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MICE AS SUBJECTS IN THE EXPERIMENTAL ANALYSIS OF BEHAVIOR

LOS RATONES COMO SUJETOS EXPERIMENTALES EN EL ANÁLISIS EXPERIMENTAL DE LA CONDUCTA

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Abstract

The experimental analysis of behavior (EAB) serves as a critical activity of ongoing scientific discovery and a means to train future behavior scientists. Despite the importance of EAB, basic research has been under threat for some time. The factors contributing to this deterioration are complicated and related to issues of funding and relevance. The current paper will explore how a shift to mice as subjects may help to ameliorate some of these threats.

Keywords: Collaborative Research, Mice

Resumen

El análisis experimental de la conducta (AEC) es una actividad fundamental para la continuación del descubrimiento científico, así como para el entrenamiento de generaciones futuras de científicos de la conducta. La investigación básica se encuentra bajo amenaza desde hace ya un tiempo a pesar de la importancia del AEC como actividad cien-

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tífica. Este deterioro ha sido complicado ya que múltiples factores han participado a lo largo del tiempo, tales como problemas de financiamiento y pertinencia del estudio. En el presente estudio se explorará cómo un cambio a ratones como sujetos experimentales puede ayudar a aliviar algunas de estas amenazas.

Mice as Subjects in the Experimental Analysis of Behavior

Basic research with animals holds a prominent place within the field of behavior science both as means of scientific discovery and as an essential component of training new behavior scientists. According to Sidman (2011) basic research is necessary for all students of behavior science whether they aspire towards a career as an experimentalist or as a clinician. Despite its critical role, many have noted that basic animal research is under threat (Neuringer, 2011; Poling, 2010; Vyse, 2013). This paper examines some of the issues threatening the field of basic research and proposes that the use of mice as subjects may help to ameliorate some of these problems. The past and present status of mouse-based research in the experimental analysis of behavior (EAB) will be explored. The authors will demonstrate how the use of mice may help to foster innovative and potentially lucrative collaborative research projects and share some examples of this type of project. Finally, some practical advantages of the utilization of mice will be discussed.

Since the 1980s ominous warnings regarding the state of EAB have been published. Nevin (1982) reported on waning submissions to the *Journal of the Experimental Analysis of Behavior* (*JEAB*). Williams & Buskist (1983) reported that the demographic characteristics of *JEAB* authors revealed reason for concern. Mace & Critchfield (2010) reported that *JEAB*'s paid circulation had dwindled to approximately one third of its peak and held only a modest impact factor, which could have a negative impact on hiring, pay and advancement of EAB investigators within academic settings. Neuringer (2011) summarized these issues by reporting simply that "the experimental analysis of behavior (EAB) is in trouble." Over the last quarter century, dwindling academic appointments for basic researchers and the closure of many prestigious animal laboratories have also been observed. Mace & Critchfield (2010) reported that when principal investigators depart, they are not replaced, and their basic labs are lost. For example, in 1998 the Harvard pigeon lab was closed following the death of Richard Herrnstein. Over its half century in operation, many prominent experimentalists were trained in the Harvard lab; among them Charlie Catania, Billy Baum, Philip Hineline, Peter Killeen, Allen Neuringer and Howard Rachlin (Baum, 2002). More recently many of the labs built by those who trained in the Harvard lab have closed.

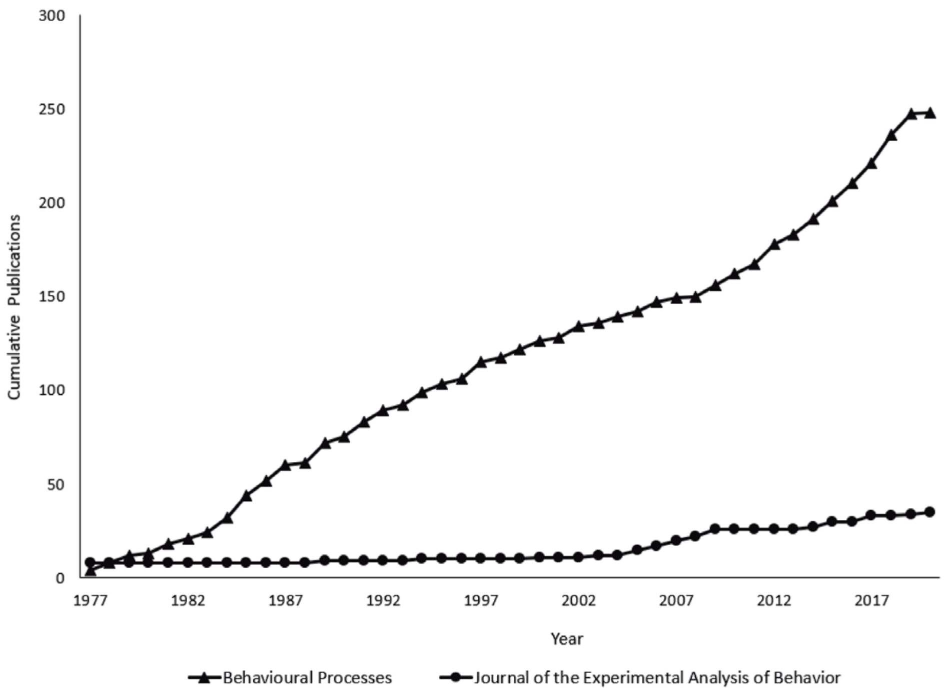
Poling (2010) outlines five basic concerns which may threaten the future of Behavior Analysis. One of these concerns pertains directly to EAB which Poling suggests might be better viewed as an acronym for "esoteric behavior analysis" given that much of the work in EAB is not obviously relevant to significant actions of people or animals in their natural environments. This is an argument shared by others (see Critchfield, 2011a, 2011b; Neuringer, 2011; Poling & Edwards, 2011; Poling et al., 1981; Vyse, 2013) including Mace & Critchfield (2010) who stated that "behavior analysis can improve both society and its status within society by tackling problems about which laypersons and diverse scientific communities care deeply." In 2013, St. Peter published an article titled "Changing Course through Collaboration" in which she suggested that to achieve mainstream relevance, we must systematically increase our connections and collaborations with others. According to St. Peter, engaging in collaborative research with those from other disciplines offers many benefits. All parties learn new methodological skills and those collaborating with behavior scientists can gain knowledge and appreciation for behavior-analytic approaches. Further, collaborators from outside of behavior science are more likely to encounter behavior analytic journals and may come away with a greater appreciation for within-subject research designs.

The perceived irrelevance of EAB has been associated with negative financial implications as society at large is hesitant to provide funding for work that is not seen as relevant (Poling, 2010). In some regions of the world a lack of funding for basic operant research has further contributed to its decline (see: Mace & Critchfield, 2010; Neuringer, 2011; Poling & Edwards, 2011; Thomas & Blackman, 1992). In the United States, the National Science Foundation (NSF) is viewed as the premier source of funding for basic science. The NSF has a Directorate of Behavioral, Social and Economic Sciences. However, this group rarely funds EAB work and instead directs much of its funding towards proposals originating from cognitive and neuroscientists (Wanchisen, 2003). According to Lee (2016) interdisciplinary or multidisciplinary team approaches increase the likelihood that a project will be funded. In the United States both the Centers for Disease Control and Prevention and the National Institutes of Health place a high emphasis on cross discipline collaboration (Wanchisen, 2003). According to Becker-Cottrill (2003), collaboration with other disciplines is not only seen by the CDC as a credit to a proposal but is often essential to its success. The same holds true in Canada where the Canadian Institutes of Health Research are more likely to fund interdisciplinary projects (Feldman & Yu, 2003).

Collaborative research has been posited as a solution to the problem of perceived irrelevance and issues related to funding. Collaborative research teams can be assembled in a number of ways (e.g. multidisciplinary, interdisciplinary, transdisciplinary). Each arrangement involves bringing together individuals from multiple disciplines to tackle a research question (Choi & Pak, 2006). If behavior scientists are to engage in more collaborative research, familiarity with the species and procedures being used in other fields is needed. While rats and pigeons have remained the species of choice for basic behavior analytic researchers, over the past two decades, mice have rapidly overtaken rats as preferred subject within biomedicine and other related fields (Ellenbroek & Youn, 2016).

For years, researchers used selective breeding methods to produce mice with specific desired traits (NIH, 2002). Mapping of the mouse genome in the early 2000s revolutionized mouse-based research. The first high-quality draft sequence of the mouse genome was completed in 2002 (NHGRI, 2012; Waterson et al., 2002). While other organisms are excellent models for studying the cell cycle and other developmental processes, mice are said to be far better subjects to study the immune, endocrine, nervous, cardiovascular, skeletal and other complex physiological systems that mammals share. Like humans, mice naturally develop diseases that affect these systems; including cancer, hypertension, diabetes, osteoporosis and glaucoma. Further, while mice do not naturally develop other common diseases such as cystic fibrosis and Alzheimer's, these human afflictions can be induced in the mouse by manipulating its genome to create a knockout (NIH, 2002). These models can be used to study the disease, while also providing a biological context in which therapies and drugs can be tested (NIH, 2015). In recent decades, the mouse has become the premier mammalian model for biomedical research (NIH, 2002) and the most commonly used species in biological research (Rosenthal & Brown, 2007). In the United States, the numbers of rats and mice used in research are not reported. However, in 2016 alone over 2.02 million experimental procedures were completed using live animals in the United Kingdom. Sixty percent of these procedures utilized mice as subjects, while rats and birds were only used for 12% and 7% respectively (UK Home Office, 2017).

Figure 1
Cumulative Publications



Note. Cumulative Number of Articles in Behavioural Processes and JEAB which include Mice

To examine the frequency of mouse related articles in behaviorally oriented journals, a literature review was conducted. Two journals were selected for this review, one primary behavior analytic journal (*JEAB*) and one journal which focuses on animal behavior and learning from multiple perspectives (*Behavioural Processes*). Using the database ULRICHSWEB dates of first publication were established for each journal; 1958 (*JEAB*) and 1977 (*Behavioural Processes*). To compare publication trends across journals, dates for the current review were limited to 1977-2020. PsycINFO was used to conduct a search for each journal using the following convention: *Journal Title* (SO Publication Name) AND Mice with the year parameters of 1977-2020. Figure 1.0 depicts a cumulative record of mouse related publications in each journal over the allotted time. As depicted in the graph, *Behavioural Processes* began to publish mouse related articles much earlier and boasts a more sustained growth in this area over time as compared to *JEAB*. To rule out publication volume as a factor that might skew these data, the proportion of mouse related articles in each journal was calculated by dividing the number of mouse related articles by the total number of articles. Over this period, the proportion of articles published in *Behavioural Processes* related to mice was 6% compared to only 1% in *JEAB*. These results indicate that the disparate data paths cannot be explained by differences in publication volume alone. Careful analysis of mouse related publications in *JEAB* indicate growth since the early 2000s with the cumulative number of publications more than doubling from 15 in 2005 to 35 at the time of this publication. While this represents substantial growth when compared to the early and sustained growth noted in *Behavioural Processes*, it appears that behavior analysts may be "missing the boat" when it comes to this important trend in animal research.

Since the early 2000's several behavior analysts have advocated for more behavior analytic research with mice (see Baron & Meltzer, 2001; McKerchar et al., 2005; Mihalick et al., 2000; Zarcone et al., 2007). To summarize the argument made by these authors: as biologists, geneticists, pharmacologists, and others work to compare wild type mice with genetic mutant mice, they need to characterize not just the genotype of the animal but also the phenotype. However, these efforts are incomplete without precise measures of learning and memory (Mihalick et al., 2000). With so few behavior analysts developing and promoting operant measures of mouse behavior, other phenotyping strategies have been widely adopted for use with the species while operant methods have been largely overlooked (Baron & Meltzer, 2001; McKerchar et al., 2005; Mihalick et al., 2000). To date, many of the most commonly used phenotyping procedures are borrowed from psychopharmacology and behavioral neuroscience including tests such as the object-recognition task, elevated plus maze, rotarod, and conditioned place preference (McKerchar et al., 2005). While these methods provide measures of overt animal behavior, they lack the precision afforded by operant methods. Some behavior analysts have attempted to call attention to this point. Papachristos and Gallistel (2006) challenged the way that those in behavioral neuroscience measure learning by demonstrating the importance of careful examination of individual learning curves, asserting boldly that "under no empirically defensible assumption can the average value of a meaningful learning-rate parameter be estimated from the group average curve." Many outside of our field have remained hesitant to adopt operant procedures, some citing concerns regarding the time required to complete operant testing. In order to help ameliorate this concern, Baron & Meltzer (2001) and McKerchar and colleagues (2005) demonstrated a rapid method to assess learning utilizing operant techniques. This method yielded reliable comparisons between various strains of mice after only two 120-minute training sessions. Studies like these have been useful in helping to demonstrate the value of operant techniques. However, as outlined by St. Peter (2013), collaboration itself can sometimes be the most effective means for dissemination. By forming interdisciplinary research teams, behavior analysts can demonstrate firsthand the benefits of operant procedures while also learning more about mice as subjects. Examples of collaborative research with mice that have taken place at the University of Nevada, Reno include work with faculty in physiology (see Publicover et al., 2009); immunology (see Washio, et al., 2011; Munoz-Blanco et al., 2011); pharmacology (see Lewon et al., 2017); and physiology and cell biology (see Lewon et al, in press).

While behavior analysts have advocated for more operant research with mice, growth in this area has remained slow. In 2008, researchers suggested that a lack of familiarity with the species may present a barrier for behavior analysts. To help to circumvent this, the group examined effective deprivation procedures for mice (Derenne et al., 2008). In similar studies Belke and Garland (2013) examined the efficacy of using contingent access to wheel running as a reinforcer for mice from various replicate lines and Zarcone et al. (2007) examined the effects of differing response-force requirements on food-maintained responding in mice. These types of studies can be very useful to behavior analysts seeking to use mice as subjects, and additional studies are needed.

A great wealth of resources can also be found by looking outside of behavior analysis either by working directly with researchers from other fields or by reading their publications. As an example, the text *Mouse Behavioral Testing* (Wahlsten, 2011) is a book written for the neuroscience community yet contains a wealth of useful information for anyone wishing to begin work with mice. The book outlines the differences between rats and mice and how these differences play out in the research lab. It provides a primer on various breeding strategies, resultant strains of mice and the characteristics of each strain. Additionally, the book outlines how one would go about ordering, unpacking, marking for identification, feeding, depriving, housing, and handling mice. There is even a chapter devoted exclusively to motivating mice, which reviews deprivation methods and compares the efficacy of various stimuli as reinforcers and aversive stimuli.

Once familiar with the species, many researchers find that there are many practical benefits to working with mice. One of these benefits is the significant cost savings of using mice over larger animals such as rats. On average, adult rats weigh roughly eight to ten times more than adult mice (Ellenbroek & Youn, 2016). This size differential means that mice can be housed at twice the density of rats, only requiring approximately half of the floor space. The fewer square feet that a researcher's animals occupy, the lower the per diem costs (National Research Council, 2000). A survey of per diem prices available online for a variety of U.S. universities reveals that per diem costs for rats are often 1.5-2.5 times higher than they are for mice. Mice also require much smaller dosages of drug compounds as compared to rats, allowing for the effects of medications to be tested at a lower cost (Ellenbroek & Youn, 2016). This feature can make mice a more cost-effective alternative to rats when doing behavioral testing that involves the use of medications or intoxicating substances, as are common in some delay discounting and addiction studies. Additionally, the cost of operant equipment for mice is often lower than it is for larger animals. Med Associates, the leading manufacture of operant conditioning chambers for rats, also makes chambers suitable for mice. This means that researchers interested in attempting to explore research with mice can likely continue to use their existing computer systems, SmartControl panels and software packages. Furthermore, the cost savings associated with lower per diem rates for mice can help cover the upfront investment in equipment such as operant mouse chambers.

Basic research with animals remains important and highly valued within our field. Unfortunately, basic research has been under threat for some time. Working on collaborative research teams can help demonstrate the relevance of our science to the wider scientific community, garner interest in our publications, our research methods, and our procedures. Collaborative research also offers investigators from all domains the ability to strengthen grant proposals. Many outside of behavior analysis seek robust measures of overt behavior. However, many may be unaware of or otherwise hesitant to use operant methods. By working collaboratively with these individuals, behavior analysts can offer precise measures of behavior related to phenomena of common interest to all parties while also continuing to demonstrate the interspecies generality of our principles. Further, behavior analysts can experience firsthand the many benefits of using mice as subjects. Mice are less expensive to care for, better candidates for a variety of common laboratory procedures and can be studied using standard operant equipment which is manufactured by the same companies that supply rat and pigeon apparatuses. In recent years researchers within our field have demonstrated that mice can be utilized in a variety of operant conditioning paradigms and there has been a growing number of publications utilizing mice as subjects. At the present time there is still much work to be done to expand the use of mice as subjects within EAB. However, for those that choose to pursue this endeavor there are many associated benefits. For these reasons, the utilization of mice as subjects in behavioral research is advocated.

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