009). Moreover, this small monkey shares cortical and behavioral features with humans that are missing in rodent models for interrogating the pathophysiology of depression (Alexander et al., 2019; Galvão-Coelho et al., 2017). As in the rodent PRT, orderly relationships between response bias and the asymmetry of rich:lean probabilistic contingencies were systematically replicated in the marmoset. In addition, pharmacological task sensitivity was again verified via selective dose-related increases in log b following treatment of the N-methyl-D-aspartate (NMDA) antagonist, ketamine, an FDA-approved fast-acting antidepressant (Coyle & Laws, 2015; Kim et al., 2019), but not phencyclidine, a pharmacologically similar NMDA receptor antagonist without known antidepressant efficacy.

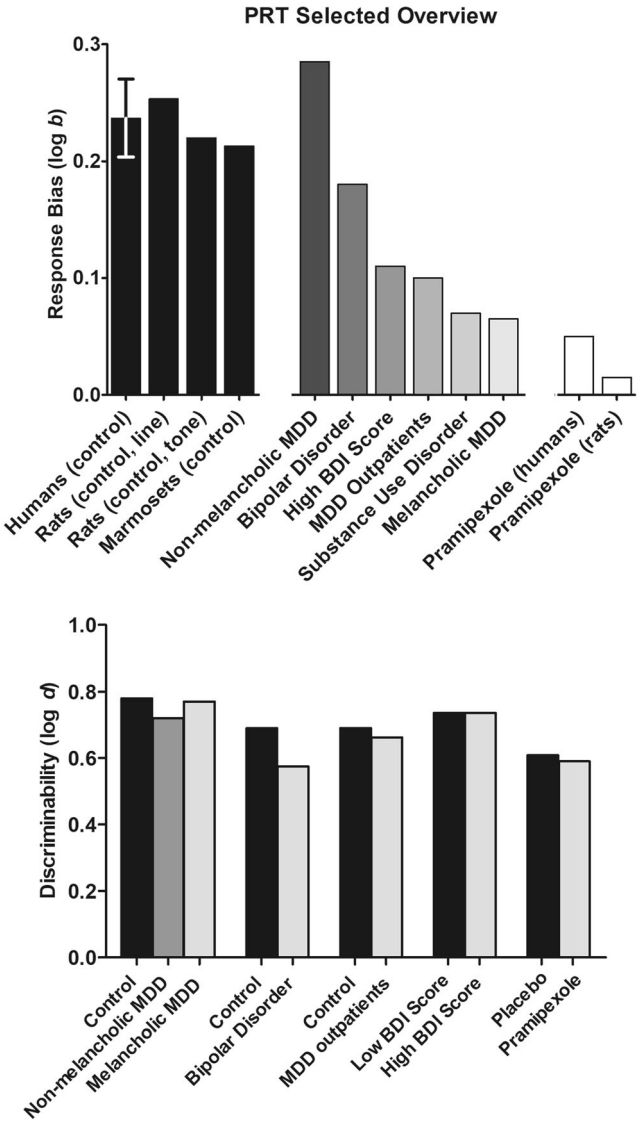

Fig. 4 Upper panel: Mean log *b* values from select PRT studies. Black bars indicate mean log *b* values from healthy control subjects across species, including humans (±range of studies referenced below), rats using line length stimuli (Kangas et al., 2020), rats using auditory stimuli (Der-Avakian et al., 2013), and marmosets (Wooldridge et al., 2021). Gray bars indicate mean log *b* values from human participants with psychiatric disorders, including non-melancholic MDD (Fletcher et al., 2015), bipolar disorder (Pizzagalli, Evins, et al., 2008a), high BDI score (Pizzagalli et al., 2005), MDD outpatients (Pizzagalli et al., 2008c), substance use disorder (Boger et al., 2014), and melancholic MDD (Fletcher et al., 2015). White bars indicate mean log *b* values following pramipexole administration in humans (Pizzagalli, Goetz, et al., 2008b) and rats (Der-Avakian et al., 2013). Lower panel: Mean log *d* values for healthy control participants (black bars) and corresponding comparisons (gray bars)

Probabilistic Reward Task: Overview of log *b* and log *d*

In order to examine quantitative similarities in PRT outcomes across clinical disorders and species more closely, average log *b* measures were derived from studies described above and plotted in the upper panel of Fig. 4. As the black bars show, response biases have been highly similar in healthy human and laboratory animal subjects exposed to 3:1 rich:lean probabilistic conditions. As shown in the gray bars, blunted response biases were observed in clinical populations across a variety of affective disorders. It is important to note that patients with non-melancholic MDD (Fletcher et al., 2015) or without anhedonia (Vrieze et al., 2013) exhibit similar response biases to control subjects, whereas patients with melancholic MDD or elevated anhedonia show a blunted response bias. This supports the assertion that the PRT is selectively assessing anhedonia which, as discussed above, is a phenotype that does not always co-occur with MDD. Finally, the white bars show blunted response biases in both humans and rats following administration of a low dose of pramipexole. Pharmacological challenges that produce comparable outcomes across species—as in this case—provide evidence that drug effects observed in laboratory animals have good predictive validity for humans. This is of crucial importance during early stages of drug development when candidate pharmacotherapeutics must be examined first in laboratory animals.

Although log *b* is the primary datum to assess reward responsiveness, as discussed above, interrogation of log *d* metrics across control and clinical populations is critical to determine whether perceptual abilities contribute to PRT outcomes as shown in the lower panel of Fig. 4. Highly similar log *d* values across control participants (black bars) and corresponding participants with affective disorders (gray bars) confirm that the blunting of response bias observed in these clinical populations, relative to healthy controls, was not due to inferior levels of discriminability. Although the selected review presented in Fig. 4 is not intended to be a comprehensive meta-analysis, the outcomes of these capstone papers are highly representative of the PRT literature. Moreover, and critical to the assumptions of the quantitative framework, these and other PRT studies confirm the independence of log *b* and log *d* metrics as first explicated by Davison and Tustin (1978). Taken together, these findings reveal shared functional outcomes in log *b* and log *d* values across a variety of clinical populations, healthy humans, and laboratory animals, highlighting rigorous translational value.

Conclusions, Caveats, and Future Directions

In conclusion, as a product of unified matching law and signal detection theory, the PRT has proven to be a useful tool in clinical settings to objectively measure anhedonic phenotypes across diverse neuropsychiatric conditions in which responsiveness to reward might be impaired. In addition, reverse-translated PRT analogs designed for rodent and nonhuman primate laboratory animals have been associated with orderly and functionally similar outcomes to findings observed in humans. However, it is also important to emphasize that reward responsiveness in general, and response bias in the PRT in particular, does not capture the full spectrum of anhedonia, which is itself heterogeneous (reviewed in Pizzagalli, 2014; Rizvi et al., 2016; Treadway & Zald, 2011). Thus, PRT performance cannot be equated to anhedonia per se. Rather, PRT

performance provides a reliable and objective measure of reward responsiveness. Indeed, the PRT is a recommended assay for the reward learning subdomain in the latest revision of the RDoC matrix (NIMH, 2016) to probe the Positive Valence Systems, a clinically important attribute implicated in anhedonic phenotypes. It should also be noted that the PRT is but one example of how integrated matching law and signal detection might serve analytic ends for studying anhedonic phenotypes. A broader paradigm could include complementary operant approaches to model dimensions of anhedonia and reward responsiveness not being assessed by the PRT. For example, recent studies by Klapes et al. (2020) have validated a laboratory procedure to rapidly obtain concurrent choice data in human subjects that conform well to predictions based on the generalized matching law, which could serve as an important supplement or complement to the PRT for evaluating sensitivity to reward in clinical populations and healthy controls. In addition, other schedule-based procedures such as differential reinforcement of low-rate responding (DRL), which have already been used successfully in the screening of candidate antidepressants (e.g., Marek & Salek, 2020; Van Hest et al., 1992; Zhang et al., 2009), could be employed in concert with the PRT to determine *selectivity* in drug effect across diverse operant classes. In general, future efforts that empirically validate enhanced variants with features that evolve from clinical or laboratory discoveries would be highly valuable. Cognizant of these considerations, development of the PRT and demonstration of pharmacological sensitivity across diverse clinical populations and laboratory animals highlighted in this review indicate that this quantitative approach is useful in accelerating the development of effective therapeutics for neuropsychiatric conditions in which anhedonic phenotypes are prominent.

Declarations

Conflicts of Interest Over the past 3 years, Dr. Pizzagalli has received funding from NIMH, Brain and Behavior Research Foundation, the Dana Foundation, and Millennium Pharmaceuticals; consulting fees from BlackThorn Therapeutics, Boehreinger Ingelheim, Compass Pathway, Concert Pharmaceuticals, Engrail Therapeutics, Otsuka Pharmaceuticals, and Takeda Pharmaceuticals; one honorarium from Alkermes; stock options from BlackThorn Therapeutics. Dr. Pizzagalli has a financial interest in BlackThorn Therapeutics, which has licensed the copyright to the Probabilistic Reward Task through Harvard University. Dr. Pizzagalli's interests were reviewed and are managed by McLean Hospital and Partners HealthCare in accordance with their conflict of interest policies. All other authors report no biomedical financial interests or potential conflicts of interest.

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