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Does Impulsivity Change Rate Dependently Following Stimulant Administration? A Translational Selective Review and Reanalysis

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Abstract

Rationale—Rate dependence refers to an orderly relationship between a baseline measure of behavior and the change in that behavior following an intervention. The most frequently observed rate-dependent effect is an inverse relationship between the baseline rate of behavior and response rates following an intervention. A previous report of rate dependence in delay discounting suggests that the discounting of delayed reinforcers, and perhaps, other impulsivity measures, may change rate dependently following acute and chronic administration of potentially therapeutic medications in both preclinical and clinical studies.

Objective—The aim of the current paper was to review the effects of stimulants on delay discounting and other impulsivity tasks.

Methods—All studies identified from the literature were required to include: 1) an objective measure of impulsivity, 2) administration of amphetamine, methylphenidate, or modafinil, 3) presentation of a pre- and post- drug administration impulsivity measure, and 4) the report of individual drug effects or results in groups split by baseline or vehicle impulsivity. Twenty-five research reports were then re-analyzed for evidence consistent with rate dependence.

Results—Of the total possible instances, 67% produced results consistent with rate dependence. Specifically, 72%, 45%, and 80% of the data sets were consistent with rate dependence following amphetamine, methylphenidate, and modafinil administration, respectively.

Conclusions—These results suggest rate dependence is a more robust phenomenon than reported in the literature. Impulsivity studies should consider this quantitative signature as a process to determine the effects of variables and as a potential prognostic tool to evaluate the effectiveness future interventions.

Impulsivity is implicated in a number of disorders and has been increasingly targeted for intervention. Here impulsivity is defined consistent with Durana et al. (1993), as actions that are expressed prematurely, entail undue risk, or appear poorly conceived and result in undesirable consequences. Conceptually, impulsivity can be characterized as either trait-like, that is considered difficult to change, or state-like, considered more susceptible to

change (Bickel, Quisenberry, Moody, & Wilson, 2014). Identifying the category to which impulsivity belongs is important because the conceptual characterization informs intervention efforts to produce change. That is, if one were interested in changing impulsivity with an intervention, then those with a state-like impulsivity would be more easily changed relative to an individual with trait-like impulsivity.

Recently, we found evidence of an impulsivity measure changing consistent with a state-like phenomenon (Bickel, Landes, Kurth-Nelson, & Redish, 2014). The task was the discounting of delayed reinforcers, which measures the decrease in value of a reinforcer as a function of the delay to its receipt. Specifically, we found that following the administration of substance-dependence interventions, delay discounting changed inversely to the baseline discounting rate.

The demonstrated phenomenon, rate dependence, refers to an orderly relationship between a baseline measure of behavior (often rate of responding) and the change in that behavior following an intervention (Dews 1977). Rate dependence demonstrates that the effect of an intervention is dependent, in part, on the level of a behavior exhibited prior to intervention. Theoretically, several quantitative relationships qualify as rate dependent (Barrett and Katz 1981) however, the most frequently observed rate-dependent effect is an inverse relationship between the baseline rate of behavior and rates of responding following an intervention (Bickel, Landes, et al., 2014; Perkins, 1999). In this frequently observed form of rate dependence, the same intervention can engender increases, decreases, and/or no change in behavior depending upon the heterogeneity of behavior at baseline. Of note, increases in low rates of responding are not required to co-occur with decreases in high rates to observe rate dependence; increases in low rates with no change in responding at high rates (or vice versa) also qualifies as rate dependence. Unless otherwise specified, we will refer only to this form of rate dependence from this point forward. Previous research has shown that rate-dependent effects can be observed in schedules of reinforcement in response to the administration of stimulants, other drugs, and non-drug interventions (Bickel, Higgins, Kirby, & Johnson, 1988; Branch, 1984; Dews, 1954; 1958; 1977). Moreover, rate dependence has been suggested as the process underlying the effects of stimulant medication on individuals with hyperactivity (Levy 2009a). One proposed mechanism is the inverted U-shaped dopamine hypothesis. This hypothesis implicates that initial baseline dopamine levels may be differentially affected by stimulant drugs to produce improvements, decrements, or no effect on outcome measures (c.f., Cools and D'Esposito, 2011).

In our previous report, we examined six intervention studies with 222 substance-dependent participants (Bickel, Landes, et al., 2014). For those interventions that were efficacious in decreasing drug use, rate-dependent effects were evident across the sample; that is, participants demonstrating more discounting of delayed rewards, were those showing the largest improvement post treatment. Rate-dependent changes were evident in three of the studies and demonstrate the quantitative signature associated with rate-dependent effects. In two of the studies where biological measures were obtained, rate-dependent effects were observed and the treatments were efficacious as indicated by the number of positive urine samples.

Based on our observation of rate dependence in delay discounting (Bickel, Landes, et al., 2014), we hypothesize that this effect is present within the greater literature, but is often overlooked. That is, the discounting of delayed reinforcers, and other measures of impulsivity, may change rate dependently following acute and chronic administration of potentially therapeutic medications in both preclinical (i.e., animal) and clinical (i.e., human) studies. If such a relationship were observed, then the quantitative signature associated with rate-dependent effects may permit empirical predictions of clinical importance; that is, identifying whether a participants' degree of impulsivity would or would not change in response to an intervention.

Given that rate dependence has been largely unexamined in studies of impulsivity (cf., Eagle, Bari, & Robbins, 2008, p. 448), the goal of this paper is to ascertain whether rate dependence should be considered as a potential factor in examining the effects of stimulants and perhaps, other interventions, on measures of impulsivity. This paper does not seek to present a comprehensive, systematic review of the effects of stimulant administration on impulsivity measures. Rather, this paper explores whether the scientific literature suggests that rate dependence is relevant to measures of impulsivity. To achieve that end, we consulted the literature to identify studies that have the potential to reveal rate dependence; that is, we identified studies that split samples (e.g., median split) into baseline impulsivity groups.

The impulsivity measures selected for this review included delay discounting, the 5-choice serial reaction time task (5CSRT), the continuous performance task (CPT), the go/no go task, the matching familiar figures test, the stroop task, the simple reaction time task (SRT), and the stop signal reaction time task (SSRT) (Bickel, Jarmolowicz, Mueller, Gatchalian, & McClure, 2012). These impulsivity measures were selected based on a previous review capturing the diversity of conceptual types of impulsivity, including impulsive choice, behavioral dis-inhibition, trait and reflection impulsivity, attention deficits, and thrill and adventure seeking (Bickel, Jarmolowicz, Mueller, Gatchalian, & McClure, 2012). We have selected stimulants because these compounds are prototypical agents used to show rate-dependent effects on schedule performance (Dews, 1977).

Methods

To identify relevant reports for data re-analysis of the impulsivity literature, a PUBMED search was conducted using the keywords "stimulant" AND one of nine different tasks identified as an impulsivity measure in Bickel et al., (2012). Specifically, these tasks/ keywords were Conners continuous performance task, delay discounting, go/no go, information sampling task, matching familiar figures test, simple reaction time, stop signal reaction time task, stroop, and 5 choice serial reaction time task. Reference sections of identified articles were also examined for additional relevant studies.

All preclinical and clinical studies identified through the search were examined for four inclusion criteria. These criteria were: 1) the inclusion of an objective impulsivity measure (e.g., delay discounting, SSRT), 2) the administration of amphetamine (AMPH), methylphenidate (MPH), or modafinil (MOD), 3) the presentation of pre- and post- drug

administration impulsivity measures in the published paper, and 4) the report of individual drug effects or results reported in groups split by baseline or vehicle impulsivity.

A total of 25 studies (17 preclinical and eight clinical studies) met inclusion criteria (see Tables 1 & 2). Individual data sets were requested from the corresponding authors in email messages. Authors who did not respond to our first email, received up to two additional email requests at least two weeks apart. When individual data was not available or an author did not respond, group mean data were obtained from published graphs using Grabit, a free software for use in Matlab (MathWorks 2014). Note that in response to email requests, corresponding authors, in addition to sending the data requested, also sent data that did not originally meet Criteria 3 (see above). However, by sending individual participant data, these data sets then met criteria. In each of those cases, data from the impulsivity measures listed above were analyzed and are included in this review.

To determine whether the data are consistent with rate dependence, we will seek evidence of an inverse relationship between change (or proportion of change) and baseline impulsivity level. This relationship could be identified in one of three ways (see Figure 1). First, if the data from the study demonstrated increases in low levels, decreases in high levels, and no change in intermediate levels we deemed the results indicative of a full range effect. Second, if the data from the study showed increases in low levels and no change in high levels we defined the results as a limited low range effect. Third, if the data in the study exhibited decreases in high levels and no change in low levels we designated the results as a limited high range effect. Note that the ranges only refer to the effect and not absolute values.

Data Analysis

Delay Discounting Studies—For the delay discounting studies, group or individual data were re-analyzed into k values based on the dependent variable presented in the published literature. These values were derived from Mazur's hyperbolic equation (Mazur 1987):

$$V = A / (1 + kD) \quad (1)$$

where V is equal to the subjective value of the reinforcer, A is the amount of the delayed reinforcer, D is the delay to receipt of the reinforcer, and k is a free parameter that represents discounting rate. For preclinical studies reporting mean adjusted delays (MAD), we solved for the value of k using Equation 1, where V was equal to the smaller reinforcer value, A was equal to the value of the larger reinforcer, and D was equal to the MAD (Stein et al. 2013).

For all other preclinical studies, k values were calculated by fitting Equation 1. For studies reporting proportion of larger choice, the data were transformed to percent larger choice and then fit to Equation 1. Similarly, for studies that reported mean number of larger choice responses, the data were transformed to percent larger choice after identifying the total number of trials completed. Similar to the preclinical analyses, group clinical discounting data was re-analyzed by obtaining group mean indifference points (similar to MAD in rodents) and fitting the points to Equation 1. For some studies, k values were log

transformed using natural log and graphs for this task represent the change in $\ln(k)$ as a function of vehicle or placebo baseline $\ln(k)$ values.

In cases in which Equation 1 did not robustly fit the indifference points, area under the curve (AUC) was calculated. AUC was calculated by summing the area of each trapezoid created by drawing vertical lines from each indifference point to the x-axis. The area of each trapezoid is equal to Equation 2 (Myerson et al. 2001):

$$(x_2 - x_1)[(y_1 + y_2)/2], \quad (2)$$

where x_1 and x_2 are consecutive delays and y_1 and y_2 are indifference points associated with those delays. The areas of each trapezoid under the curve are summed for AUC. In AUC analyses, individuals who discount at a low rate have a higher AUC and individuals who discount at a high rate have a lower AUC.

SSRT, 5CSRT, CPT, SRT, Matching Familiar Figures Test, and Go/No-Go

Studies—Re-analysis of the data involved calculating the proportion of change under each drug treatment condition compared to the value obtained during the vehicle or placebo baseline condition. Proportion of change was calculated by subtracting the vehicle or placebo group mean from the drug group mean and dividing the difference by the vehicle or placebo treated mean. For studies representing individual data, change or proportion of change was calculated for the individual.

All data displayed graphically represent change or proportion of change of the dependent variables as a function of vehicle or placebo baseline impulsivity. The dotted line represents no change from baseline performance. Linear regression lines were fit for all studies. To be clear, rate dependence for individual data was determined solely by Oldham's method (described below). The regression lines are presented only to assist in the visual interpretation of the data.

Testing for Rate Dependence—Oldham (1962) described a method to test for a differential effect of initial value post intervention without two specific confounds: mathematical coupling and regression to the mean. Mathematical coupling is when one variable (i.e., change score) consists of all or part of another variable (i.e., baseline value), which results in artificially inflated association when determining correlations (Oldham 1962). For example, when x and y are two random numbers with the same standard deviation the correlation of x (baseline value) and $x-y$ (change score) generates a strong relationship of approximately 0.71 (Oldham 1962). Thus, the null hypothesis, using this correlation, is erroneous. Moreover, regression to the mean is a change in the variation due to repeated measurements, most often seen as a product of measurement error for the baseline value (Tu and Gilthorpe 2007).

Oldham proposed a method in which change from baseline value is measured using variables that are not dependent on each other. An important feature of this method is that it can determine whether there is a rate-dependent treatment effect independent of mathematical coupling and regression to the mean. This is assessed through Equation 3:

$$\text{Corr}(x-y), \frac{(x+y)}{2} = \frac{s_x^2 - s_y^2}{\sqrt{(s_x^2 + s_y^2)^2 - 4r_{xy}^2 s_x^2 s_y^2}} \quad (3)$$

where y is the post-treatment measure, x is the baseline measure, s_y^2 is the variance of y and s_x^2 is the variance of x . The correlation between x and y is r_{xy}^2 (Tu and Gilthorpe 2007). The numerator of Equation 3 tests the difference between the variance of the pre-and post-measures to determine if those measures are correlated. If the correlation is zero, no baseline-dependent effect is present. Elimination of the correlation between x and y in the numerator of Equation 3 protects Oldham's correlation against mathematical coupling and regression to the mean (Blance et al. 2007). To determine if a relationship between the variables exists independent of mathematical coupling and regression to the mean, the correlation ($r_{\text{mean}(x,y), y-x}$) between the change score and the average responses of the vehicle and drug sessions was calculated for all studies where individual data were provided via publication or through personal contact. Our goal was to illustrate the presence of rate dependence, not to compare relative effect sizes between tasks, different sample characteristics or doses administered. All individual data sets referred to below as being consistent with rate dependence represent cases where Oldham's correlation revealed a Pearson correlation coefficient of 0.3 or greater (see Tables 1 & 2; (Cohen 1992; Browne et al. 2010). A guideline for determining rate dependence via the magnitude of the correlation has been suggested before (Browne et al. 2010) using a magnitude of $r = 0.3$ based on a medium effect size derived from Cohen (1992).

All data analyses were conducted using GraphPad Prism version 6.0 (San Diego, CA USA, www.graphpad.com).

Results

For all results, re-analyzed studies are separated by task type and drug administered. Studies are presented first for those with individual data and then group data in the following order: (1) those that provide evidence of a full range effect of baseline impulsivity; (2) those representing limited high or low range effects of baseline impulsivity; and (3) those not demonstrating a rate-dependent effect.

Preclinical Literature

Evaluation of the preclinical studies that met criteria revealed data from four different tasks (see Table 1 for an outline of these studies) with primary impulsivity dependent variables (Bickel et al., 2012). Of those identified, there were eight delay discounting tasks, three SSRT tasks, five 5CSRT, and one 5CPT. Individual data sets were obtained from eight of the 17 studies, which are graphed in lieu of group data. All studies used within-subject drug treatment and the rat species with the exception of 3 studies (Loos et al. 2010; Yan et al. 2011; Fletcher et al. 2013), represented by the pound sign (#) in Table 1 and associated figures, which utilized mice as experimental subjects. Responses under vehicle conditions were collected in all studies and thus graphical baseline measures were derived from vehicle conditions.

Delay Discounting

Amphetamine—In the studies examining AMPH administration and delay discounting, effects consistent with rate dependence were found in all studies for at least one dose of AMPH tested, usually at the highest dose. Individual data were obtained from five of these studies. In three studies investigating a limited high range effect consistent with rate dependence (Barbelivien et al., 2008; Huskinson et al., 2013; Krebs and Anderson, 2012) represented in Figure 2 panels A–C, AMPH decreased discounting rate in the high baseline discounters whereas no change occurred in the low baseline discounters. In Figure 2C, effects consistent with rate dependence were found only for the highest dose (1.0 mg/kg). Two studies with limited low range effects (Figure 2D and E) represented no change in high discounters, while AMPH administration increased discounting rates in low discounters (Wooters and Bardo, 2011; Stanis et al., 2008).

In the group data analysis, one study demonstrated effects across the full range consistent with rate dependence (Figure 3A). That is, high discounters decreased discounting rate after drug administration, while low discounters increased discounting rate (Perry et al., 2008). Data from another study evaluated a limited high range effect of baseline impulsivity scores (Figure 3B). In this study, the low discounters in the sample did not change, whereas the high discounters decreased discounting rate after AMPH administration (Winstanley et al., 2003). The last study reported data with a limited low range effect consistent with rate dependence, represented in Figure 3C, where low discounters increased discounting rate after AMPH administration and no change was revealed in the high discounters (Stanis et al. 2008; Hand et al. 2009).

Methylphenidate—Evaluation of the delay discounting literature utilizing MPH resulted in two studies that met criteria represented in Figures 2F and 3D. In the MPH delay discounting study (Wooters and Bardo 2011) the individual data represented a full range effect. The high discounters decreased discounting rate after administration of MPH (except for 3.0 mg/kg), while the low discounters increased discounting rate after MPH administration consistent with rate dependence.

Re-analysis of group data from one study depicting a limited high range effect (Perry et al. 2008) revealed decreased discounting rates in the high discounters at the 5 and 10 mg/kg doses, while no change occurred with the 2.5 mg/kg dose nor after any dose in the low discounters.

Stop Signal Reaction Time Task

Amphetamine—Results from two studies with AMPH were identified and the first represents the limited high range effect. Data from Feola et al. (2000), represented in Figure 4A, showed a decrease in stop time for the slow stoppers at all doses and minimal change in the fast stoppers. Results inconsistent with rate dependence were reported in the second identified study (Eagle & Robbins, 2003) revealing decreased stop time in fast stoppers and no change in slow stoppers (Figure 4B).

Methylphenidate—One MPH study was identified that demonstrated a directional relationship consistent with rate dependence with a limited low range effect. The fast stoppers increased stop time after treatment with 1.0 mg/kg MPH, whereas the slow stoppers did not change post-treatment (Figure 4C; Eagle, Tufft, Goodchild, & Robbins, 2007). When these authors examined the animals at the extreme ends of each group, the distribution was more representative of a full range effect. The fast stoppers increased stop time, while the slow stoppers decreased stop time at 0.3 and 1.0 mg/kg MPH (Figure 4D), consistent with rate dependence.

Modafinil—The same group tested MOD in this paradigm and showed a differential effect between baseline impulsivity groups representing a full range effect. The fast stoppers increased stop time and the slow stoppers decreased stop time, depicted in Figure 4E (Eagle et al., 2007).

5 Choice Serial Reaction Time Task

Amphetamine—The individual data from Yan et al. (2011), represented in Figure 5A and one of the three studies to use mice, demonstrated decreased percent premature responses in the high baseline group and increased premature responses in the low baseline group representative of a full range effect and consistent with rate dependence for the highest dose. One additional study (Figure 5B), where individual data was obtained, showed increased premature responses in mice with low baselines, representing a limited high range effect and consistent with rate dependence (Fletcher et al. 2013).

Group data from Harrison, Everitt, & Robbins (1997) showed increased premature responses in the low baseline group at 0.4 and 0.8 mg/kg AMPH with no change in the high baseline group (i.e., high number of premature responses), depicted in Figure 6A. This study is consistent with rate dependence and represents a limited low range effect. Another study (Loos et al. 2010) showed the limited low range effect and found increases in percent premature responses in low baseline mice after 1.0 mg/kg AMPH and no change in high baseline mice (Figure 6B). No rate-dependent consistent effects were evident following 0.25 and 0.5 mg/kg AMPH administration.

Methylphenidate—One identified investigation utilizing MPH (Fernando et al. 2012) where individual data was also obtained, revealed differential changes across baseline conditions. Increased premature responses after drug treatment were evident in low baseline animals, but decreased premature responses occurred in the high baseline animals. Figure 5C shows full range effects consistent with rate dependence for the highest MPH dose.

Continuous Performance Task

Methylphenidate—Data from the only CPT study (Tomlinson et al. 2014) demonstrated a full range effect consistent with rate dependence (Figure 6C). The high baseline group showed a decreased number of premature responses at the two lowest doses (0.5 and 1.0 mg/kg) and the low impulsivity group increased premature responses at the intermediate dose (1.0 mg/kg). Both groups improved and changed in the same direction after treatment of the highest dose (2.0 mg/kg), indicating no demonstrated rate dependence at this dose.

Summary

In sum, 17 preclinical studies met inclusion criteria. In all studies, effects consistent with rate dependence were demonstrated at some dose of each particular drug administered. There were 29 instances where rate dependence could be observed in individual data sets. Of those instances, 19 demonstrated this effect measured by the strength (i.e., above $r = 0.3$) of the correlation (see Equation 3; Oldham, 1962). There were 33 instances in which rate dependence could be observed in data analyzed as group means. Of those, 26 instances appeared consistent with rate dependence. When individual and group instances were combined, this quantitative signature was observed at most doses greater than 1.0 mg/kg AMPH, though results were equivocal for lower doses. After MPH administration, 8 of 15 instances revealed effects consistent with rate dependence. In the only MOD preclinical study evaluated, effects consistent with rate dependence were observed at all doses examined.

Clinical Literature

Evaluation of the clinical studies that met criteria revealed data from six different tasks (see Table 2 for an outline of these studies) with primary impulsivity dependent variables (Bickel et al., 2012). A total of one delay discounting task, three SSRT tasks, two simple reaction time tasks, one matching familiar figures test, and one go/no-go task were identified and met analysis criteria. Four additional data sets that did not originally meet criteria 3; specifically, data from two delay discounting tasks, one probability discounting task, and one go/no-go task were provided by corresponding authors. A total of ten data sets containing individual data were re-analyzed; the remaining three studies were analyzed as group means. All studies analyzed used within-subject drug treatment with the exception of two studies (de Wit et al., 2000, 2002). Responses under placebo conditions were collected in all but one study and thus graphical baseline measures were derived from placebo conditions. The exception (Figure 13A and B) did not report placebo responding so control (i.e., off MPH) baseline responding was graphed instead (Vaidya et al. 1998).

Delay Discounting

Amphetamine—A total of three human delay discounting studies were re-analyzed. Of those, two studies measured discounting rates between placebo and AMPH. First, Figure 7A represents individual data (de Wit et al. 2002) showing a limited high range effect on placebo discounting ($\ln k$) baseline. Although the high dose (20 mg) of AMPH produced a correlation that approached the cut-off ($r = -0.254$), neither the 10 nor 20 mg AMPH dose produced a baseline-dependent effect. Second, Acheson and de Wit (2008) reported that AUC was a better representative measure of discounting rate due to a lack of goodness of fit of the individual data to Equation 1. Upon re-analysis, AUC proportion of change following 20 mg AMPH administration was also not consistent with rate dependence (Figure 7B).

Modafinil—The third human delay discounting study (Schmaal et al. 2014) reported that alcohol-dependent males discounted at a high rate and healthy control participants discounted at a low rate. We examined the data as a function of AUC due to a lack of fit to Equation 1. Figure 7C shows a full range effect of placebo condition levels, however the

proportion of change in AUC after 200 mg MOD treatment was not consistent with rate-dependent effects.

Probability Discounting

Amphetamine—Acheson and de Wit (2008) also examined probability discounting AUC following (20 mg) AMPH administration. The individual data represented a limited low range effect. While Oldham's correlation ($r = -0.233$) approached the cut-off the results were not consistent with rate dependence. Figure 8 shows the relationship between AUC proportion of change as a function of placebo baseline AUC, in which participants with low baseline AUC increased AUC following AMPH treatment; while those with high baseline AUC did not change.

Stop Signal Reaction Time Task

Amphetamine—Two studies utilizing SSRT following AMPH administration were re-analyzed, one using individual data and another using group data. de Wit et al. (2002) measured SSRT between groups administered AMPH and placebo. Figure 9A represents a full range effect and shows the relationship between the proportion of SSRT change under AMPH treatment compared to placebo. Performance under 10 mg was consistent with rate dependence, however the results from 20 mg are inconsistent with rate dependence. Figure 10 represents group data of a limited high range effect in which (10 and 20 mg) AMPH decreased reaction time in slow stoppers and fast stoppers did not change (de Wit et al. 2000).

Modafinil—Two studies utilizing SSRT following MOD administration were reanalyzed, both with individual data. Proportion of change in SSRT was measured following (200 mg) MOD compared to placebo administration within-subjects (Zack and Poulos 2009). Figure 9B shows individual data indicating full range effects consistent with rate dependence between proportion of change in SSRT compared to placebo baseline. That is, participants initially identified as impulsive decreased SSRT following MOD treatment; whereas those identified as less impulsive, increased SSRT.

Simple Reaction Time

Amphetamine—Two studies utilizing a simple reaction time task met criteria. Acheson & de Wit (2008) performed a median-split to separate high and low deviators from the mode reaction time (a measure of attention deficits). Figure 11A shows a limited high range effect consistent with rate dependence. Specifically, 20 mg AMPH decreased reaction time in those with initially high deviations from the mode and reaction time did not change in those who had low initial deviations from the mode. Similarly, Hamidovic, Dlugos, Palmer, & de Wit (2010) measured deviations from the mode following two doses of AMPH. The mean deviation from the mode measured between three genotypes differed under placebo conditions. Further, when treated with (10 and 20 mg) AMPH, participants who deviated little from the mode under placebo conditions did not change; whereas those with higher initial scores reduced deviation following AMPH treatment, representative of a limited high range effect (Figure 11B).

Matching Familiar Figures Test

Methylphenidate—One study met criteria utilizing the matching familiar figures test. Rapport, DuPaul, Stoner, Birmingham, & Masse (1985) reported error percentile rankings for seven individual participants in which lower rank indicated fewer errors. Consistent with rate dependence and representing a limited high range effect of placebo levels, Figure 12 illustrates effects inconsistent with rate dependence under all doses of MPH. In particular, 5 and 10 mg MPH produced results in the opposite direction of our specified form of rate dependence, but still produced Oldham's correlations above 0.3.

Go/No Go Task

Amphetamine—We obtained individual data from de Wit et al. (2000). Percent of commission errors were significantly reduced following (10 and 20 mg) AMPH. Figure 13A illustrates a full range effect consistent with rate dependence when plotted as a proportion of change from placebo responses.

Methylphenidate—Finally, one study met criteria that utilized two go/no go task variations (Vaidya et al. 1998). These tasks were the only re-analyzed clinical data sets that lacked a placebo condition; instead proportion of change was compared to the control condition where no MPH was administered. Ten ADHD and six control participants were individually assessed on commission error percentages with and without MPH in two versions of a go/no go task: stimulus controlled and response controlled tasks. Figures 13B and C both illustrate limited high range effects, however only the response controlled task produced results consistent with rate dependence. That is, the proportion of change in percent commission errors, in the response controlled task, decreased in those with initially high commission error percentages and those with initially low percent commission errors did not change following MPH administration.

Summary

A total of ten clinical study data sets were re-analyzed using individual data, and three were analyzed as group means. In most cases, effects consistent with rate dependence were demonstrated at some dose of AMPH, MPH, or MOD administration. There were a total of 15 possible instances in which to observe rate-dependent effects from individual data. Of those instances, 5 demonstrated effects consistent with rate dependence as measured by Oldham's correlation (Oldham 1962). Furthermore, there were five instances in which rate dependence could be observed in the group data. Of those, all five appear to show rate dependent effects following stimulant administration. When individual and group instances were combined, 8 of 13 instances exhibited this quantitative signature following AMPH administration. When MPH was administered, 1 of 5 instances were consistent with rate dependence. Finally, when MOD was administered 1 of 2 instances were consistent with rate dependence.

Discussion

In this review, we re-analyzed 25 research reports for evidence consistent with rate dependence. Given that multiple doses were examined, there were a total of 82 instances in

which effects consistent with rate dependence could be observed. Of that total, 55 demonstrated evidence consistent with the quantitative signature (i.e., rate dependence). Collectively, these results support examining whether rate-dependent effects are relevant when investigating the effects of independent variables on impulsivity. Below we make six comments addressing these results.

First, 67% of the total possible instances and 77% of the highest doses tested produced results consistent with rate dependence, which suggests that this is a more robust phenomenon than reported in the literature. Although our previous report (Bickel, Landes, et al., 2014) investigated several substance-dependence interventions and the current report examined stimulant administration, these are likely not the only occasions under which rate dependence may be observed. For example, baseline-dependent consistent results have been previously reported following nicotine administration in both preclinical and clinical studies (for review see Perkins, 1999), d-amphetamine in temporal discrimination procedures (Odum et al. 2002), and stimulants in working memory paradigms (Kalechstein et al. 2010; Finke et al. 2010). Subsequent studies would be justified to explore this effect following a variety of treatments including behavioral, pharmacological, and exploratory interventions (e.g., transcranial magnetic stimulation). Perhaps, measures of executive function, including measures of impulsivity, not reviewed here, should be examined to determine whether rate-dependent effects are operative in the data (Bickel et al. 2012).

Second, the observation that the same intervention may be able to produce increases, decreases, or no change dependent upon the baseline level of behavior has important implications in data evaluation. Consider a study examining a heterogeneous group of impulsive individuals with a novel treatment that concluded the intervention has no effect. The lack of observed treatment effect may be a result of an equal number of participants with high, medium, and low impulsive baselines producing a net no change when summarized as a group. For example, one study reviewed here reported no main effect of stimulant administration on one of the impulsivity measures examined, yet when we re-analyzed the data as a function of baseline impulsivity a rate-dependent effect was evident. This example demonstrates that undifferentiated analysis of impulsivity without sensitivity to rate dependence could falsely conclude the intervention has no effect when, indeed, participants show effects consistent with this quantitative signature.

Third, the important clinical implication of these results is that individuals who may demonstrate a positive therapeutic effect of intervention may be identified *a priori* (Tu and Gilthorpe 2007; Bickel et al. 2014). Consider for example the discounting of delayed rewards, which has been identified as a marker for drug dependence (Bickel, Koffarnus, Moody, & Wilson, 2014). If it is a marker and if changing discounting rate could have positive clinical effects, then identifying who would be susceptible to a particular intervention would be useful to consider as a clinical innovation. Specifically, the adoption of such an innovation could not only protect individuals from receiving ineffective or harmful interventions, but also define the sub-group that may receive the greatest therapeutic benefit. Moreover, development of such a prognostic tool could permit participants, who would not otherwise benefit from a treatment, to receive an alternative or adjunctive intervention that may produce efficacious outcomes (Bickel et al., 2014b).

Fourth, the ubiquity of rate dependence (Perkins 1999; Odum et al. 2002; Kalechstein et al. 2010; Finke et al. 2010), although impressive, raises an important challenge for mechanistic study. To date, no specific mechanism has been empirically determined to explain rate dependence although here, we build on one previously proposed hypothesis and begin by considering that hypothesis in the context of a dual systems model. The Competing Neurobehavioral Decision Systems (CNDS) hypothesis (Bickel et al., 2007; Bickel, Jarmolowicz, Mueller, & Gatchalian, 2011) states that the regulatory balance of two neural systems results in choices for delayed or immediate reinforcers in delay discounting tasks, which can be generalized to other impulsivity measures. The two neural systems are comprised of, the evolutionarily older, impulsive limbic and paralimbic brain regions and, the evolutionarily younger, executive decision system, which includes the prefrontal and parietal cortices. These two systems work in relative balance in normally functioning individuals. However, individuals with hypoactive executive control or hyperactive control by the impulsive decision system are likely individuals with higher baseline rates of impulsivity. The relative balance of the systems can be affected by motivation, context, stress level, or therapeutic interventions (Bickel et al., 2014; Bickel et al., 2014b). Moreover, stimulant medications increase dopamine activity in the prefrontal cortex and, in individuals with low baseline functioning, can move the dual systems toward regulatory balance for some duration. Therefore, those with more executive dysfunction and less prefrontal activation would sustain a greater proportional increase in executive function after treatment whereas individuals with baseline regulatory balance and normal dopamine activity would exhibit less change in executive function post-treatment.

This explanation is consistent with the previously expressed inverted-U-shaped dopamine action hypothesis, often associated with attention deficit disorder (Levy 2009a). Specifically, the dopamine hypothesis refers to endogenous levels of dopamine in the prefrontal cortex and striatum affecting executive function (Levy 2009b; Cools and D'Esposito 2011). First, baseline dopamine levels, prior to drug treatment, are reflective of the differential initial baseline levels observed in behavioral measures. Then, following stimulant administration, catecholamines (including dopamine) and adrenergic activation increase to the maximum levels of the inverted-U-shaped function in individuals with initially low baselines thereby increasing executive function. Conversely, stimulant administration reduces, or does not change, activity in those with high baseline dopamine levels (Cools and D'Esposito 2011). While reduction of dopamine activity seems counter-intuitive, Solanto (1998, 1984) suggested that stimulants increase catecholamine release so much that inhibitory pre-synaptic autoreceptors are activated to reduce dopamine transmission. Evidence of the inverted-U-shaped dopamine action hypothesis in working memory and attention performance (Levy 2009b; Arnsten 2009), and the antipode relationship between impulsivity and some executive function measures (Bickel et al., 2012), suggests that this mechanism should be explored as a possible explanation of rate-dependent effects in impulsivity tasks. Perhaps, neuroimaging studies could verify this relationship and future investigations should strive to confirm this hypothesis with neuroimaging data.

Fifth, several weakness of this review must be acknowledged. An important alternative process to rule out when evaluating rate dependence is whether the data can be explained simply by regression to the mean. In our prior paper, one of the six data sets examined,

qualified as regression to the mean (Bickel, Landes, et al., 2014) and therefore could not be considered rate dependent. Here we applied Oldham's correlation to individual data so as to differentiate rate dependent effects from mathematical coupling and regression to the mean. In the papers reviewed above where individual data was not obtained, we could not re-analyze the data with the Oldham's correlation. Given this constraint, some of the studies where only group data were available could qualify as regression to the mean. That is, impulsivity groups who were retrospectively split (e.g., median-split) prevented analysis of the full range of the behavior dependent on baseline performance. Relatedly, those studies with only group data were analyzed with two data points and many of those with individual data analyzed small sample sizes. The possibility also exists that potential outliers occurred in the previously published data and thus, were also present in the current analysis and may have influenced results. Moreover, basement or ceiling effects, a limitation of task sensitivity, could influence the number of instances considered consistent with rate dependence. For example, if a participant scored zero errors at baseline, the possible directions for post-treatment change were an increase in errors or no change, which does not preclude measurement for rate-dependent effects. Another weakness of this review is that our selection criteria (Criteria 4) may have resulted in a positive publication bias. However, we note that the purpose of this paper was not to review every study that examined stimulant administration on impulsivity baselines. Indeed such a review across all of the measures of impulsivity would likely be prohibitively long. Our purpose was to illustrate that rate dependence is a phenomenon that may be observed when examining impulsivity baselines. The extent to which it would be observed across the full breadth of studies in this area would require more in depth re-analysis or additional prospective study.

Sixth and finally, this review and re-analysis suggests that rate dependence may be evident across a wide variety of impulsivity measures and resulting from a diverse set of interventions (e.g., substance-dependence treatments and stimulant administration). The purpose of this review is to bring this seemingly robust phenomenon to the attention of the field so that it can be recognized and exploited for the benefit of treatment-seeking individuals. Repeating the current procedure with different treatment modalities (e.g., drug administration, cognitive therapies) or behaviors other than impulsivity is relevant to extending our results and determining the regularity with which rate dependence occurs. Only additional research will determine the domains that are relevant to this phenomenon and the boundary conditions that limit its effects.

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Figure 1.

Representation of the three ways rate dependence may be visually represented. When the full range of baseline values are examined, low baseline values increase while high baseline values decrease. When the limited low range is examined, low baseline values increase while high baseline values show no change. When the limited high range is examined, low baseline values do not change while the high values decrease.

Figure 2.

Graphical re-analysis of individual preclinical delay discounting studies that met criteria represented by the change in discounting as a function of baseline discounting rate. Rate dependence was determined solely by Oldham's method.

Figure 3.

Graphical re-analysis of group preclinical delay discounting studies that met criteria represented by the change in discounting as a function of baseline discounting rate.

Figure 4.

Graphical re-analysis of group preclinical stop signal reaction time studies that met criteria represented by proportion of change in reaction time as a function of baseline reaction time.

Figure 5.

Graphical re-analysis of individual preclinical 5 choice serial reaction time and continuous performance task studies that met criteria represented by proportion of change in responding as a function of baseline responding. For additional details see description of Figure 2.

Figure 6.

Graphical re-analysis of group preclinical 5 choice serial reaction time and continuous performance task studies that met criteria represented by proportion of change in responding as a function of baseline responding.

Figure 7.

Graphical re-analysis of the individual clinical delay discounting studies that met criteria represented by the proportion of change of AUC or change in $\ln(k)$ as a function of placebo baseline AUC or $\ln(k)$. For additional details see description of Figure 2.

Figure 8.

Graphical re-analysis of the individual clinical probability delay discounting study that met criteria represented by the proportion of change of AUC as a function of placebo baseline AUC. For additional details see description of Figure 2.

Figure 9.

Graphical re-analysis of individual clinical stop signal reaction time studies that met criteria represented by proportion of change in reaction time as a function of placebo baseline reaction time. For additional details see description of Figure 2.

Figure 10.

Graphical re-analysis of group clinical stop signal reaction time studies that met criteria represented by proportion of change in reaction time as a function of placebo baseline reaction time.

Figure 11.

Graphical re-analysis of group clinical simple reaction time studies that met criteria represented by proportion of change in reaction time as a function of placebo baseline deviation from the mode.

Figure 12.

Graphical re-analysis of individual clinical matching familiar figures test study that met criteria represented by the proportion of change in error percentile rankings as a function of baseline percentile rankings. For additional details see description of Figure 2.

Figure 13.

Graphical re-analysis of individual clinical Go/No Go task study that met criteria represented by the proportion of change in commission error percentages as a function of control percentages. For additional details see description of Figure 2.

Table 1

Outline of preclinical studies that met criteria.

Task	Authors	Subjects	Dependent Variable	Drug	Doses	Range Effect	Rate Dependent (Y/N)	Oldham's Correlation
Delay Discounting	Huskinson et al. (2012)	Individual data	ln(k)	AMPH	0.1 mg/kg		N	0.08684
					0.3 mg/kg		N	0.05456
					1.0 mg/kg	Limited High	Y	0.4029 *
					1.7 mg/kg		Y	0.432 *
	Krebs & Anderson (2012)	Individual data	ln(k)	AMPH	0.03 mg/kg		Y	-0.7108 *
					0.1 mg/kg		Y	0.483 *
					0.3 mg/kg	Limited High	Y	0.5192 *
					0.56 mg/kg		Y	-0.59 *
					1.8 mg/kg		Y	0.9766 *
	Barbelivien et al. (2008)	Individual data	ln(k)	AMPH	0.5 mg/kg		N	0.07
					1.0 mg/kg	Limited High	Y	0.543 *
	Stanis et al. (2008)	Individual data	ln(k)	AMPH	0.3 mg/kg		Y	0.341 *
					0.6 mg/kg	Limited Low	Y	0.395 *
					1.0 mg/kg		N	0.077
	Wooters & Bardo (2011)	Individual data	ln(k)	AMPH	0.1 mg/kg		Y	0.3594 *
					0.3 mg/kg	Limited Low	N	0.1876
					0.56 mg/kg		Y	0.4191 *
					1.0 mg/kg		Y	0.361 *
				MPH	1.0 mg/kg		N	-0.03
					3.0 mg/kg	Full	Y	-0.395 *
					5.6 mg/kg		N	0.103
					10 mg/kg		N	0.023
	Perry et al. (2008)	Between subjects (enriched, isolated)	ln(k)	AMPH	0.5 mg/kg		N	N/A
					1.0 mg/kg	Full	Y	
					2.0 mg/kg		Y	
					2.5 mg/kg		N	N/A
				MPH				

Task	Authors	Subjects	Dependent Variable	Drug	Doses	Range Effect	Rate Dependent (Y/N)	Oldham's Correlation
Stop Signal Reaction Time	Winstanley et al. (2003)	Between subjects (sham, lesion)	ln(k)	AMPH	5.0 mg/kg	Limited High	Y	
					10.0 mg/kg		Y	
					0.3 mg/kg		N	N/A
					1.0 mg/kg		Y	
					1.5 mg/kg	Limited High	Y	
	Hand et al. (2009)	Between subjects (SHR, WKY)	ln(k)	AMPH	2.3 mg/kg		Y	
					1.0 mg/kg		Y	N/A
					3.2 mg/kg	Limited Low	Y	
					5.6 mg/kg		Y	
5CSRT/5CPT	Feola et al. (2000)	Within treatment median split (slow, fast responders)	Change in SSRT	AMPH	0.125 mg/kg		Y	N/A
					0.25 mg/kg		Y	
					0.5 mg/kg	Limited High	Y	
					1.0 mg/kg		Y	
	Eagle et al. (2007) **	Within treatment median split (slow, fast responders)	SSRT	MPH	0.3 mg/kg	Limited Low	Y	N/A
					1.0 mg/kg		Y	
					3 mg/kg		Y	N/A
					10 mg/kg	Full	Y	
5CSRT/5CPT	Eagle & Robbins (2003)	Between subjects (lesion, sham)	SSRT	AMPH	30 mg/kg	N/A	N	N/A
					0.3 mg/kg		Y	
					1.0 mg/kg		Y	
	Yan et al. (2011) #	Individual data	Percent premature responses	AMPH	0.3 mg/kg	Full	Y	0.242
					1.0 mg/kg		Y	0.5622*
					0.25 mg/kg	Limited High	Y	-0.5238*
					0.5 mg/kg		Y	0.5838*
5CSRT/5CPT	Fletcher et al. (2013) #	Individual data	Number of premature responses	AMPH	0.25 mg/kg		Y	
					0.5 mg/kg		Y	
					0.25 mg/kg	Limited Low	N	N/A
					0.5 mg/kg		Y	
					1.0 mg/kg		Y	
	Loos et al. (2010) #	Between subjects (C57BL/6J, DBA/2J)	Percent premature responses	AMPH	0.25 mg/kg		N	N/A
					0.5 mg/kg		Y	
					1.0 mg/kg		Y	
					0.2 mg/kg		N	N/A
					0.4 mg/kg	Limited Low	Y	
5CSRT/5CPT	Harrison et al. (1997)	Between subjects (sham, lesion)	Mean number premature responses	AMPH	0.8 mg/kg		Y	

Task	Authors	Subjects	Dependent Variable	Drug	Doses	Range Effect	Rate Dependent (Y/N)	Oldham's Correlation
	Fernando et al. 2012	Individual data	Number of premature responses	MPH	0.3 mg/kg 1.0 mg/kg 3.0 mg/kg	Full	N N Y	-0.158 0.1248 -0.9847*
	Tomlinson et al. (2014)	Within treatment median split (low, high premature responses)	Number of premature responses	MPH	0.5 mg/kg 1.0 mg/kg 2.0 mg/kg	Full	Y Y N	N/A

studies that used mice

* significant

** analyzed both as high and low groups and with the extremes of each group

Table 2

Outline of clinical studies that met criteria.

Task	Authors	Subjects	Dependent Variable	Drug Treatment Design	Drug	Doses	Range Type	Rate Dependent (Y/N)	Oldham's Correlation (Pearson r)
Delay Discounting	de Wit et al. (2002)	Individual Data	Ink	Between Subjects	AMPH	10 mg	Limited High	N	0.00515
	Acheson & de Wit (2008)	Individual Data	AUC	Within Subjects	AMPH	20 mg	Limited High	N	-0.2539
	Schmaal et al. (2014)	Individual Data	AUC	Within Subjects	MOD	200 mg	N/A	N	-0.05611
Probability Discounting	Acheson & de Wit (2008)	Individual Data	AUC	Within Subjects	AMPH	20 mg	Limited Low	N	-0.2334
Stop Signal Reaction Time	de Wit et al. (2002)	Individual Data	SSRT (msec)	Between Subjects	AMPH	10 mg	Full	Y	-0.3322*
	de Wit et al. (2000)	Within Treatment Post hoc Median Split (Fast, Slow Stoppers)	SSRT (msec)	Between Subjects	AMPH	20 mg		N	-0.1284
						10 mg		Y	
	Zack & Poulos (2009)	Individual Data	SSRT (msec)	Within Subjects	MOD	200 mg	Limited High	Y	-0.4857*
Simple Reaction Time Task	Acheson & de Wit (2008)	Within Treatment Post hoc Median Split (High, Low Deviation from the Mode)	Mean RT (msec)	Within Subjects	AMPH	20 mg	Limited High	Y	
	Hamidovic et al. (2010)	Between Subjects (High, Med, Low Deviation from the Mode)	DevMod	Within Subjects	AMPH	10 mg		Y	
						20 mg	Limited High	Y	
Matching Familiar Figures Test	Rapport et al. (1985)	Individual Data	Error Percentile Ranking	Within Subjects	MPH	5 mg	Limited High	Y	0.482*

Task	Authors	Subjects	Dependent Variable	Drug Treatment Design	Drug	Doses	Range Type	Rate Dependent (Y/N)	Oldham's Correlation (Pearson r)
Go/No Go Task	de Wit et al. (2002)	Individual Data	Percent Commission Errors	Between Subjects	AMPH	10 mg	Limited High	Y	0.5499*
						15 mg	N/A	N	0.08927
	Vaidya et al. (1998)	Individual Data	Percent Commission Errors	Within Subject	MPH	10 mg	Full	N	-0.4666^
						20 mg	Full	N	-0.3774^
						7.5-30 mg (prescribed dose)	Limited High	Y	Response: -0.5563*
								N	Stimulus: -0.1123

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^ indicates Oldham's correlation above 0.3 cut-off; postitive rate dependent effect