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The Return of Rate Dependence

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Abstract

Rate dependence, a well-known phenomenon in behavioral pharmacology, appears to have declined as a topic of interest, perhaps, as a result of being viewed pertinent to only the preclinical investigation of drugs on schedule-controlled performance. Obstacles to data interpretation due to conflation with regression to the mean also appear to have contributed to the topic's decline. Despite this reduction in exposure, rate dependence is a useful concept and tool that can be used to determine sources of variability, predict therapeutic outcomes, and identify individuals that are most likely to respond therapeutically. Armed with new statistical methods and an understanding of the broad range of conditions under which rate dependence can be observed, we urge researchers to revisit the concept, use the appropriate analysis methods, and to design empirical studies *a priori* to further explore rate dependence.

Keywords

rate dependence; sources of variation; Oldham; regression to the mean

> "Suppose we take the position that variability is not intrinsic to behavior. What alternative conception is available to explain the fact that variability is observed?"
>
> - M. Sidman (1960 p. 145)

Our charge, as scientists, is to investigate beyond the cursory explanation of intrinsic variability in behavior and identify other sources of variability, as Sidman (1960) suggested. Consider an example in which an intervention produced no significant effect when evaluated across all individuals. However, further exploration revealed that individuals systematically changed following the intervention as a function of differential baseline rates of behavior. The variability within the intervention effect was therefore systematically related to the data and, in fact, a product of the individual's baseline rate. Thus, the phenomenon known as rate dependence was functioning within the data to obscure an intervention effect and described seemingly unexplained variability within the sample.

Rate dependence is a well-known behavioral phenomenon, in which change in responding following an intervention is dependent upon the baseline rate of behavior. Rate dependence was first demonstrated when baseline responding was maintained by different schedules of

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reinforcement. Following the establishment of baseline rates, drugs were administered as interventions in behavioral pharmacological studies (Dews & Wenger, 1977; Dews, 1958; Wenger & Dews, 1976). The classic inverse rate-dependent relationship is demonstrated when low rates are increased, high rates are decreased, and intermediate rates are unchanged following drug administration. Subsequent research has identified that a variety of different interventions, both pharmacological and non-pharmacological, produce rate-dependent effects not only on reinforcement schedule performance but also a wide variety of different impulsivity measures (Snider, Quisenberry, & Bickel, 2016). For example, the introduction of a new reinforcement schedule as an intervention in rats with different baseline response rates has demonstrated rate dependence (Bickel, Higgins, Kirby, & Johnson, 1988). In humans, both working memory training and a combination buprenorphine and contingency management treatments have revealed rate-dependent effects on rates of delay discounting (Bickel, Landes, Kurth-Nelson, & Redish, 2014). Therefore, rate dependence is operative both under schedule-controlled responding and generalizes to a broader range of conditions.

Despite this well-known and easily identified source of variation, the exploration of rate dependence has declined to a low level in the published literature. For example, a Web of Science (“Web of Science,” 2016) citation report of the oft-cited original rate dependence manuscript (i.e., Dews, 1958) revealed a short-term increase in citations up to a peak of 15 between 1972-1983 (see Figure 1). Since the 1980's, with the exception of a few years, citations of this report show a decreasing trend. Two reasons may explain the evanescence of the investigation of rate dependence. First, rate dependence has been viewed as only pertinent to the preclinical investigation of drugs on schedule-controlled performance. Thus, as behavioral pharmacology expanded to other techniques of interest, such as drug discrimination and receptor binding assays, the focus of behavioral pharmacology shifted away from rate dependence (Branch, 1984). Second, the phenomenon of rate dependence can be conflated with regression to the mean, an instance in which extreme initial values tend to fall closer to the average with repeated measurements, posing an obstacle to data interpretation (Hayes, 1988; Tu & Gilthorpe, 2007). For example, a decrease in a high rate of responding in one individual and an increase in another's low rate of responding may appear to be rate dependent, but in fact, could be regression toward the mean. However, the latter limiting condition is no longer germane with appropriate statistical analyses. Here we focus on addressing these concerns and assert that rate dependence is still operative in the data and as such, opens new doorways for rate dependence to be used as a tool and not just a post-hoc explanation.

Although the majority of the rate dependence literature was generated from the preclinical laboratory investigating drug administration on schedule-controlled performance (Dews & Wenger, 1977; Wenger & Dews, 1976), at least two reviews have reported rate-dependent consistent results in clinical populations and with a variety of dependent variables, such as neurocognitive tasks. The first review focused on rate dependence following nicotine administration and illustrated that individual differences in nicotine dependence may produce differential effects on myriad of outcome indices in preclinical and clinical samples (Perkins, 1999). Second, we performed a re-analysis of the published literature investigating stimulant administration on impulsivity measures and found that rate dependence is an overlooked phenomenon that occurs in approximately 50% of the analyzed preclinical and

clinical studies (Bickel, Quisenberry, & Snider, 2016). Together these reviews illustrate that rate dependence is operative in at least some cases outside of the preclinical behavioral pharmacology laboratory and highlight the notion that intervention data is often not analyzed as a function of baseline responding. A deeper understanding of the appropriate analysis methods to identify rate dependence (see Snider, Quisenberry, & Bickel, (2016) for a detailed description) is of utmost importance to promote a resurgence of an invaluable and overlooked concept, which can also be used *a priori* to predict magnitude of treatment outcome and direction of change.

Rate dependence was originally and remains understood simply as a description of behavior following some intervention (Dews, 1977; McKearney, 1981). The classic analysis method in which a change in behavior following some intervention is regressed on or correlated with the baseline rate of that behavior (Jin, 1992) has been adopted and incorrectly perpetuated through the literature. Using the classic equation ($r_{x,\ x\text{-}y}$), a significant association can be found 71% of the time when using random numbers (Oldham, 1962), potentially producing a type 1 error indicating a differential baseline effect. Instead, the use of Oldham's (1962) method or other related statistical methods (Blance, Tu, & Gilthorpe, 2005; Browne, Van der Meulen, Lewsey, Lamping, & Black, 2010; Y. K. Tu & Gilthorpe, 2007; Y.-K. Tu, Baelum, & Gilthorpe, 2005) eliminate the mathematical coupling and regression to the mean inherent in analyzing data using the classic equation (see Snider et al., 2016, for a review of these methods). Oldham's method annuls these biases by correlating the average of pre- and post-response with change from baseline ($r_{mean\ xy,\ x\text{-}y}$) eliminating the common variable in both the numerator and denominator of the correlation. Using these lesser-known statistical methods allows us to identify rate dependence and eliminate confounds inherent in the classic method; that is, regression to the mean and mathematical coupling.

Unfortunately, rate-dependent analyses are often conducted post-hoc upon determining no significant effect of a particular intervention. That is, when a treatment produces heterogeneous effects and renders the group statistics non-significant, some researchers examine their data by baseline values (Bickel et al., 2016). Although this method analyzes data in the way we are suggesting, the post-hoc nature of the analyses is less desirable than using hypotheses and associated planned comparisons.

Thus, rate dependence should not only be considered a last resort effort to find some effect, but instead should be used as a tool to describe and predict the outcomes of heterogeneous intervention data. In fact, we propose that researchers should acknowledge that rate dependence could be more than a simple description of the data. That is, researchers should plan rate-dependent analyses *a priori* while designing intervention protocols to predict outcomes based on baseline rate of behavior and answer important questions related to the range of conditions in which rate dependence operates.

Peter Dews, one of the patriarchs of behavioral pharmacology, endorsed the term *rate-dependence hypothesis* and emphasized that the unanswered questions regarding the mechanism and the conditions under which rate dependence occurs must be further explored (Dews, 1977). The few scientists who have since attempted to test the rate-dependency hypothesis directly by *a priori* designing procedures to test it (Baschnagel & Hawk, 2008;

Bickel et al., 1988), have found effects consistent with rate dependence and often in the form of the classic inverse relationship. One study that was designed to test the rate-dependence hypothesis evaluated the introduction of a tandem fixed-interval fixed-ratio schedule implemented following a history of either an IRT >t seconds or a fixed-ratio schedule, which produced different fixed-interval response rates (i.e., different baseline rates; Bickel et al., 1988). Rats with the IRT >t seconds history, exhibited low response rates and those rates increased after the intervention (i.e., tandem fixed-interval fixed-ratio schedule). Conversely, those rats with the fixed-ratio history exhibited higher response rates, which decreased after the intervention (Bickel et al., 1988; see Baschnagel & Hawk, 2008 for another example). This study illustrates the ability to *a priori* design a procedure to intentionally test the rate-dependence hypothesis. Although many of Dews' questions still remain unanswered, some hypotheses related to the mechanism of rate dependence have been proposed (Arnsten, 2009; Bickel et al., 2007; Bickel, Snider, Quisenberry, Stein, & Hanlon, 2015; Dews, 1962; Levy, 2009; Schuster & Balster, 1977; Snider et al., 2016) and several reviews have identified that rate dependence is operative in both preclinical and clinical populations (Bickel et al., 1988, 2016; Perkins, 1999), with a variety of impulsivity tasks (Baschnagel & Hawk, 2008; Bickel, Landes, et al., 2014; Bickel et al., 2016), self-report measures (Perkins, 1999), and pharmacological (Bickel et al., 2016; Perkins, 1999) and non-pharmacological (Bickel et al., 1988; Herremans et al., 2016) interventions.

In addition to developing protocols to test the rate-dependence hypothesis, determining the conditions under which we can predict treatment outcome in clinical populations could also be a useful application of rate dependence (Bickel, Quisenberry, Moody, & Wilson, 2014). For example, if a rate-dependent relationship was established between a specific intervention and outcome variable, an individual in treatment with a high baseline rate of behavior would likely decrease that behavior following the intervention. Simultaneously, an individual with baseline behavior within the mid-range would not change and an individual's low baseline behavior would increase. The latter two cases provide a precise reason for using the established rate-dependent relationship as a tool to differentiate those individuals who will respond most to a specific intervention, would actually be worsened by that intervention, or may need an adjunctive therapy to induce change (Bickel, Landes, Kurth-Nelson, & Redish, 2014; Bickel, Moody, & Quisenberry, 2014; Bickel, Quisenberry, et al., 2014).

To determine if a rate-dependent effect exists and in order to use this information as a tool, researchers must first design procedures to test the rate-dependence hypothesis and then ascertain the range of conditions under which it can occur. Questions that remain related to Dews' (1977) and Pickens' (1977) questions about the range of conditions are: (1) under what dependent variables, (2) under what intervention types, and (3) with what type of task, is rate dependence operative? Based on previous delay discounting research that found rate-dependent effects after drug administration (Bickel et al., 2015) and non-pharmacological behavioral addiction treatments (Bickel et al., 2014), a study could be designed to assess, in part, the remaining questions. In phase one, a population could be recruited to complete a specific task, delay discounting for example, in the laboratory to establish the baseline range of delay discounting rates. In phase two, some intervention, perhaps a mild stimulant, could be administered to all participants along the baseline range while delay discounting is measured to examine a possible differential effect in responding post-intervention. Phase

three could then be used to (1) identify those participants who were not influenced or adversely affect by the treatment and then provide them an adjunctive intervention to change discounting and (2) predict the response of naive participants based on their baseline delay discounting rate.

In sum, rate dependence appears to be a robust phenomenon that can help us understand the variability observed when an intervention is administered. By applying the concept of rate dependence we may come to see that the inconsistency in treatment responses is in fact an orderly relationship based on the baseline behavior of the participants. Using rate dependence as a conceptual and empirical tool, we may be able to predict therapeutic outcomes and identify individuals most likely to respond to a particular treatment. Many questions are left to be answered so we urge researchers to revisit the concept, the appropriate methods of analysis, and how to best design empirical studies to use *a priori* testing rather than post hoc explanation. Embracing alternative statistical methods, such as Oldham's method, for identifying rate dependence eliminates the biases inherent in the traditional analyses and provides information to support this phenomenon as a potentially useful diagnostic tool and a lawful, predictive relation between baseline behavior and change following intervention.

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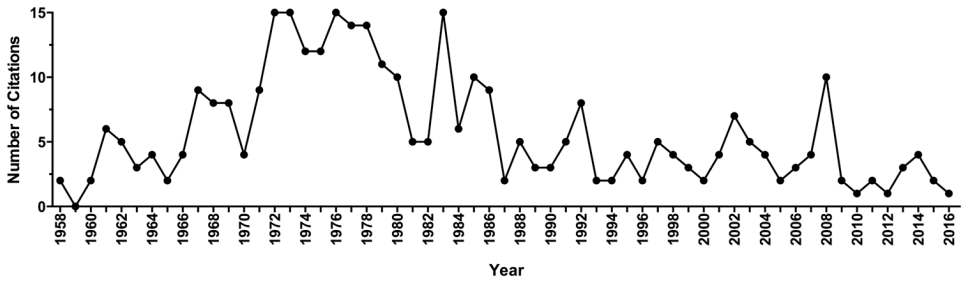

Figure 1.

Citations of the seminal rate-dependence paper by Dews (1958) from publication to 2016. Data retrieved from Web of Science, 04-11-2016.