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Review

Order in the absence of an effect: Identifying rate-dependent relationships

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ABSTRACT

The heterogeneity of group data can obscure a significant effect of an intervention due to differential baseline scores. Instead of discarding the seemingly heterogeneous response set, an orderly lawful relationship could be present. Rate dependence describes a pattern between a baseline and the change in that baseline following some intervention. To highlight the importance of analyzing data from a rate-dependent perspective, we (1) briefly review research illustrating that rate-dependent effects can be observed in response to both drug and non-drug interventions in varied schedules of reinforcement in clinical and preclinical populations; (2) observe that the process of rate-dependence likely requires multiple parts of a system operating simultaneously to evoke differential responding as a function of baseline; and (3) describe several statistical methods for consideration and posit that Oldham's correlation is the most appropriate for rate-dependent analyses. Finally, we propose future applications for these analyses in which the level of baseline behavior exhibited prior to an intervention may determine the magnitude and direction of behavior change and can lead to the identification of subpopulations that would be benefitted. In sum, rate dependence is an invaluable perspective to examine data following any intervention in order to identify previously overlooked results.

Contents

1. Introduction

"You take the blue pill—the story ends, you wake up in your bed and

believe whatever you want to believe.

You take the red pill—you stay in Wonderland and

I'll show you how deep the rabbit hole goes"

In the movie the Matrix the hero, Neo, is presented with a choice between a world he has always believed in and a world that is completely different. Often scientists may be seeking a cure for some disorder and may conclude that the intervention has no effect. However, sometimes the absence of an effect may be hiding an alternative explanation. Sidman (1960) observed that two individuals may have opposing responses to the same independent variable and suggested that researchers are dismissing a valuable controlling variable: differential baseline rates of behavior. Moreover, perhaps the heterogeneity of group data obscures a significant effect of an intervention in participants with the lowest or highest

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initial baseline rates. In this case, an intervention may actually be an efficacious therapy for a specific subset of the tested population and the study a worthwhile endeavor. Thus, in an effort to highlight the importance of analyzing the data from all angles, re-examining data from a rate-dependent perspective should not be overlooked.

Consider a dataset[1] using the Balloon Analogue Risk Task (BART) in which participants were asked to inflate incrementally a computerized balloon image. Each pump would earn the participant a set amount of money provided the balloon did not pop. The participant could choose to stop pumping at any time, bank the earnings, and move to the next trial. If the balloon popped, no money was earned for that trial. The published dataset found no effect of Bupropion (300 mg) on responding during the BART when compared to placebo in a within-subject study (Acheson and de Wit, 2008). When the data from this task were re-analyzed as a function of average pumps under placebo conditions, average pumps following 300 mg Bupropion administration changed rate dependently. Fig. 1 depicts the same data set in three important iterations. The left-most graph depicts the group average pumps following placebo and 300 mg Bupropion administrations. The middle graph illustrates the traditional representation of the proportion of change in average pumps (i.e., (drug pumps – placebo pumps)/placebo pumps) as a function of responding under placebo conditions. The right-most graph represents Oldham's correlation (a statistical method to determine rate dependence described in detail below) between the change in responding from placebo to drug and the average of responding under both conditions. Here, while there is clearly no difference between group responding under placebo and drug (see left-most graph), the middle graph illustrates that participants who performed fewer average pumps under placebo performed proportionally more following drug administration; while participants who pumped more under placebo performed proportionally less following Bupropion. This re-analysis explicitly illustrates the idea that drugs can differentially affect individuals based on placebo responses. Oldham's correlation of these data (see right-most graph) determined that this effect is indeed rate dependent and highlights how examining data in a different way may reveal a valuable orderly relationship.

This orderly relationship is referred to as rate dependence and describes a pattern between a baseline or initial value and the change in that behavior following some intervention (Dews, 1977). That is, the level of the behavior exhibited prior to an intervention determines, in part, the magnitude and direction of behavior change. Theoretically, several quantitative relationships qualify as rate dependent (Barrett and Katz, 1981a) 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 (Dews and Wenger, 1977; Perkins, 1999; Bickel et al., 2014a). Depending upon the baseline value, increases, decreases, and/or no change in behavior can occur following intervention. The greater literature has since generally accepted the idea that a correlation between baseline (x) and change from baseline (x-y) or the log of the proportion of baseline (x/y) and the log of baseline (x) represents the relationship between baseline value and change (as noted by Benjamin, 1967). However, as previously suggested (Jin, 1992) and expanded on below, inherent biases in analyzing within-subject change scores exist with this methodology.

Previous research has shown that rate-dependent effects can be observed in response to drug administration and non-drug interventions in varied schedules of reinforcement in both clinical and preclinical populations (Dews, 1958b, 1977; Branch, 1984; Bickel et al., 1988, 2014a, 2015b). While this paper is not intended to be an exhaustive literature review, it will review the relevant history of rate dependence, suggest possible mechanisms, highlight the importance of the analysis methods, and conclude with the assertion that awareness of this phenomenon is crucial amongst scientists performing intervention research. Of note, while this phenomenon has been illustrated in dependent measures beyond response rates, throughout the manuscript we refer to the concept of an inverse relationship between a baseline value and the change in that value following some intervention as rate dependence to maintain consistency with the historical literature.

2. History and current status of rate dependence

While the idea of rate dependence has been widely acknowledged within the psychological and pharmacological literature, the law of initial value, first defined by Wilder (1967, p. viii), describes a relationship in the data that may have been a relative of the rate dependence phenomenon. The law of initial value theorizes that the magnitude and direction of a response following some intervention can be predicted by an organism's pre-stimulus response. That is, when the initial value is high, responses post-stimulus are smaller, while when initial value is low responses post-stimulus can be larger.

The emergence of behavioral pharmacology ignited the explicit definition and dissemination of the concept of rate dependence to the greater scientific community. Early investigations studying drug effects on schedule-controlled behavior determined that drugs have a unique effect on different rates of responding, which are often dependent upon the reinforcement schedule (Dews, 1958a; Dews, 1958b; Dews and Wenger, 1977), where the interaction between drugs and schedules of control differentially influence the drug effect. For example, Dews found that chlorpromazine and promazine had different effects during portions of the interval in fixed-interval[2] schedules based upon the previous component of the schedule. The differences in response rates over the course of the interval have been used as baseline measures in studies investigating the effects of drugs on responding and provide a convenient baseline to observe rate-dependent effects (Branch, 1984).

The typical inverse rate-dependent relationship was first illustrated by behavioral pharmacological studies administering amphetamines (Dews, 1958b; Barrett and Katz, 1981b; Goudie, 1985), nicotine (Stitzer et al., 1970), and other stimulant-like compounds (Goudie, 1985) using simple schedule-controlled manipulations of baseline performance. Rate dependence can also be observed when behavior is maintained on complex schedules of reinforcement. When using more complex, multiple[3] or conjunctive[4] schedules with fixed-interval and fixed-ratio components to induce different baseline rates of behavior, the effects of phencyclidine (PCP), ketamine, pentobarbital, diazepam, chlordiazepoxide, chlorpromazine, imipramine, and d-amphetamine were also dependent upon response rate in the absence of drug (McMillan, 1973; Barrett, 1974; Wenger and Dews, 1976; Leander, 1981; Newland and Marr, 1985). For example, PCP (see Fig. 2) and ketamine administration increased low baseline rates while high baseline rates either decreased or did not change (Wenger and Dews, 1976) during a multiple schedule, illustrating that dif-

[1] The authors, Acheson and de Wit (2008), graciously provided the raw data for this task and gave permission for its use in this manuscript.

[2] A schedule of reinforcement that evokes initially low responding, which increases over each interval and is often described as a scallop. Reinforcers are delivered after a specific amount of time has passed.

[3] A multiple schedule is a compound schedule in which two or more components alternate and are each associated with a unique stimulus. Reinforcers are delivered after completion of any one component.

[4] A conjunctive schedule is a compound schedule in which two or more components must be satisfied prior to delivery of a reinforcer.