

EFFECTS OF BUPROPION ON NICOTINE SELF-ADMINISTRATION AND FOOD-MAINTAINED RESPONDING IN RATS

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A Thesis Submitted to the
University of North Carolina at Wilmington in Partial Fulfillment
of the Requirements for the Degree of
Masters of Arts

Department of Psychology
University of North Carolina at Wilmington

2003

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ABSTRACT

Over the past 40 years various behavioral techniques and pharmaceutical adjuncts have been developed to aid in smoking cessation. The continued need for the development of new and more effective pharmaceutical adjuncts for smoking cessation is evident by the large number of individuals continuing to smoke despite their knowledge of the significant health risks associated with tobacco use. Bupropion recently has been found to be a useful pharmaceutical agent in furthering smoking abstinence, but the long-term effectiveness of the drug is mediocre at best. In order to gain a better understanding of how bupropion affects smoking, the current studies investigated the effects of bupropion in a rodent model of nicotine self-administration. In the nicotine study, subjects self-administered nicotine (0.03 mg/kg/inf) under a fixed-ratio 3 (FR3) 60 s timeout (TO) schedule of reinforcement. The effects of bupropion on food-maintained responding using two levels of food deprivation (food-deprived and food-satiated) were used to assess the specificity of the effects of the drug on nicotine self-administration. Once subjects acquired stable rates of responding, they were pretreated 15 min prior to 60 min sessions with various doses of bupropion (0, 10, 30, 56 mg/kg, IP). The 30 mg/kg dose of bupropion resulted in an increase in nicotine intake while the drug dose-dependently decreased food-maintained behavior under deprivation conditions. When more comparable rates of behavior in the food-satiated group were investigated, bupropion had similar effects on nicotine and food-maintained responding. The current studies indicate that response rate must be considered when evaluating selective effects of drugs. The findings that bupropion can increase moderate rates of nicotine self-administration at

doses that decrease higher rates of responding maintained by food suggest that adding alternative reinforcers to the environment of individuals attempting to quit could affect the drug's ability to sustain abstinence.

ACKNOWLEDGEMENTS

I would like to thank the members of my committee, Drs. Raymond Pitts, Mark Galizio, Carol Pilgrim, and Christine Hughes for their unwavering support as well as their professional and educational guidance during completion of this thesis. I would like to send a very special thank you to my mentor, Dr. Steven I. Dworkin. Through his stern encouragement and guidance, I have discovered the level of devotion and patience that is required to succeed in the field of science. I would like to thank Dr. Dworkin for the financial support and use of his laboratory, which has served as a second home for the past few years. I greatly appreciate all the input Dr. Dworkin has given me the past few years; if it wasn't for his vast knowledge in this area of research, I wouldn't have gained the understanding that I currently have.

I would also like to take this opportunity to say thank you to Dr. Brady J. Phelps and Dr. Debra Spear, who provided me with a wonderful undergraduate training that allowed for an easier transition into graduate school.

Most of all I would like to thank my parents for their undying love, patience, and understanding that is allowing me to pursue a long-term goal which I am so very passionate about.

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INTRODUCTION

Nicotine is a natural, pharmacologically active alkaloid compound, found in the tobacco plant. Although nicotine is only one of approximately 4,000 chemicals found in the smoke from tobacco products, it has been determined to be the major component responsible for maintaining human smoking (Stolerman & Jarvis, 1995). The first reported use of smoked tobacco dates back to the late 15th century when European explorers discovered Native Americans smoking tobacco leaves. The use of tobacco products grew rapidly across North America and Europe. With the development of more efficient manufacturing techniques in the late 19th century, use of tobacco products in the early 20th century skyrocketed. Tobacco use increased in the twentieth century until use declined around 1964 following the surgeon general's report linking tobacco use to various illnesses.

Although the detrimental effects of smoking have been known for over 30 years, the rate of tobacco use in the United States continues to be extensive with an estimated 57 million Americans using cigarettes and an additional 7.6 million individuals using smokeless tobacco products (National Institute on Drug Abuse, 2000). The amount of tobacco use worldwide is even more striking, with an estimated one billion smokers currently in the world (Vainio, Weiderpass, & Kleihues, 2001). Such wide spread use of tobacco products results in detrimental health consequences to the world's population. Nearly 430,000 Americans die each year due to tobacco-related diseases. The World Health Organization predicts that health-care problems associated with tobacco use will be the leading health concern by the year 2020 and is currently associated with nearly 8.4 million deaths per year worldwide (Vainio et al.). The exact cause of death associated

with tobacco use varies depending on the geographical area. In the United States, the leading causes of smoking-related death are lung cancer and vascular diseases (Vainio et al.).

Most of the adverse health effects of tobacco products are not directly related to nicotine but rather to the estimated 50 carcinogens contained in cigarette smoke (Shields, 2000). Two of the most potent carcinogens are tobacco-specific nitrosamines (TSN), which results from the curing process of the tobacco leaf, and polycyclic aromatic hydrocarbons (PAHs), which results from incomplete burning of the tobacco leaf. Both carcinogens result in DNA damage that increases the likelihood of lung and other types of cancers (Shields). There are several factors that affect the amount of exposure to these carcinogens: length of inhalation, number of cigarettes smoked, puff volume, and number of puffs per cigarette (Shields). An interesting note is that in recent years tobacco manufacturers have decreased the amount of tar and nicotine the individual is exposed to in cigarettes in order to market a safer cigarette. The companies may have inadvertently achieved the opposite effect, because humans will self-titrate their levels of nicotine by increasing the number of cigarettes smoked, puff duration, and length of inhalation, in effect putting themselves at greater risk for carcinogens (Shields).

With the adverse health effects widely known, there has been a decline in smoking rates in the United States since the 1960s (Fiore et al., 1990). Although 70% of current smokers say they want to quit smoking, only 46% of these smokers attempt to quit each year (NOP Omnibus Services, 1992), and only 10% of the individuals who attempt to quit succeed (Fiore et al.). The difficulty in smoking cessation is illustrated by the fact that 97% of smokers who attempt to quit smoking without treatment relapse

within the first 6 months of cessation (Hughes, 1992). The benefits that can result from smoking cessation are substantial; quitting smoking greatly reduces the likelihood of developing lung cancer when compared to individuals who continue to smoke (Peto et al., 2000). Individuals who stop smoking at around 30 years of age can evade more than 90% of the health risks attributed to tobacco use (2000); by avoiding these health risks a considerable number of future deaths associated with tobacco use can be averted or eliminated.

The most common use of tobacco products in the United States is cigarette smoking. Smoking allows for nicotine to be delivered rapidly to the lungs of the individual. Nicotine is taken into the lungs as tiny particles or tars, which are suspended in the tobacco smoke. Once into the lungs, nicotine binds to hemoglobin and is then transported throughout the body. Nicotine acts on the nicotinic acetylcholine receptors (nAChRs) that are located in both the peripheral and central nervous system. In the peripheral nervous system the effects of nicotine are due to the activation of nAChRs on ganglion cells and the neuromuscular junctions of the skeletal muscles, where it stimulates the release of acetylcholine. In the central nervous system there are two major cholinergic projections: one originates in the tegmentum with terminal fields in the thalamus and midbrain, and the second major cholinergic projection starts in the basal forebrain and projects to the hippocampus and throughout the cortex (Dani, 2001). Nicotinic receptors that appear to be responsible for the compulsive and chronic use of tobacco products by humans are located primarily in one area of the brain, the mesolimbic dopamine pathway (Balfour, 1994; Corrigall, Franklin, Coen, & Clarke, 1992; Dani & Heinemann, 1996). The mesolimbic dopamine pathway originates in the

Ventral Tegmental Area with neural projections to the nucleus accumbens and to the prefrontal cortex. Nicotine's activation of this pathway results from the binding of nicotine to nAChRs found on the cell bodies of neurons in the ventral tegmental area and on their terminal regions in the nucleus accumbens (Calabresi, Lacey, & North, 1989; Corrigall, Coen, & Adamson, 1994). The binding of nicotine to these receptors results in an increase in the levels of extracellular dopamine in the nucleus accumbens, a property it shares with other drugs of abuse such as amphetamine, cocaine, alcohol, and opiates (Pontieri, Tanda, Orzi, & Di Chiara, 1996).

Nicotinic acetylcholine receptors in the central nervous system and peripheral nervous system are ligand-gated receptors that are composed of different combination of α , β , γ , δ , and ϵ proteins or subunits (Itier & Bertrand, 2001). Once a neurotransmitter binds to the appropriate protein of a ligand-gated receptor, the signal is transmitted by a change in the conformation of the channel, which alters the flow of ions into the neuron. The different subunits combine in various ways to create functionally different receptors. A receptor composed of a particular set of subunits may have a higher affinity for acetylcholine than a receptor composed of a different set of proteins. For example, nAChRs with the $\alpha 7$ subunit have a high permeability for calcium and have a rapid activation and desensitization. Receptor agonists can facilitate the activation of receptors; antagonists can block the activation of receptors. Drugs such as nicotine and black widow spider venom function as nicotinic agonists. Mecamylamine, chlorisondamine, and Dihydro- β -erythroidine (DH β E) are drugs that function as central nicotinic antagonists. Researchers have found that the β_2 subunit is one of the subunits found to be important in the reinforcing effects of nicotine (Picciotto et al., 1998). This is

evident from the Picciotto et al. study where mice that lacked the gene which encodes for the β_2 subunit showed marked decrease in the levels of self-administered nicotine compared to mice that did not lack the β_2 subunit. The β_2 subunit was specific to nicotine self-administration in that mice which lacked the β_2 subunit did acquire cocaine self-administration (Picciotto et al.).

In order to gain a better understanding of how nicotine and other drugs lead to addiction, researchers have developed laboratory models of drug abuse. Researchers often bring subjects into a laboratory setting where the environment and dosing of the drug can be controlled. In early human laboratory self-administration studies involving nicotine, acute pretreatment with mecamylamine caused an increase in the rate of cigarette smoking in chronic smokers (Stolerman, Goldfarb, Fink, & Jarvik, 1973). The increase in rate of smoking was suggested to be a compensatory response to the effects of mecamylamine resulting from the subjects self-triturating the level of nicotine in their body (Pomerleau, Pomerleau, & Majchrzak, 1987). This effect of nicotinic antagonists increasing the rate of cigarette smoking is comparable to the increase in cigarette smoking seen by individuals that smoke cigarettes with less nicotine.

Researchers have also developed animal models of human drug abuse that result in even more experimental control within a study. The animal self-administration model has been widely accepted as a valid means to study the abuse liability of drugs (Schuster & Thompson, 1969). One way to judge the abuse potential of drugs is to determine whether the drug will be self-administered, or function as a reinforcer in an animal self-administration paradigm (Schuster & Thompson, 1969). A reinforcer is an event that increases the probability of the behavior that produced it. In self-administration studies, a

subject is placed into an experimental chamber in which some behavior (often a lever press) must be performed to gain access to a drug. If the required behavior increases in frequency, compared to alternative behaviors (e.g. grooming), then the drug may be acting as a positive reinforcer and may have abuse potential in humans (Schuster & Thompson, 1969).

In early animal self-administration studies involving nicotine, monkeys were placed into an experimental chamber and allowed to suck on a tube that resulted in the delivery of cigarette smoke (Ando & Yanagita, 1981; Glick, Canfield, & Jarvik, 1970; Glick, Jarvik, & Nakamura, 1970; Yanagita, Ando, Kato, & Takada, 1983). The subjects were given a choice between a tube that resulted in cigarette smoke and an alternative tube that resulted in the delivery of air (Glick, Canfield et al., 1970; Glick, Jarvik et al., 1970). These studies found that a majority of monkeys chose smoke over air and persisted to choose smoke over air under a concurrent choice schedule of reinforcement. When the subjects were administered mecamylamine, the subjects switched their behavior to the tube that supplied only air. These results offered some evidence that nicotine was maintaining smoking (Glick, Jarvik et al.). As mentioned above, the Stolerman et al. (1973) study demonstrated that administration of mecamylamine to humans resulted in an increase in smoking while the Glick, Jarvik et al. study reported a decrease in non-human primates. The difference in the effects of mecamylamine between the non-human primate and human studies can most likely be attributed to the differences in the length of mecamylamine treatment and the subjects' differences in smoking history (Stolerman et al.). For instance, in the Glick, Jarvik et al. study monkeys

were repeatedly administered mecamylamine, while human subjects in the Stolerman et al. study received only a single dose of the drug.

Inhalation is not the only route of administration that is used in animal models of drug self-administration. An intravenous route of self-administration is more often used in animal studies. This route involves surgically implanting a catheter into a vein, often the jugular vein, of the animal, which allows the drug to be delivered directly to the heart. Investigations using the intravenous route of administration have increased the generality of the conditions under which nicotine functions as a reinforcer.

The first study to demonstrate that intravenous infusions of nicotine could function as reinforcers was reported by Goldberg, Spealman, and Goldberg (1981) using a second-order schedule of reinforcement with squirrel monkeys. A second-order schedule consists of two or more simple schedules where behavior under one schedule is reinforced under another schedule. Two schedules that are often used in a second-order schedule are fixed-interval (FI) and fixed-ratio (FR) schedules. Under an FI schedule of reinforcement, the first response by a subject following a fixed amount of time results in the delivery of a reinforcer. An FR schedule of reinforcement requires the subject to emit a set or fixed number of responses before a reinforcer is delivered. For example, in a second-order schedule of FI 2 min(FR 10:S_p) every tenth response results in the brief onset of some sort of stimulus, the first FR 10 completed after the FI 2 min elapses resulted in the delivery of a reinforcer and the onset of the stimulus. This schedule is often used because the experimenter can control the temporal spacing of infusions, and it produces a stable rate of responding (Swedberg, Henningfield, & Goldberg, 1990). In the Goldberg et al. (1981) study, a second-order schedule of FI 2 min(FR 10:S_p) was used.

The stimulus lights flashed after every tenth response and the stimulus light came on during the delivery of the reinforcer, which was an infusion of nicotine (0.03 mg/kg). When the stimulus lights were removed, the rate at which the subjects responded decreased; when the stimulus lights were reinstated, the rate of behavior returned to the original baseline rate of responding (Goldberg et al., 1981). This experiment revealed that nicotine could act as a reinforcer under a second-order schedule and that environmental cues associated with nicotine delivery are important in the persistence of drug-seeking behavior (Goldberg et al., 1981). These results were the first to indicate that intravenous injections of nicotine could maintain high and persistent rates of responding since a previous study had found that nicotine would not maintain responding in baboons (Griffiths, Brady, & Bradford, 1979).

The generality of the hypothesis that nicotine functions as a reinforcer was further increased when it was found that humans (Henningfield & Goldberg, 1983) and rats (Corrigall & Coen, 1989) would self-administer intravenous injections of nicotine. In the procedure developed by Corrigall and Coen, the experimental session was limited to one hour, using a FR 5 schedule of nicotine infusion. Each nicotine infusion was followed by a 1 min signaled timeout (TO); during the TO periods no further reinforcers could be delivered. By limiting the number of infusions delivered within a session and the rate at which the infusions can be obtained, the subjects could self-administer nicotine without being exposed to toxic levels. In the Corrigall and Coen study, the animals were first trained to respond using food as the reinforcer; then the animals were implanted with a jugular catheter. Following recovery from surgery, animals were exposed to experimental sessions in which food was replaced with nicotine infusions. Using this

procedure Corrigan and Coen found that nicotine could act as a reinforcer in rats under limited-access conditions and that pre-treatment with mecamylamine (a nicotinic antagonist) decreased nicotine self-administration. These findings were replicated by Donny, Caggiula, Knopf, and Brown (1995), providing additional support that intravenous infusions of nicotine under a limited-access schedule could function as a reinforcer.

The Donny et al. (1995) study also determined that the conditions under which nicotine will maintain responding appear to be much restricted than with other drugs of abuse. Under schedule contingencies different than Corrigan and Coen (1989) and Goldberg et al. (1981), nicotine has been shown to suppress responding (Goldberg & Spealman, 1983), or to maintain responding that postpones its programmed infusion (Spealman, 1983). A study involving a schedule similar to the limited-access schedule used by Corrigan and Coen found that nicotine would not maintain consistent responding (Dworkin, Vrana, Broadbent, & Robinson, 1993). Despite the fact that Dworkin et al. did not show nicotine self-administration under a standard FR schedule, the study did report that nicotine self-administration might be dependent on the level of food deprivation under more complex schedules. Dworkin et al. found that when rats were placed under concurrent schedules of nicotine, food, and water presentation, and underwent extinction in the food schedule, nicotine self-administration increased. Extinction of the water component did not result in an increase in nicotine self-administration. The importance of food deprivation is noted in other studies with nicotine (Corrigan & Coen, 1989; Donny et al., 1995; Donny et al., 1998) and is congruent with experiments that demonstrate increases in levels of food deprivation

result in increases in self-administration of several different drugs (e.g. Carroll & Meisch, 1981, 1984).

Another important variable that appears to have an effect on nicotine self-administration is the genetic strain of the rodent that is used (Shoaib, Schindler, & Goldberg, 1997). These results may account for the Dworkin et al. (1993) study's inability to show consistent nicotine self-administration. Also, the speed of the infusion of nicotine was found to be an important variable in maintaining nicotine self-administration in a study by Valentine, Hokanson, Matta, and Sharp (1997) using an unlimited access schedule. Valentine et al. (1997) found that as the injection time increased from 2-3 seconds the reinforcing efficacy of nicotine, or its ability to maintain responding, decreased.

With the development and refinement of experimental paradigms which assess the reinforcing effects of nicotine research was quickly undertaken to determine the neural mechanisms associated with nicotine self-administration. Corrigall, Franklin, Coen, and Clark (1992) demonstrated that the administration of nicotine resulted from the drug's effects on the central nervous system by assessing the effects of injecting chlorisondamine (a long-lasting nicotinic antagonist) into the brain. Central administration of chlorisondamine resulted in a decrease in nicotine self-administration (Corrigall et al., 1992). It was found that lesions to the mesolimbic dopamine pathway produced by infusion of 6-hydroxydopamine into the nucleus accumbens (NA) resulted in decreases in nicotine self-administration (Corrigall et al., 1992). The lesions to the mesolimbic dopamine pathway resulted in a decrease in the amount of dopamine in the terminal field of the mesolimbic dopamine pathway in the NA (Corrigall et al., 1992).

The mechanism by which nicotine increases levels of extracellular dopamine in the NA was clarified when it was found that infusions of the nicotinic antagonist DH β E into the ventral tegmental area (VTA) produced a significant decrease in nicotine self-administration (Corrigall et al., 1994). The decrease in responding following the delivery of the nicotinic antagonist was specific to nicotine self-administration in that infusions of DH β E into the VTA had no effect on cocaine self-administration or food-maintained responding (Corrigall et al., 1994). As mentioned earlier, molecular genetic research also has made use of the self-administration paradigm when investigating which nicotinic receptor subtypes (β_2) are involved in nicotine self-administration (Picciotto et al., 1998).

Animal self-administration studies have allowed for a better understanding of three important components of substance abuse: acquisition, maintenance, and reinstatement or relapse (Dworkin & Stairs, 2002). This better understanding of drug abuse can aid in the development of potential pharmacotherapeutic treatments for drug addiction as well as for smoking cessation. When developing pharmacotherapeutics it is important to determine whether the compound has reinforcer-specific effects. One procedure often used to test the specificity of the drug is to determine the effect of the drug on food-maintained responding (Mello, 1992). If a novel compound was found to decrease nicotine self-administration with little to no effect on behavior maintained by food, this would indicate that the drug's effects on nicotine self-administration were selective.

In addition to reinforcer selectivity, there are additional concepts to consider when investigating the effects of drugs on schedule-controlled behavior. One very important concept that must be considered is rate dependency. Rate dependency is the notion that,

the rate of the ongoing behavior at the time the drug is administered may influence the effect of the compound on responding. It is widely known in behavioral pharmacology research that stimulants tend to decrease high rates of behavior and increase low rates of behavior that are maintained through positive reinforcement (Dews, 1955, 1958; McMillan & Leander, 1976). While many have described the effects of stimulants on schedule-controlled behavior in terms of rate dependency, others have described the data using the notion of rate constancy. Rate constancy is the notion that administration of stimulants causes behavior to become more constant or less variable, and that as the dose of the drug is increased the behavior becomes less and less variable (Gonzalez & Byrd, 1977). Despite the description used to describe the effects of stimulants on the schedule-controlled behavior, the consistent effects of stimulants on schedule-controlled behavior must be considered when using animal self-administration procedures as well as food control studies to test for potential pharmacotherapeutics.

Some of the current pharmacotherapeutics available for smoking cessation include nicotine substitution therapy (Transdermal Nicotine Study Group, 1991) and the use of nicotinic antagonists (Rose, Behm, & Westman, 1998). In addition, combination treatments have also been used involving both nicotine substitution and the blockade of nicotinic receptors (Rose, Behm, & Westman, 2001). The recent use of bupropion, an atypical anti-depressant, has likewise been found to be an effective aid in smoking cessation (Hurt et al., 1997; Jorenby et al., 1999).

Nicotine substitution therapy involves replacing the nicotine usually acquired from cigarette smoke with nicotine from gum, patches, nasal spray, or a vapor delivery system (Transdermal Nicotine Study Group, 1991). Individuals who use the nicotine

substitution therapy are 2-3 times more likely to remain abstinent than individuals who received placebo (Fiore, Smith, Jorenby, & Baker, 1994). Although nicotine substitution therapy performs better than placebo in sustaining smoking abstinence, this therapy alone does not guarantee complete abstinence from smoking. For instance, in a meta-analysis review of the clinical trials for the nicotine patch, it was found that the nicotine patch performed statistically better than placebo (Fiore et al.), but only 27% of the individuals who received the nicotine patch remained abstinent by the end of the treatment. In addition, in the Gourlay et al. (1995) study, only 2.5% of individuals abstained continuously from smoking for 56 days after the quit date, compared to 2.2% for placebo.

In an effort to improve the success rate of smoking cessation, other pharmaceuticals such as nicotinic antagonists have been investigated and compared to nicotine substitution. These pharmacological adjuncts may be used alone or in combination with nicotine substitution therapy. Recently, investigators testing the possibility of nicotinic antagonists to aid in smoking cessation have resulted in some success (Rose et al., 1998; Rose et al., 1994; Rose, Westman, Behm, Johnson, & Goldberg, 1999). Rose et al. (1998) found that administering mecamylamine (a nicotinic antagonist) two weeks prior to the start of smoking cessation increased the duration of continuous abstinence when compared to nicotine substitution therapy alone. The combination of mecamylamine and nicotine substitution delivered before the start of cessation increased rates of continuous abstinence higher than mecamylamine alone (Rose et al., 1998).

Recently, a sustained release form of bupropion (Zyban, Glaxo Wellcome, Inc) has been approved for use in smoking cessation. Bupropion is a psychostimulant that

acts primarily on the CNS and blocks the reuptake of monoamine neurotransmitters (Cooper, Hester, & Maxwell, 1980). Recent evidence shows that bupropion may be a nicotinic antagonist (Slemmer, Martin, & Damaj, 2000). The effectiveness of bupropion as an adjunct in smoking cessation was founded by two clinical studies that showed bupropion to perform better than placebo in furthering smoking cessation (Hurt et al., 1997; Jorenby et al., 1999). Hurt et al. found in a randomized, double blind study that the effect of bupropion was significant over placebo in increasing smoking cessation rates after six weeks. The percentage of subjects not smoking at six weeks was dose dependent, with higher rates of abstinence occurring among subjects receiving the larger dose of sustained release bupropion. Rates of abstinence continuously declined throughout the remaining year. In a second randomized, double blind, placebo-controlled study investigating the effects of bupropion in combination with nicotine transdermal patches on smoking cessation, researchers found that 150 mg of bupropion with a nicotine patch had significant effects on smoking abstinence (Jorenby et al.). Jorenby et al. found that at six months, bupropion alone produced higher rates of abstinence than did placebo or nicotine patch alone. Bupropion in combination with the nicotine patch produced significantly higher rates of abstinence than bupropion alone or nicotine patch alone. The results from these clinical trials appear promising, although rates of abstinence in both studies consistently declined with the passage of time, with only 24.4% of the subjects receiving the highest dose of bupropion remaining abstinent at 12 months.

The effects of bupropion on smoking cessation may be better understood by the use of operant techniques in the animal self-administration design. The effects of this

drug on nicotine-taking behavior as well as behavior maintained by food reinforcement under a similar schedule can shed light on how bupropion is having an effect on smoking cessation. The current studies were undertaken to determine whether bupropion has reinforcer-specific effects on nicotine by testing the drug on nicotine self-administration and food-maintained behavior in rats.

METHODS - NICOTINE EXPERIMENT

Subjects

Fifty male Sprague Dawley (from Harlan International) rats were used as subjects in this study, while seven subjects are shown in results section due to catheter failure or inability of nicotine to maintain responding. The subjects were approximately two months old at the start of the experiment, and their weights during the experiment were approximately 300 g. The subjects were individually housed in Plexiglas cages with cedar bedding. The animals had unlimited access to water except during experimental sessions. The subjects were fed 13-15 g of standard rat chow (LabDiet) following each daily session and were housed in reverse light-dark cycle (lights on from 19:00 to 07:00).

Apparatus

Daily sessions were conducted in operant chambers inside sound-attenuating boxes (Med Associates). Each sound-attenuating box contained an operant chamber, tone generator, white house light, pellet dispenser, ventilation fan, and an infusion pump (Med Associates, PHM-103). The dimensions of the operant chambers were 22.86cm X 21.59cm X 20.32cm. The floor of the chambers consisted of metal bars spaced 1.27cm apart. The two sidewalls and lid of the chambers were made of Plexiglas. The front and back walls were constructed of aluminum. On the front wall there was an active lever

that was 2.57cm above the floor and 2.57cm in from the right sidewall. A minimum of approximately 0.25 N of force was required to operate the active lever. Centered 5.08cm above the active lever was a green-jeweled light. A food cup was located 5.08cm from the left of the active lever and 2.57cm up from the floor. On the back wall was an inactive lever that was 2.57cm from the left sidewall and 2.57cm above the floor. Centered 5.08cm above the inactive lever was a red-jeweled light.

Surgery

Subjects were implanted with an indwelling jugular venous catheter. The subjects were anesthetized with sodium pentobarbital (Nembutal, 40 mg/kg, i.p.), and injected with atropine sulfate (10 mg/kg) before the surgery. The catheter, a small polyvinyl tubing, was inserted into the right facial vein. The catheter was pushed down into the jugular vein, and rested just outside the right atrium of the heart. The catheter was secured down and threaded subcutaneously out the back of the animal. The catheter exited the subject through a polycarbonate back-plate that was implanted under the skin. The catheter was then passed through a spring leash and connected to a liquid swivel. The spring leash was connected to the back-plate of the animal by two nylon screws. The swivel was then connected to a counterbalanced arm, which allowed the subject virtually unrestricted movement in the operant chamber. The swivel was connected to a saline pump while the animals were in their home cages by a piece of polyvinyl tubing. The tubing was cut and a luer lock connection was inserted in to the line in order to allow for easy transportation of the animals from their home cages to the operant chambers. The luer lock connection consisted of a 20 gauge blunted needle inserted into one end of the

polyvinyl tubing, and a blunted Vacutainer brand luer adapter inserted into the other end of the tubing.

Subjects were observed immediately following surgery until they regained consciousness before being placed into their home cages. Following surgery, the animals were allowed to recover for 7 days before experimental sessions started. In order for the catheters to remain patent, they were flushed every 90 min with a 2 s infusion of heparinized saline (1.7U/ml; 266.67 μ l/hr) while the animals were in their home cages. The patencies of the catheters were checked every two weeks with sodium methohexital (Brevital, 0.2 ml/injection). If the catheters were still patent, the animals would lose consciousness shortly after injection of sodium methohexital.

Procedure

The subjects were removed from their home cages and placed into the operant chamber at the start of the experimental sessions. Prior to surgery, lever pressing was shaped by successive approximation on the active lever located on the front wall of the chamber. Responses on the active lever resulted in the delivery of a food pellet (Noyes 45mg pellets) on a FR 1, 60 s TO schedule of reinforcement. Following acquisition of responding on the active lever the animals underwent surgery as described above. After recovery from surgery, the subjects were given experimental sessions during which food reinforcement was replaced by infusions of nicotine. All other aspects of the schedule remained the same.

On the first day of experimental sessions in which nicotine maintained behavior, the number of infusions obtained within a session was limited to 10. This was done in order to limit the subjects' exposure to any toxic effects from an overdose of nicotine.

Acquisition of nicotine self-administration progressed in the order of FR 1 for the first five experimental sessions, FR 2 for the next three sessions, and FR 3 for the remainder of the experiment. All active lever presses resulted in an infusion of nicotine bitartrate (free base) at a dose of 0.03 mg/kg/inf. Each dose of nicotine was delivered in 50 μ l at 100 μ l/sec.

During experimental sessions the jeweled lights above both levers and the house light were on and white noise was fed into the chambers. Responses on the active lever resulted in a brief flash of the jeweled lights and a feedback click. After completion of the ratio, an infusion of nicotine was delivered through the catheter; the jeweled lights and houselight were darkened with the onset of a tone for the duration of the 60 s TO. Responses during the timeout were recorded but had no scheduled consequences. Responses on the inactive lever (“back responses”) were recorded throughout the entire session and had no scheduled consequences. Upon completion of the 60 min session, the catheters were disconnected from the infusion pump and flushed with .1 ml of heparinized saline. The subjects were then removed from the chamber and placed back into their home cages. Approximately 20-25 min following the experimental sessions, the subjects were feed 13-15 g of rat chow.

Stable responding was defined as having 5 or more infusions within an experimental session for 5 consecutive sessions, without any obvious increasing or decreasing trends over the 5 sessions. Once stable responding was maintained by nicotine on the FR 3 schedule, subjects received intraperitoneal (i.p.) injections of Bupropion HCL (0, 10 mg/kg, 30 mg/kg, 56 mg/kg) 15 min prior to an experimental session. After 15 min had elapsed, the subjects were placed into the operant chambers,

connected to the infusion pumps, and allowed to complete a session. Additional injections of bupropion were not studied until the number of nicotine infusions returned to five or more for two consecutive sessions. If any of the subjects did not reach criterion by the third day following an injection, they were given more experimental sessions until they reach the preceding criterion.

Each dose of bupropion was administered in a pseudorandom order. The dose of bupropion was randomly chosen with the constraint that once a particular dose of bupropion was administered all other doses in the dose effect curve must be administered before the dose was repeated. Once all doses were administered, the dose response curve was again tested starting with saline, as long as the animal's catheter remained patent.

METHODS – FOOD-DEPRIVED EXPERIMENT

Subjects

Four Fisher 344 rats were used as subjects in this study. The subjects were individually housed in standard hanging metal home cages and were given unlimited access to water except during experimental sessions. The subjects received a restricted food diet of 20g of standard rat chow following each daily session. The animals were housed in reverse light-dark cycle (lights on from 19:00 to 07:00).

Apparatus

The same experimental chambers as described in the previous two experiments were used.

Procedure

Lever pressing on the active lever was shaped by successive approximations, and resulted in the delivery of a food pellet (45 mg). Once the lever-press response was acquired, the subjects were placed on an FR 1 60 s TO schedule of food reinforcement. The schedule of reinforcement was increased to an FR 3 60 s TO, then to a terminal schedule of FR 5 60 s TO. During each 60 min session, the jeweled lights above both levers were illuminated and white noise was fed into the chambers. Responses on the active lever resulted in a brief flash of the jeweled lights and a feedback click. After completion of the ratio, the food pellet was delivered and the jeweled lights were darkened, the house light and tone turned on for 20 s. Following 20 s, the house light and tone shut off and the chamber remained dark for the remaining 40 s. of the timeout period. Responses during the timeout were recorded but had no scheduled consequence. Responses on the inactive lever were also recorded throughout the entire session and had no scheduled consequences.

Once the number of reinforcers obtained within a session did not fluctuate by more than 2 reinforcers for five consecutive sessions, the subjects received intraperitoneal (i.p.) injections of bupropion (0, 10, 30, 56 mg/kg) 15 min prior to the experimental session. After 15 min had elapsed, the subjects were placed into the operant chamber and allowed to complete the sessions. Following a dose of bupropion, the number of reinforcers obtained within a session had to be within two reinforcers of the number of reinforcers obtained on the day prior to the drug session before another dose of bupropion was administered. Each dose of bupropion was administered at least twice in pseudorandom order, as previously described.

METHODS - FOOD-SATIATED EXPERIMENT

Subjects

Four male Sprague Dawley rats with an age of approximately one month were used in this study. The subjects were individually housed in standard hanging metal home cages and had unlimited access to water except during experimental sessions. The subjects received 25 g of standard rat chow for 1.5 hrs immediately prior to their daily sessions. The animals were housed on a reverse light-dark cycle (lights on from 19:00 to 07:00).

Apparatus

The same experimental chambers were used as previously described in the nicotine experiment.

Procedure

Subjects were not fed for 24 hrs prior to an experimental session in which the lever-press response on the active lever was shaped by successive approximations. Each lever-press resulted in the delivery of a 45 mg food pellet. Once the lever-press response was acquired, the animals were placed on the same FR1 60 s TO schedule of reinforcement previously used for the nicotine experiment, with the exception that food pellets maintained behavior instead of nicotine infusions throughout the entire study. The subjects progressed, in a manner identical to the subjects described in the nicotine study, to a terminal schedule of FR3 60 s TO. All discriminative stimuli and stimuli changes were identical to the changes that occurred in the nicotine study.

While the animals were in the experimental chambers completing the experimental sessions, the amount of remaining food was weighed to determine the

amount of food that had been consumed. The subjects consumed an average of 16.61 g of food with a standard deviation of 4.34 g prior to the session. Once the remaining food was weighed, it was discarded. Following the sessions, the animals were placed back into their home cages and not fed until 1 and ½ hrs prior to the next day's experimental session.

Once stable responding was established under the preceding conditions, subjects were given intraperitoneal (i.p.) injections of bupropion (0, 10, 30, and 56 mg/kg) 15 min prior to the experimental session. Stable responding was determined by visual inspection of graphs displaying the number of reinforcers obtained in each daily session. The graphs were observed to make sure that no upward or downward trend could be seen. Following the 15 min pretreatment, the subjects were placed in the experimental chambers and allowed to complete the 60 min sessions. Another dose of bupropion was not administered for at least two sessions, with the stipulation that no obvious trend could be seen by visual inspection of the graphs for number of reinforcers obtained within the sessions, and that the number of reinforcers returned to within the range of that seen prior to the previous injection. The doses were given in a pseudorandom order as previously described in the nicotine study until each dose was given twice.

Drugs

The drugs used in this study were nicotine di-d-titrate (free base), and 2-(tert-Butylamino)-3'-chloropropio-phenone Fumarate (bupropion) RTI-6037-41. Nicotine was purchased from RBI, dissolved in heparinized 0.9% injection sodium chloride. Nicotine was dissolved in a solution that allowed the drug to be delivered at a dose of 0.03 mg/kg of the animal's body weight at a volume of 50 µl at 100 µl/s. Bupropion was

purchased from RTI, and dissolved in 0.9% bacteriostatic sodium chloride in a volume of 2.0 ml per mg of the drug the evening before an injection. Each dose of the drug was studied at least twice in each animal.

Data Analysis

An alpha level of .05 was used for all statistical tests. The data were analyzed by conducting oneway ANOVAs on the dose-response curves of bupropion for the four dependent variables that were measured during the experimental sessions for both the group averages of the three different studies and all the individual subjects. The main dependent variables of interest were number of reinforcers delivered during the session, overall response rate (responses/second), inactive lever response rate (responses/second, from this point on referred to as back response rate), and the number of timeout responses made per reinforcement opportunity (number of TO responses/number of reinforcers obtained within the session). If the oneway ANOVA was found to be significant, a post hoc analysis was done. A Bonferroni post hoc test was used for all post hoc analysis. If the effect could not be found with a Bonferroni test (a more conservative test), a Least Squared Difference (a more liberal test) test was used to determine which dose was having a significant effect. If a Least Squared Difference test was required to find the significant effect, then the letters LSD will precede the symbols on the graph.

Cumulative response records were collected to determine the pattern of responding as it varied across the different doses of bupropion. The cumulative records were also used to assess differences in the patterns of behavior related to the different conditions among the three different studies.

The data were analyzed looking at the percentage of change from control following administration of doses of drug as a function of the control rate of behavior for the three rates of behavior (overall response rate, back lever response rate, and timeout response rate) for all three studies. The percent of control for each drug dose (0, 10, 30, and 56 mg/kg) was plotted on a log scale against the control rate of the behavior that was also plotted on a log scale; these graphs are referred to as rate-dependency plots. To calculate percent control, the rate of the behavior following drug administration at each dose was divided by the control rate of that behavior, with the product then multiplied by 100. The percent control was then plotted on a log scale against the control rate, which is also on a log scale. Trend lines were fit to the data points on each graph and the r^2 value for the trend line was displayed on the graph. This analysis was done for each study, for each dose administered, and for all three studies.

The final type of analysis that was conducted was the percent control of the overall response rate (resp/sec) (same as previously described) as a function of bupropion dose for each of the three studies. This analysis resulted in dose response curves in which percent control was plotted against the dose of the drug for the nicotine group, food-satiated group, and the food-deprived group. Oneway ANOVAs and post hoc analyses were run between the three studies and within studies across the different doses of bupropion.

RESULTS – NICOTINE EXPERIMENT

The group averages for the dose effect curves for the effects of bupropion on nicotine self-administration are shown in Figure 1. Bupropion tended to increase the overall response rate at the two highest doses administered with the peak effect being at

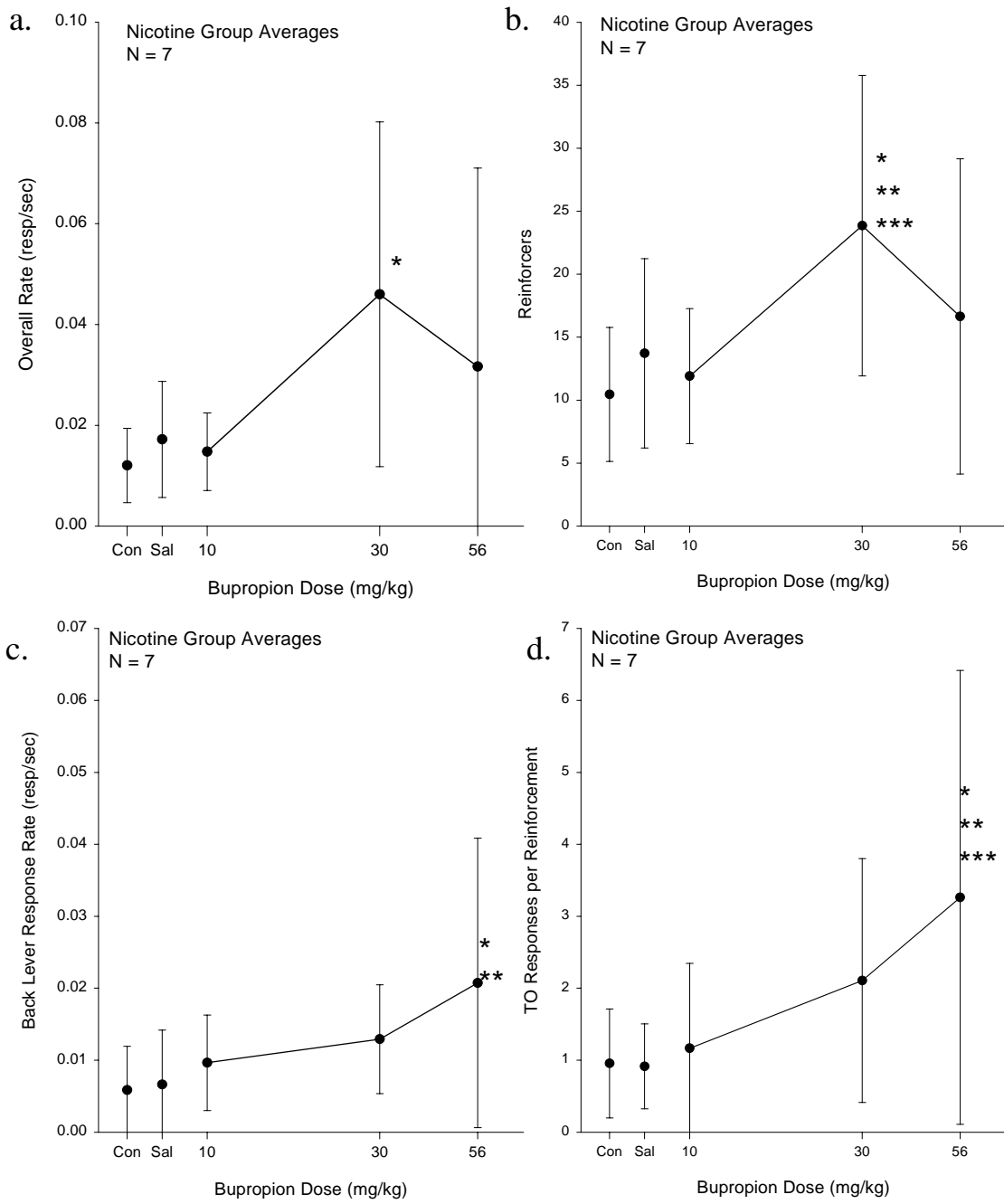


Figure 1. The effects of bupropion (10, 30, 56 mg/kg) on nicotine self-administration (0.03 mg/kg/inf). The four dependent measures depicted include; overall response rate (a.), the number of nicotine infusions obtained or reinforcers (b.), the back lever response rate (c.), and the number of timeout responses per reinforcement (d.). The closed circles represent group averages from seven rats and the error bars indicate + -1 standard deviation of the mean. * significantly different from control, ** different from saline, *** different from 10 mg/kg, + different from 30 mg/kg, ++ different from 56 mg/kg, +++ different from all other conditions. $P < 0.05$.

the 30 mg/kg dose. There was a main effect of dose for overall response rate found with a oneway ANOVA, $F(4, 77) = 3.773, p = .007$. The results for all the post hoc analyses are illustrated on the figures with corresponding symbols which are explained in the caption. The 30 mg/kg dose of bupropion tended to increase the number of infusions obtained within a session. There was a main effect of bupropion dose found for the number of reinforcers obtained within a session, $F(4, 77) = 6.699, p = .000$. Bupropion also increased the back lever response rate at the highest dose administered, $F(4, 77) = 5.729, p = .000$. Furthermore, there were dose-dependent increases in the number of timeout responses per reinforcement, $F(4, 77) = 6.216, p = .000$.

Figure 2 shows the dose effect curves for bupropion on nicotine self-administration in a single representative subject (Bup30). Bupropion tended to increase both the overall response rate and the number of reinforcers at the moderate and high dose tested. There was a significant effect of dose on the overall response rate, and number of reinforcers for Bup30, $F(4, 9) = 6.635, p = .009, F(4, 9) = 6.7, p = .009$, respectively. The drug increased back lever responding at the 56 mg/kg dose, $F(4, 9) = 18.196, p = .000$. For subject Bup30 bupropion also resulted in dose-related increases in the number of timeout responses per reinforcement; this main effect of dose was found to be significant, $F(4, 9) = 9.191, p = .003$. The effects of bupropion on the dependent measures for subject Bup52 are illustrated in Figure 3. The 30 mg/kg dose of bupropion tended to increase both the overall response rate and the number of reinforcers obtained, although there was a considerable amount of variation between different administrations of these doses. There were no consistent effects of the drug on the back lever response

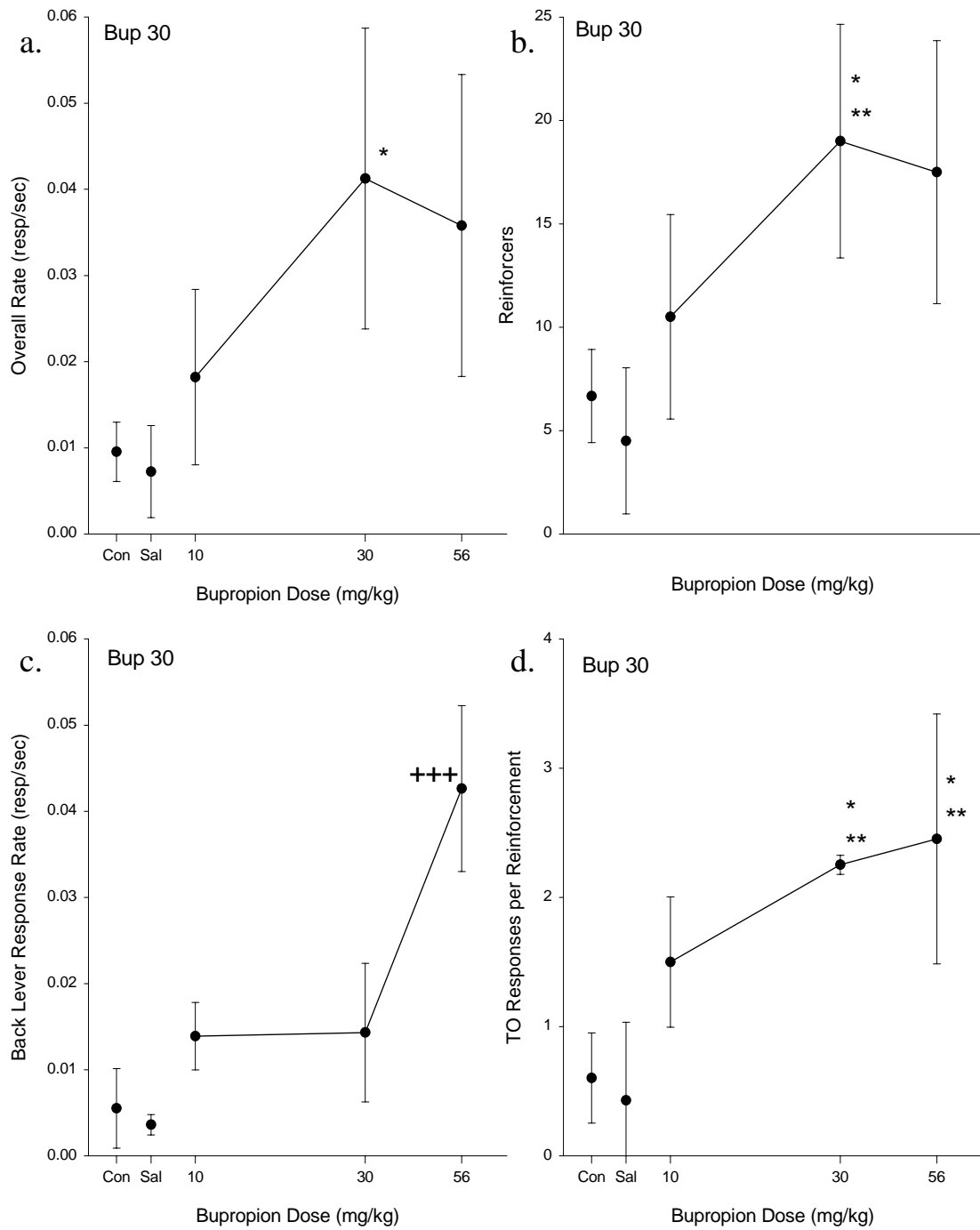


Figure 2. The effects of bupropion (10, 30, 56 mg/kg) on nicotine self-administration (0.03 mg/kg/inf) for rat Bup30. The closed circles represent averages of two or more administrations at each dose, the error bars indicate \pm 1 standard deviation of the mean. For explanation of symbols, refer to Figure 1.

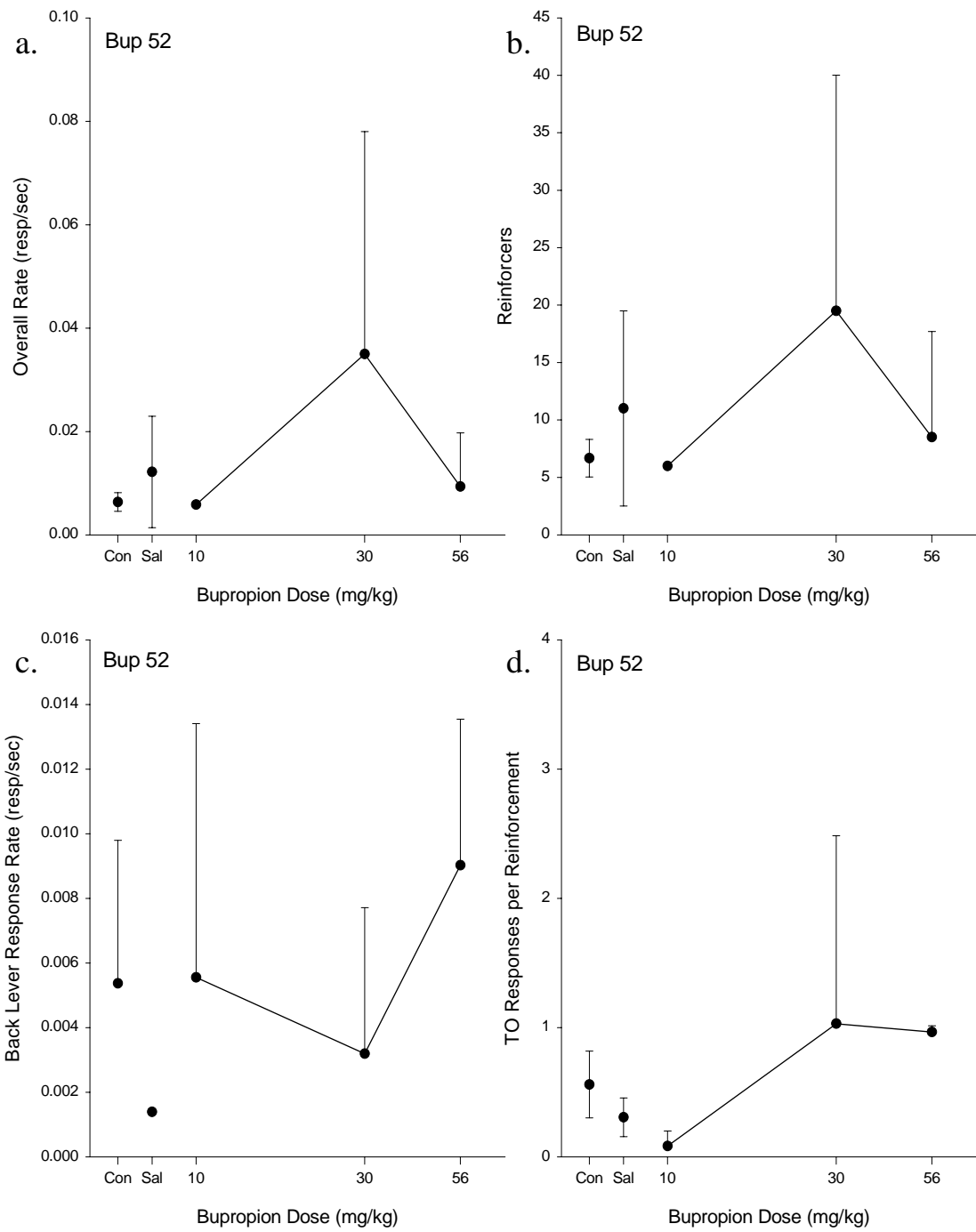


Figure 3. The effects of bupropion (10, 30, 56 mg/kg) on nicotine self-administration (0.03 mg/kg/inf) for subject Bup52. For description of the graphs, refer to Figure 2.

rate, or the number of timeout responses per reinforcement for Bup52. There were no significant effects of drug dose on any of the dependent measures for subject Bup52.

Figure 4 shows the data obtained for subject Bup58. For Bup58 only two of the dose effect curves had significant effects; overall response rate and back lever response rate. There was a main effect of dose on overall response rate for Bup58, $F(4, 11) = 4.040$, $p = .030$. This effect resulted from saline consistently increasing response rate while doses of bupropion failed to have consistent effects. Although doses of bupropion did not contribute to the effect found in overall response rate, the moderate dose of the drug increased responding on the back lever and resulted in a main effect of dose, $F(4, 11) = 31.494$, $p = .000$.

The effects of bupropion on the four dependent variables for subject Bup51 are shown in Figure 5. Bupropion again tended to increase the overall response rate and number of reinforcers at the middle and high dose. These effects were significant for Bup51, $F(4, 8) = 10.415$, $p = .003$, $F(4, 8) = 28.684$, $p = .000$, respectively. There was also a main effect of drug on the number of timeout responses per reinforcement with the drug dose-dependently increasing timeout responses, $F(4, 8) = 11.408$, $p = .002$. The dose-effect curve for bupropion on back lever responding, for Bup51, resulted in a U-shaped function although the effects were not significant. Figure 6 shows the effects of bupropion on nicotine self-administration for subject Bup36. There were no statistically significant results for the four dependent variables for Bup36. However, Figure 6 does illustrate a trend for the 30 mg/kg dose of bupropion to increase overall response rate and number of reinforcers obtained within a session. Bupropion did not alter back-lever responding or the number of timeout responses for Bup36.

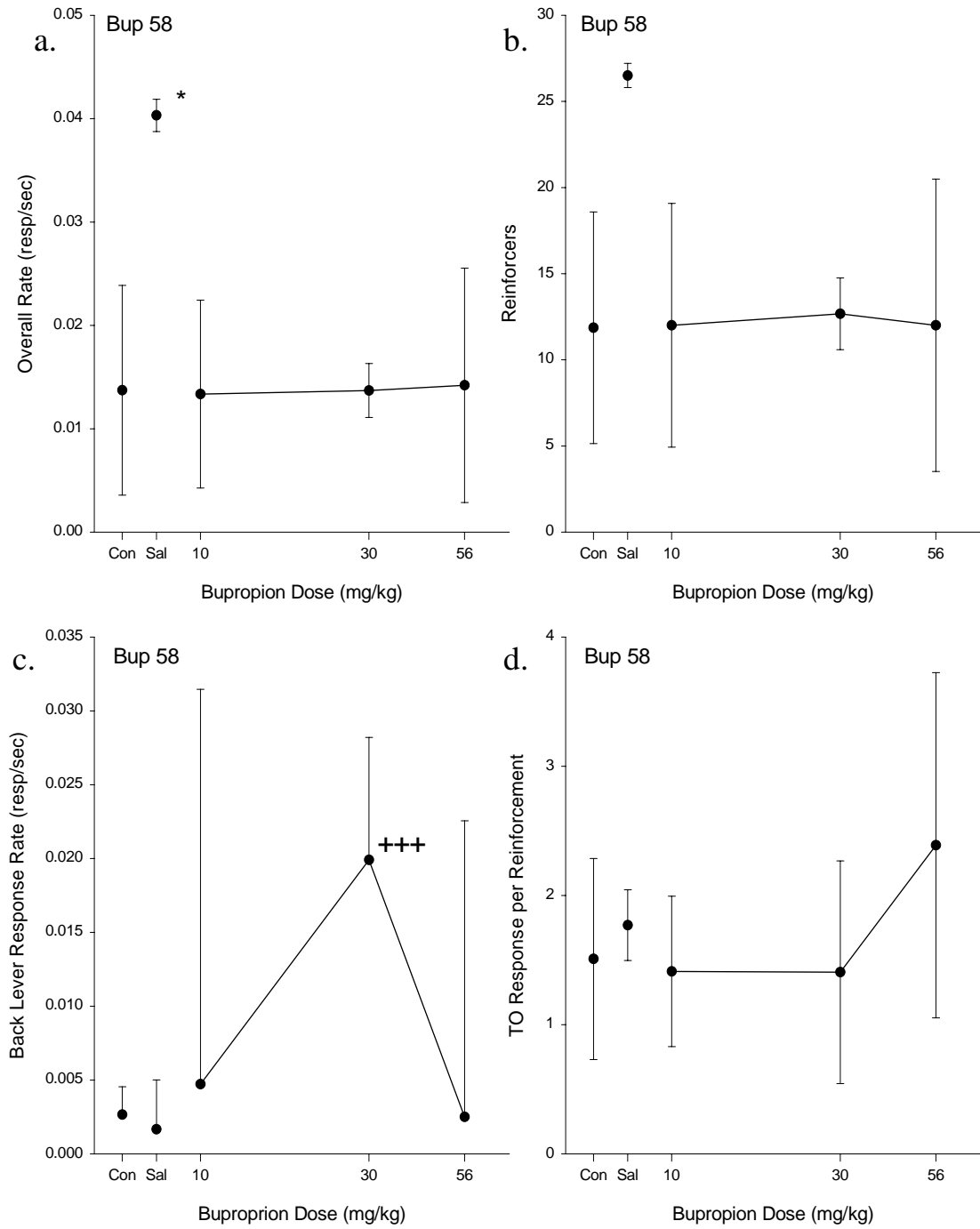


Figure 4. The effects of bupropion (10, 30, 56 mg/kg) on nicotine self-administration (0.03 mg/kg/inf) for subject Bup58. For description of the graphs, refer to Figure 2.

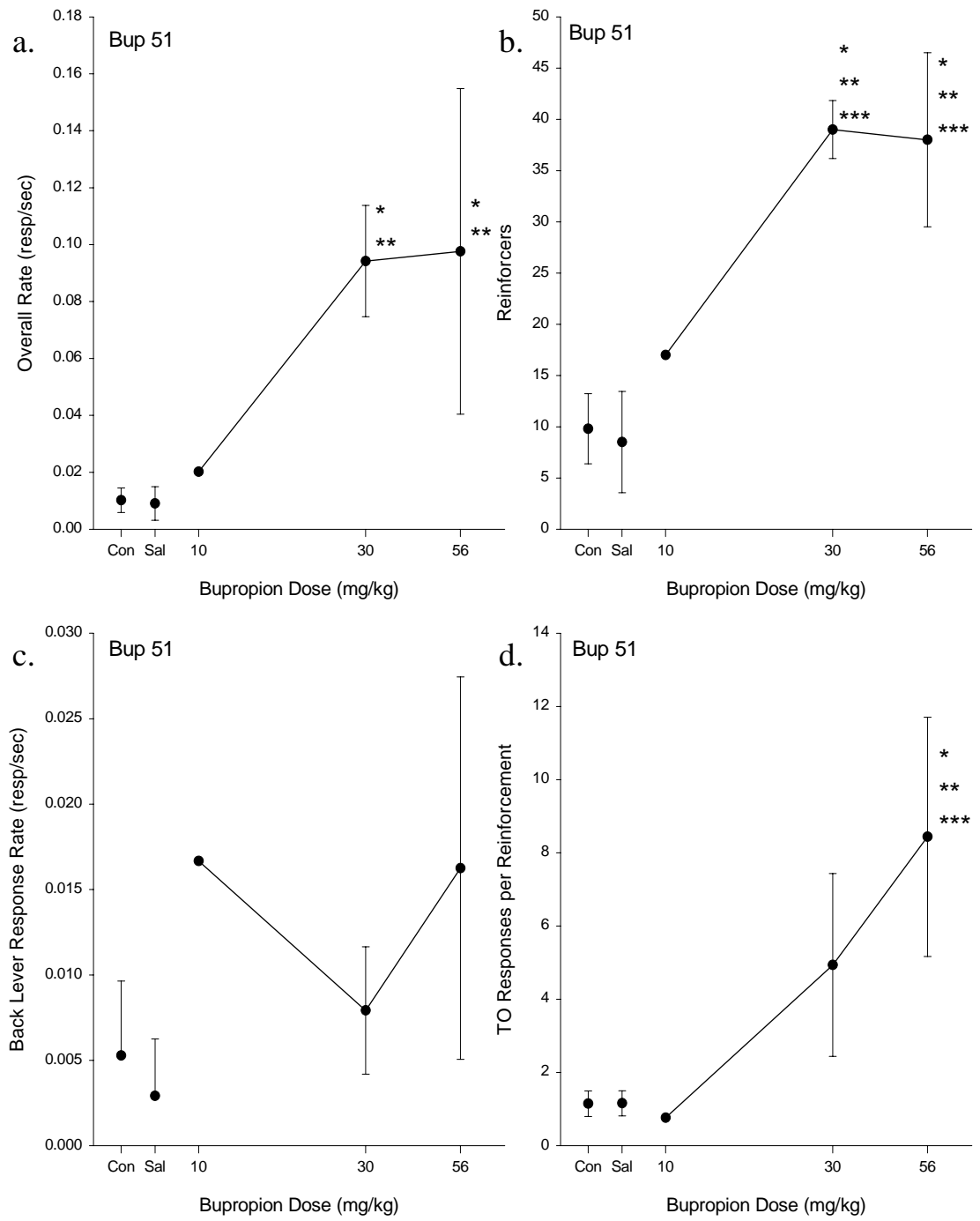


Figure 5. The effects of bupropion (10, 30, 56 mg/kg) on nicotine self-administration (0.03 mg/kg/inf) for rat Bup51. For description of the graphs, details refer to Figure 2.

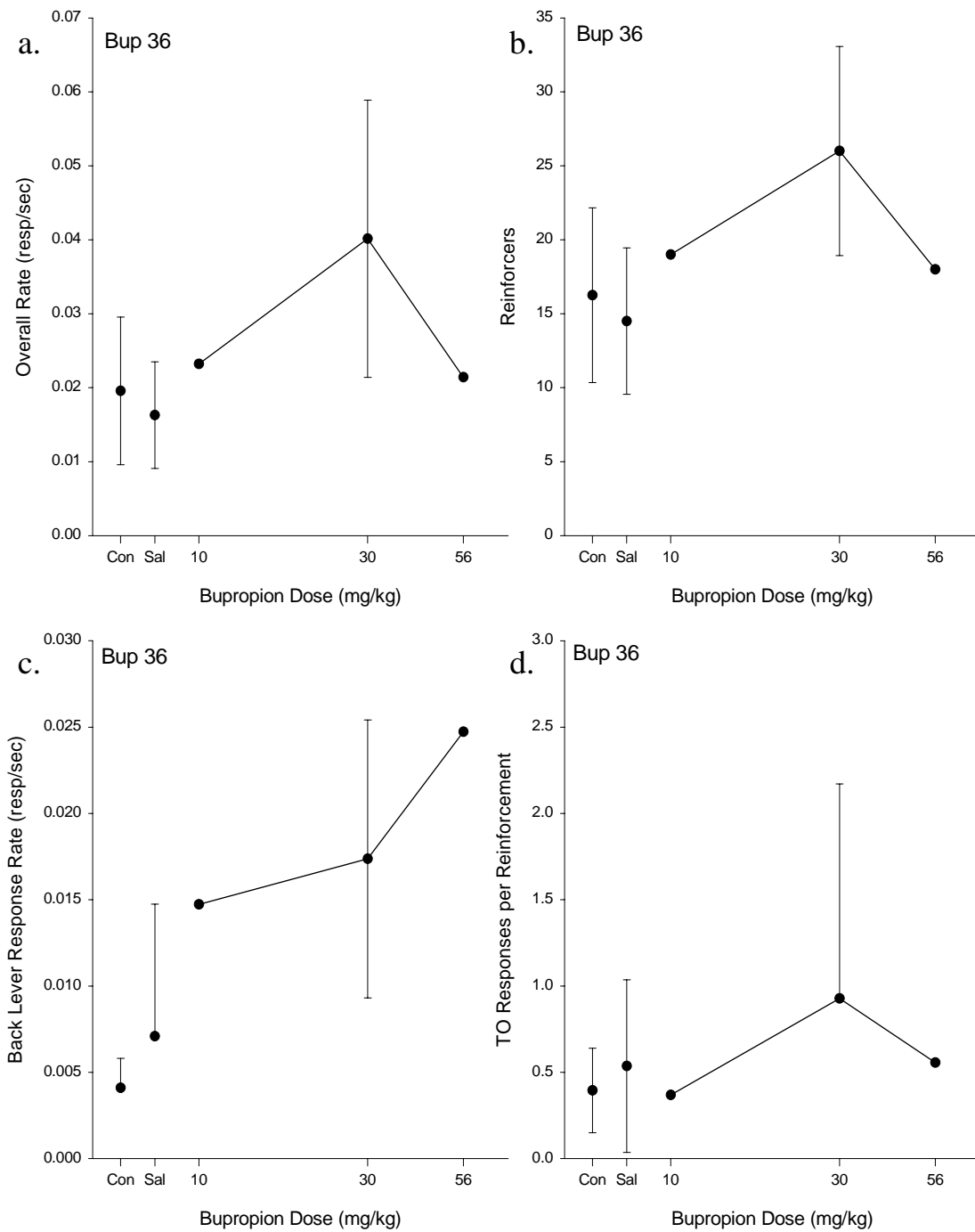


Figure 6. The effects of bupropion (10, 30, 56 mg/kg) on nicotine self-administration (0.03 mg/kg/inf) for rat Bup36. There was only one administration of both the 10 and 56 mg/kg doses of the bupropion for this subject due to catheter failure. For description of the graphs, refer to Figure 2.

The effects of bupropion for subjects Bup57 and Bup59 are shown in Figures 7 and 8, respectively. Post hoc analyses were not run on these two subjects because the dose-effect curve of bupropion was only administered once before their catheters lost patency. Figures 7 and 8 again illustrate the increasing effect of the moderate dose of bupropion on both the overall response rate and the number of reinforcers for both subjects.

The cumulative response records for subjects Bup30 and Bup51 are shown in Figures 9, 10, 11, and 12. These records were selected because the graphs best represent the overall effects of bupropion on nicotine self-administration. The cumulative response records for subject Bup30 are shown in Figures 9 for control days (the day prior to an injection), and saline, and in Figure 10 for the 10, 30, and 56 mg/kg doses of bupropion. Explanation of the records can be found in the Figure 9 caption. The increase in nicotine self-administration after the administration of the moderate and high dose of bupropion are clearly evident by the increased height of the y-axis and more pen displacements in the 30 and 56 mg/kg graphs compared to saline or control graphs. The increase in back-lever response rate can also be seen by the increased number of diagonal displacements on the bottom line for both the 30 and 56 mg/kg records. The increase in the number of timeout responses is represented by the pen stepping up during timeout periods for both the 30 and 56 mg/kg records. The cumulative response records for subject Bup51 are shown in Figures 11 and 12 for control, saline, and drug conditions. Again, the increases in nicotine self-administration following the administration of the 30 and 56 mg/kg doses of bupropion are illustrated by the increase in the height of the y-axis and the number of pen displacements for this subject.

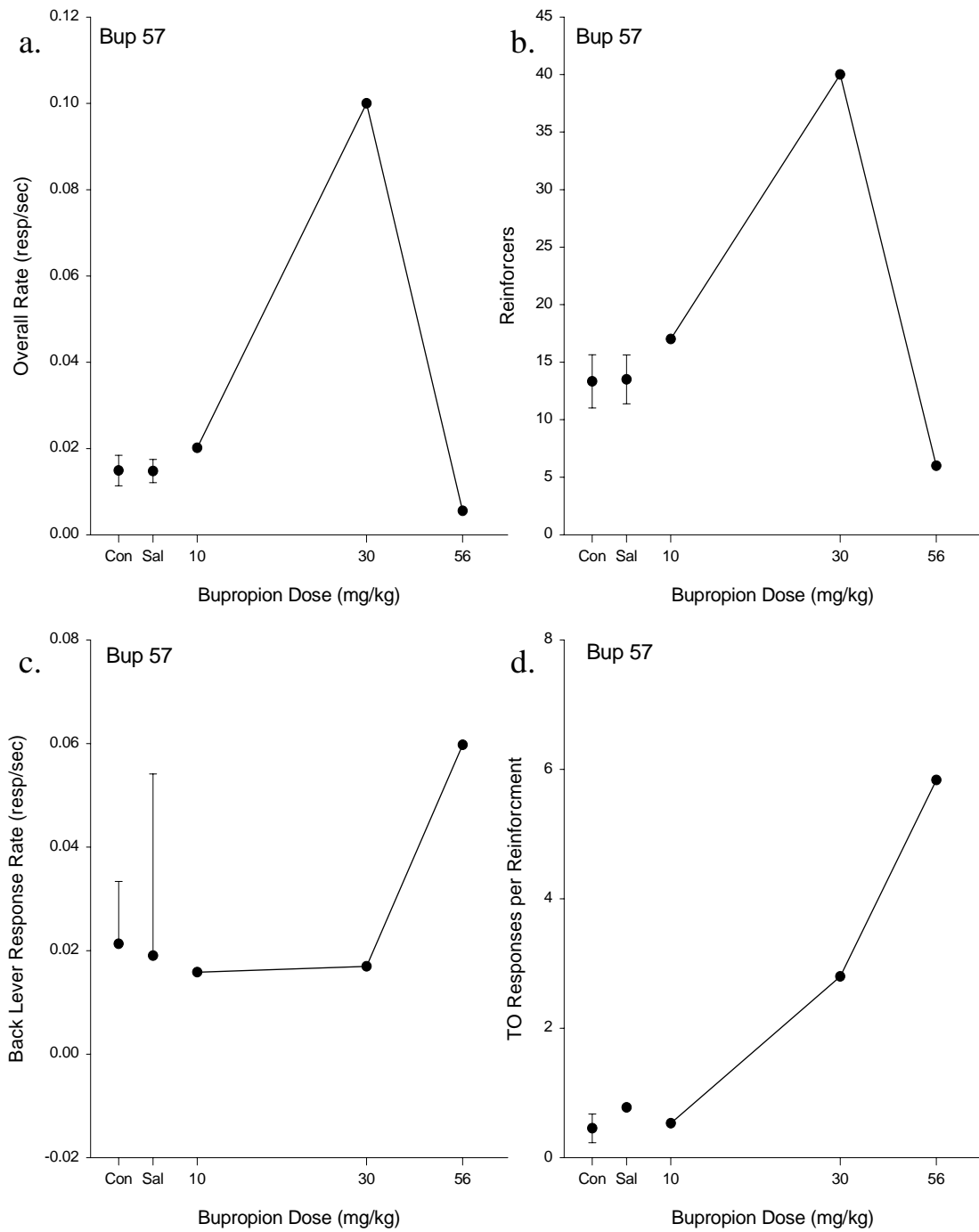


Figure 7. The effects of bupropion (10, 30, 56 mg/kg) on nicotine self-administration (0.03 mg/kg/inf) for subject Bup57. There was only one administration of the 10, 30, and 56 mg/kg doses of bupropion for this subject due to catheter failure. For description of the graph, refer to Figure 2.

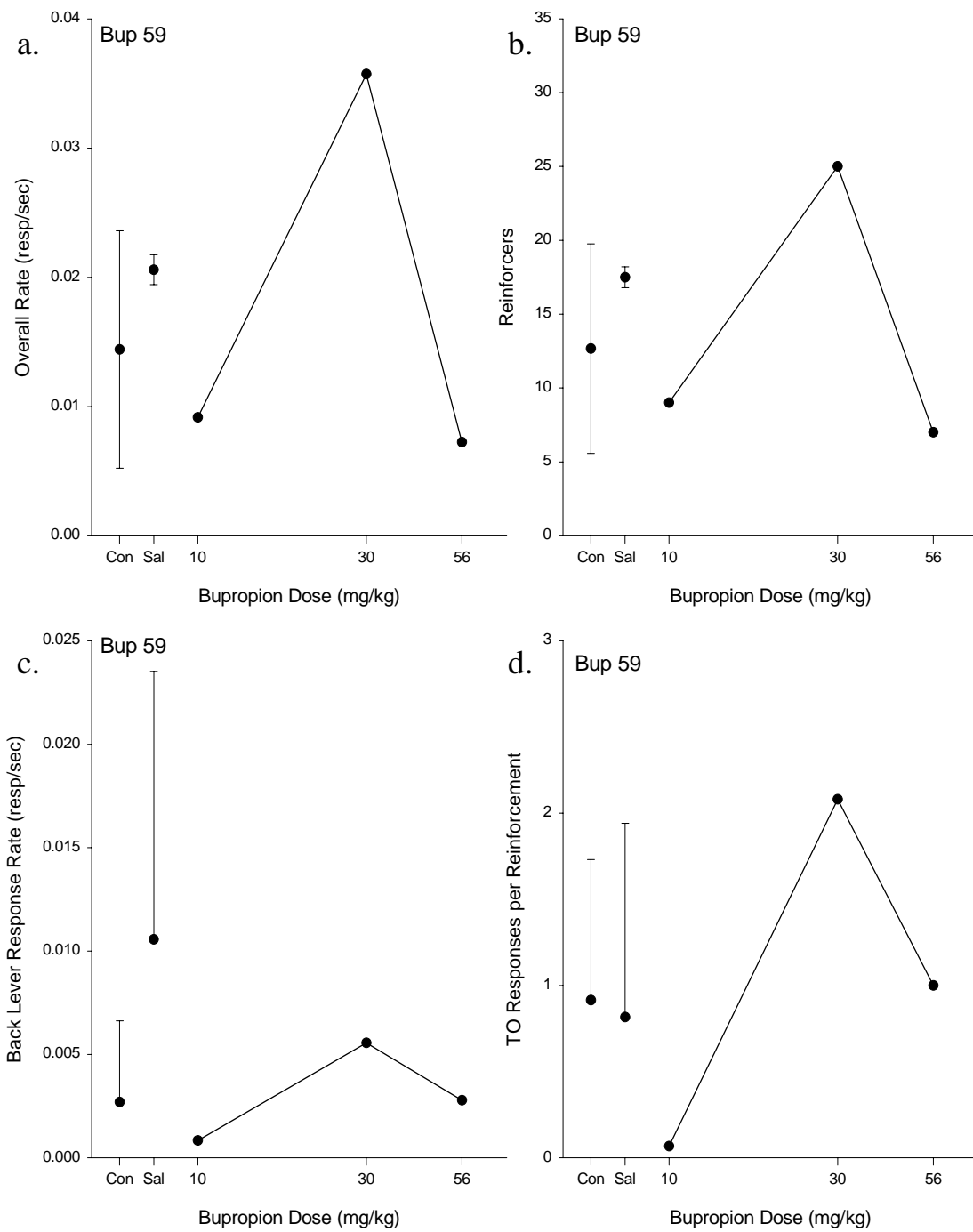


Figure 8. The effects of bupropion (10, 30, 56 mg/kg) on nicotine self-administration (0.03 mg/kg/inf) for subject Bup59. There was only one administration of the 10, 30, and 56 mg/kg doses of bupropion for this subject due to catheter failure. For description of the graph, refer to Figure 2.

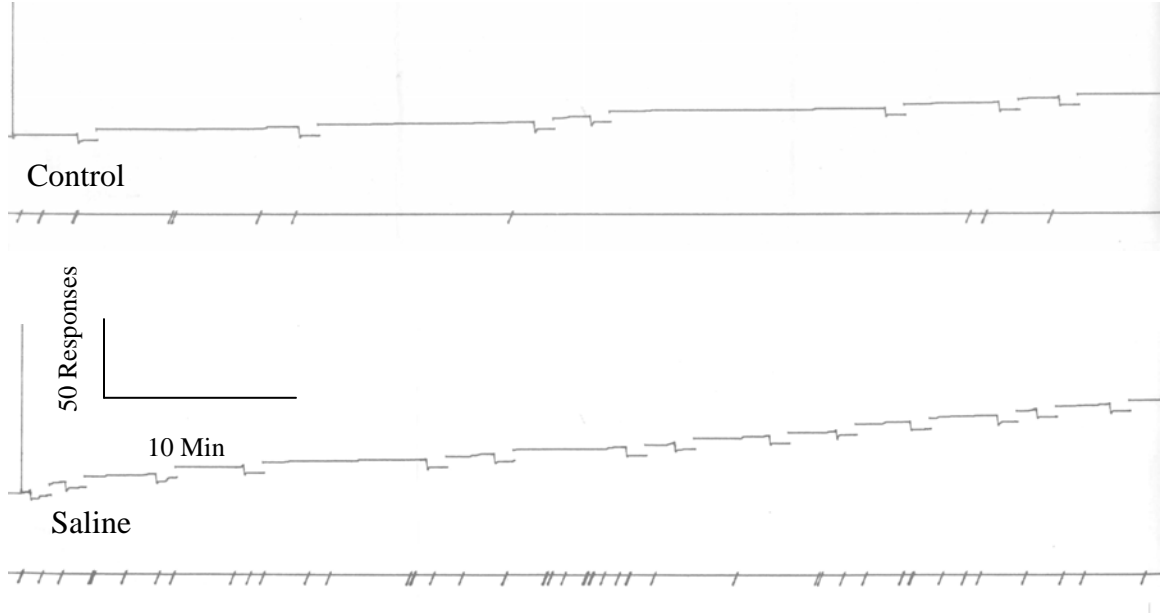


Figure 9. Cumulative response records of subject Bup30 self-administering nicotine (0.03 mg/kg/inf) under control, saline conditions. Each response by the subject on the active lever results in the vertical movement of the pen. Upon completion of the ratio the pen was diagonally displaced indicating the delivery of the reinforcer, the pen remained displaced down during the 60 s TO following reinforcement. The vertical movement of the pen while in the displaced position indicates responses on the active lever during timeout periods. Following the completion of the 60 s TO the pen was reset to its normal position. On the lower event line, any displacement of the event pen indicates a response on the back lever.

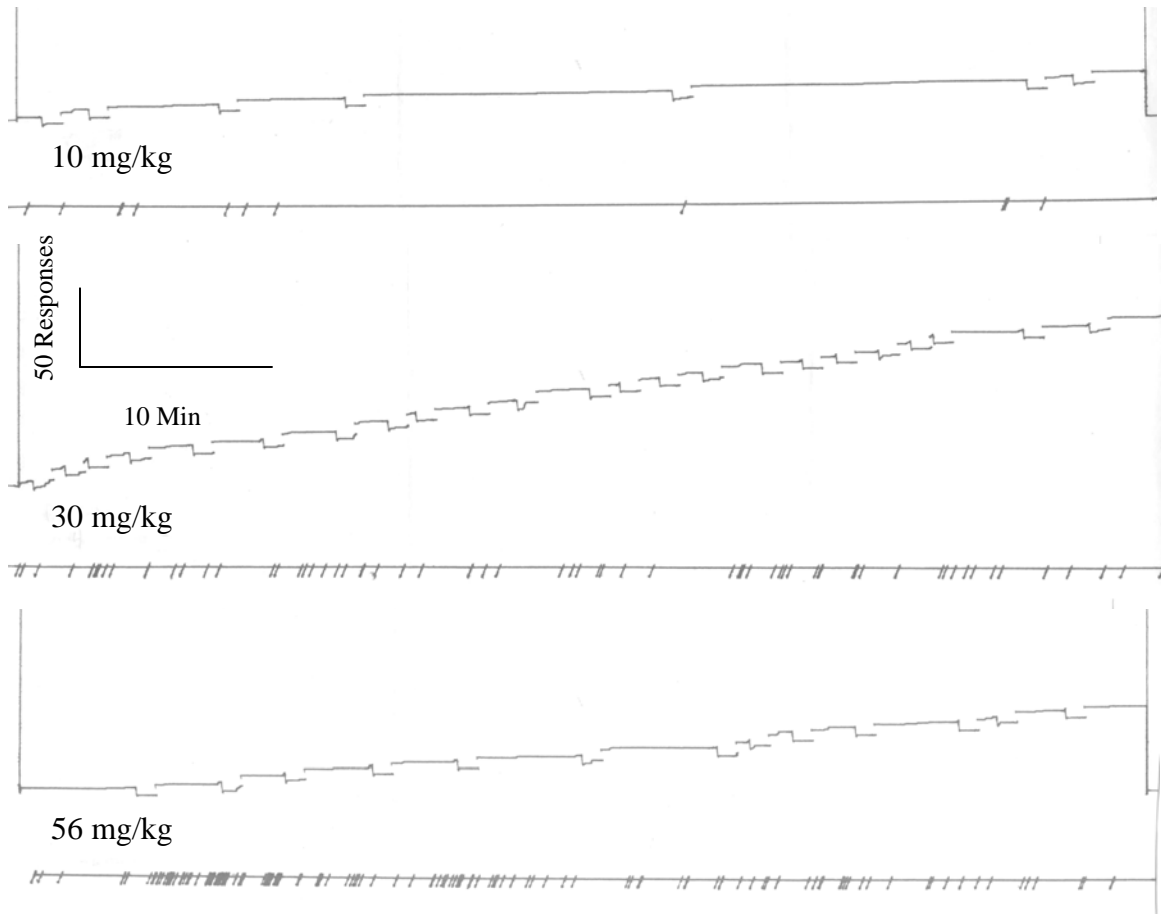


Figure 10. A representative cumulative response record for subject Bup30 following administration of various doses of bupropion (10, 30, and 56 mg/kg).

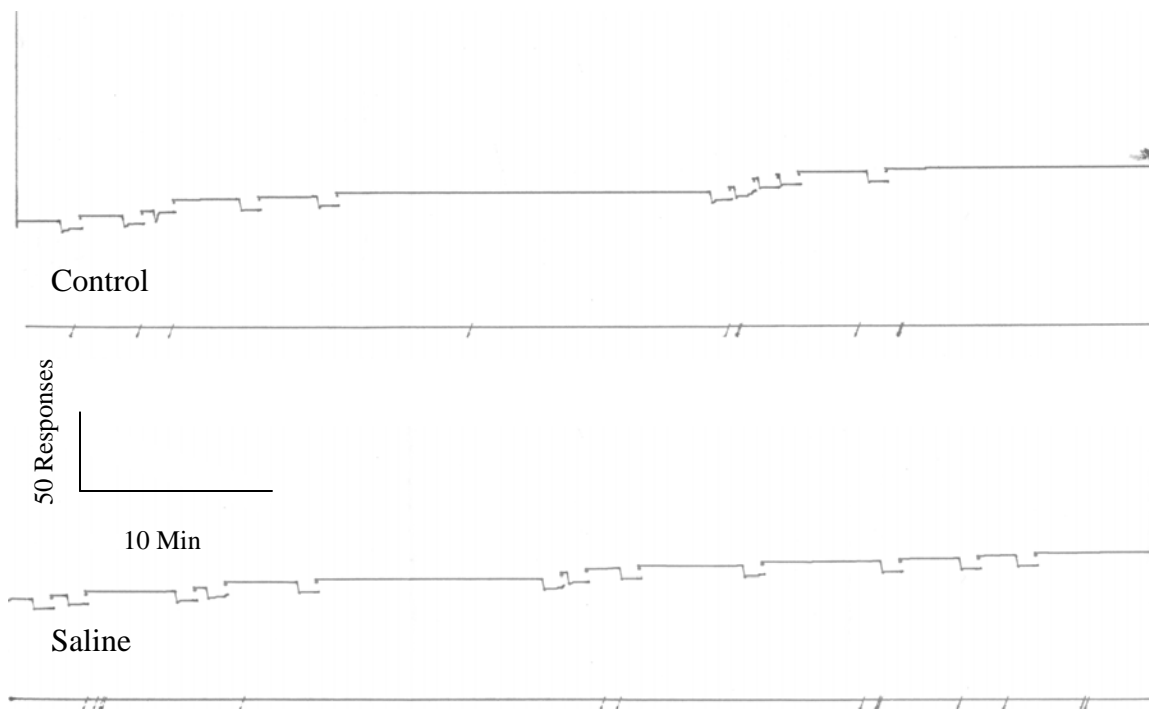


Figure 11. Cumulative response records for subject Bup51 self-administering nicotine (0.03 mg/kg/inf) under control, saline conditions. For description of the cumulative response, records refer to Figure 9.

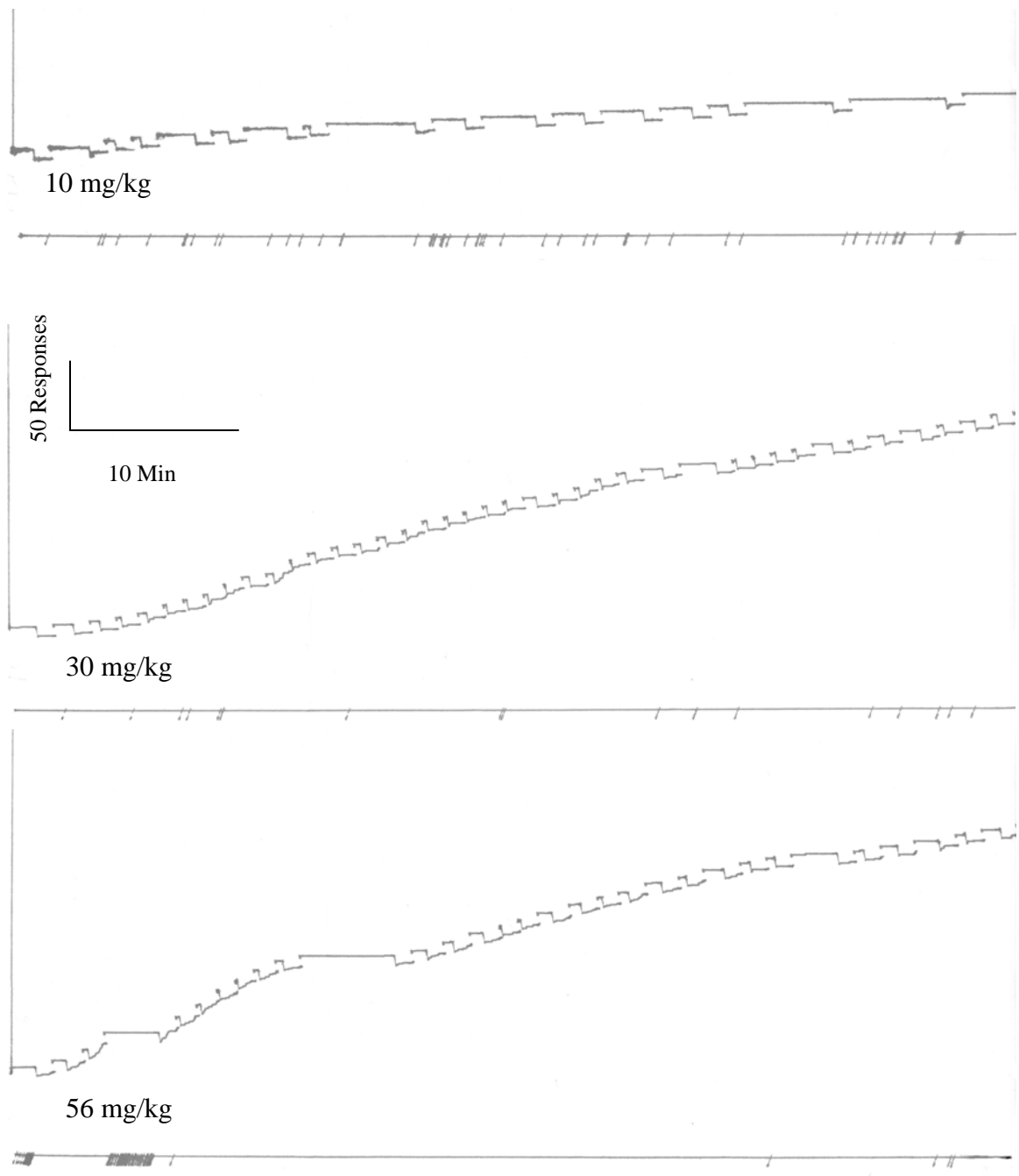


Figure 12. A representative cumulative response record for subject Bup51 following administration of various doses of bupropion (0, 10, 30, and 56 mg/kg).

To further elucidate the effects of bupropion, the data were analyzed for rate-dependent effects on back-lever response rate, timeout response rate, and overall response rate. Figure 13 shows the rate-dependency plots for these three different behaviors for saline and 10 mg/kg injections. In the rate-dependency plots, the percent control is plotted on the y-axis against the control rate of responding plotted on the x-axis. Saline and the 10 mg/kg dose resulted in flat trend lines and majority of points around control levels. Figure 14 contains the rate-dependency plots for the three different behaviors following injections of 30 and 56 mg/kg doses of bupropion. These plots indicate that bupropion was not resulting in rate-dependent effects within the nicotine study.

RESULTS – FOOD-DEPRIVED EXPERIMENT

Figure 15 shows the group averages for the effects of bupropion on food-deprived animals under a FR5 60 s TO schedule of food reinforcement. Bupropion tended to slightly increase the overall response rate at the low dose, while the moderate and high doses resulted in dose-dependent decreases in the overall rate of response. The highest dose of bupropion decreased the number of reinforcers obtained within the session. The effects of the drug on the overall response rate and the number of reinforcers were found to be significant, $F(4, 56) = 11.923, p = .000$, and $F(4, 56) = 12.289, p = .000$, respectively. Bupropion also resulted in a dose dependent increase in the number of timeout responses per reinforcement, $F(4, 56) = 3.000, p = .026$. However, there were no significant effects of drug on back-lever responding. The dose-effect curves for subject Bup9 are shown in Figure 16. The moderate and high dose of bupropion resulted

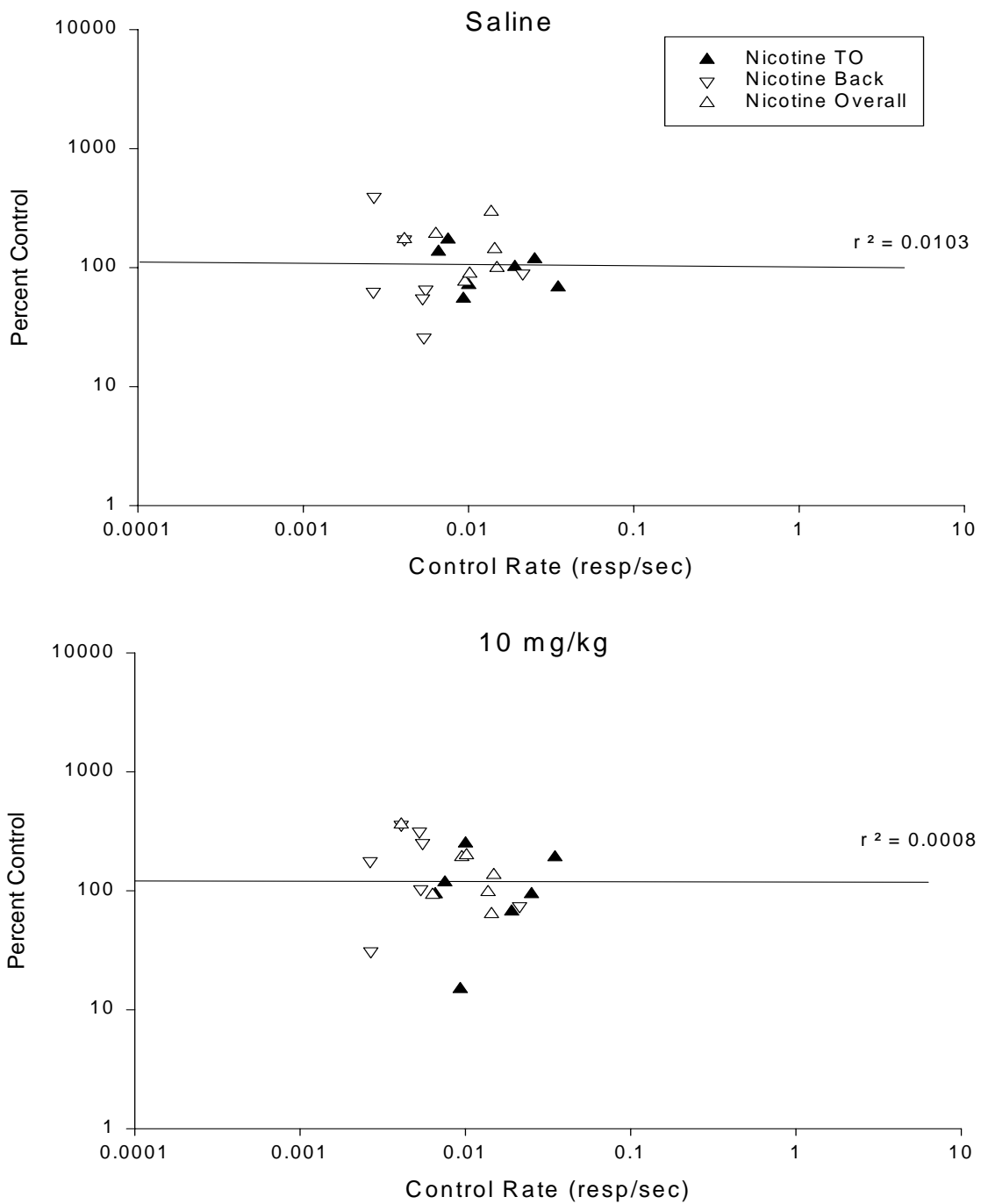


Figure 13. Rate dependency plots of the three ongoing rates of behavior; timeout response rate (Nicotine TO), back lever response rate (Nicotine Back), and the overall response rate (Nicotine Overall). All rates are expressed in terms of the percentage of control plotted against the control rate of the subject. Trend lines are fit to all data points, the r^2 values for the trend lines are illustrated on each graph. The figure illustrates the effects following saline administration and 10 mg/kg dose of bupropion for seven rats self-administering nicotine.

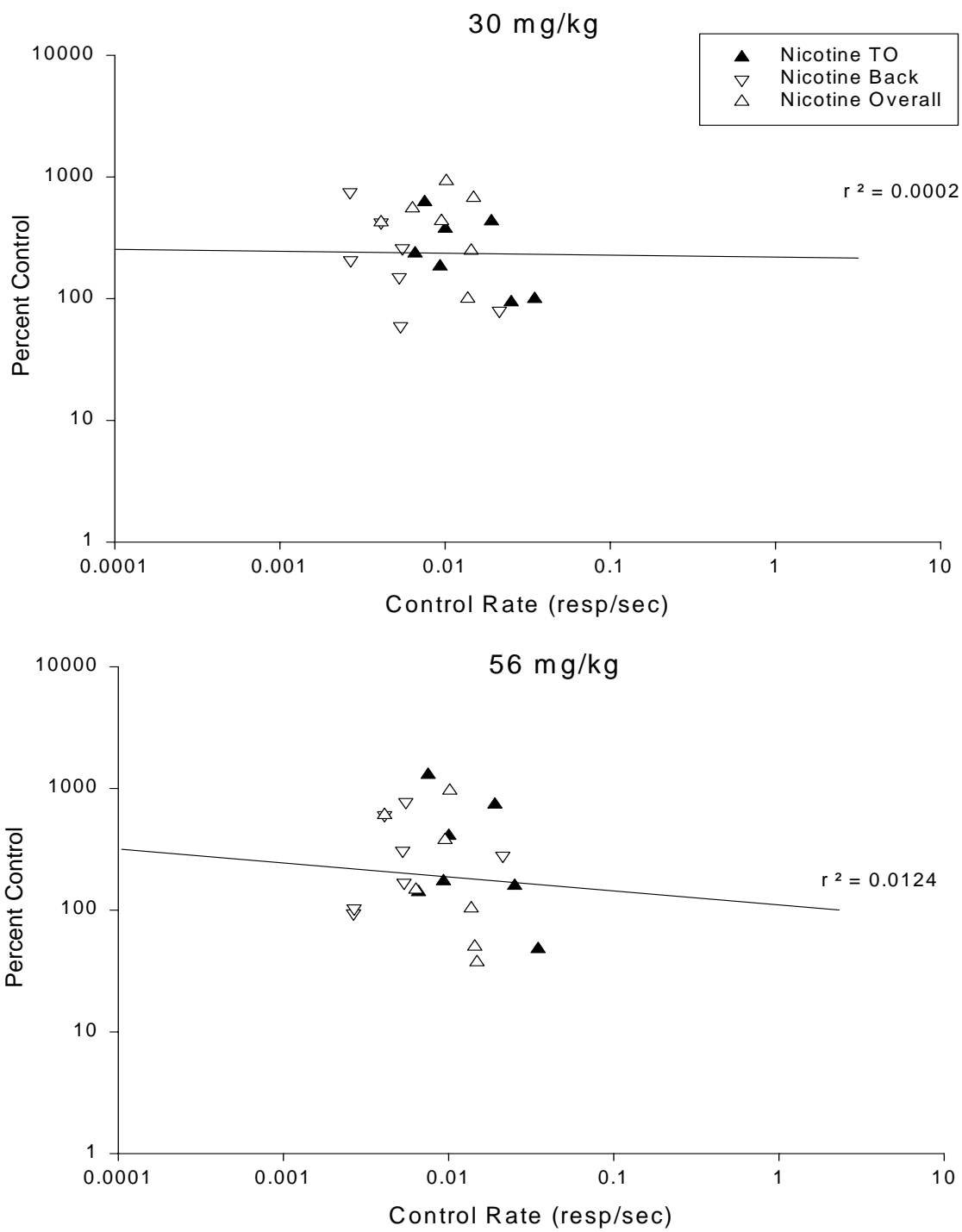


Figure 14. Rate dependency plots for seven rats following the administration of 30, and 56 mg/kg doses of bupropion. For description of the graph, refer to Figure 11.

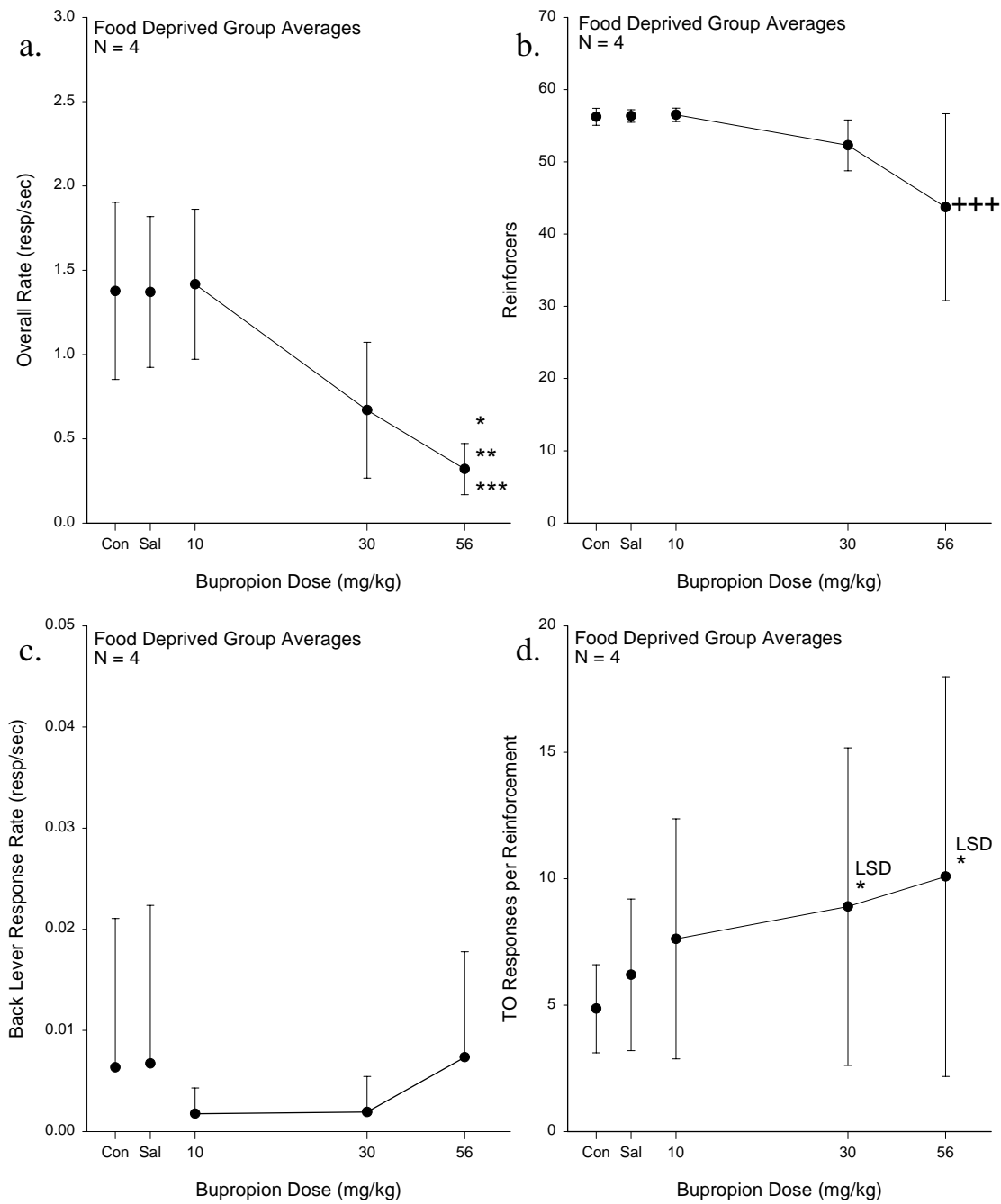


Figure 15. The effects of bupropion (10, 30, 56 mg/kg) on behavior maintained by an FR5 60 s TO schedule of reinforcement in food-deprived animals. The closed circles average for the four rats, the error bars indicate ± 1 standard deviation of the mean. For further description of the graphs, refer to Figure 1.

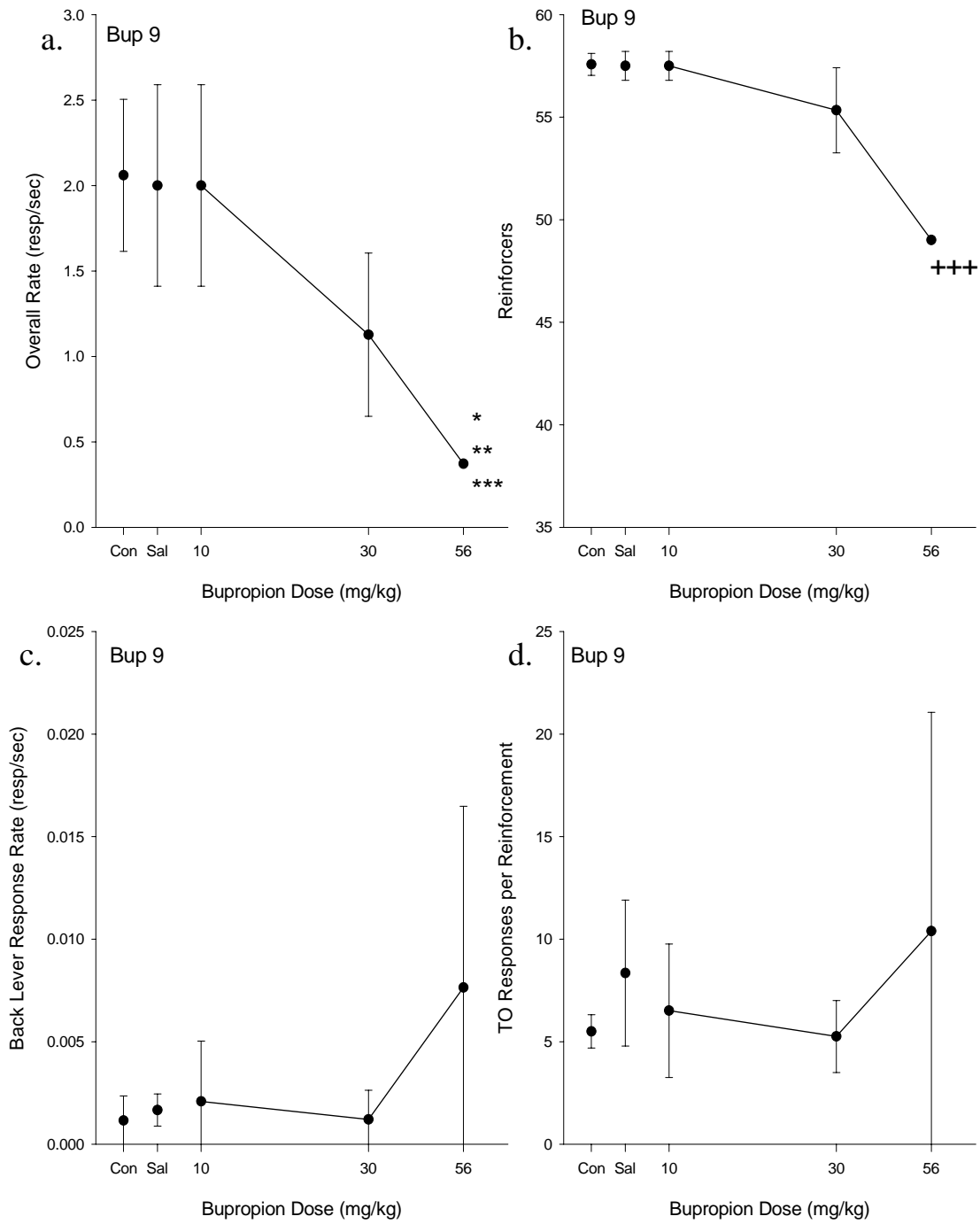


Figure 16. The effects of bupropion (10, 30, 56 mg/kg) on food-maintained behavior under food derivation conditions for subject Bup9. For description of graph, refer to Figure 1.

in dose-dependent decreases in the overall response rate and the number of reinforcers, while having no consistent effect on back-lever responding or timeout responses. A statistical analysis of this subject's data revealed a significant effect of drug on the overall response rate, $F(4, 11) = 6.760$, $p = .005$, and the number of reinforcers obtained within a session, $F(4, 11) = 30.338$, $p = .000$. Figure 17 shows the dose-effect curves for subject Bup10. Again there were significant dose-related effects on overall response rate, $F(4, 4) = 8.049$, $p = .034$, and number of reinforcers, $F(4, 4) = 271.040$, $p = .000$. For subject Bup10 there were also a significant dose-related increases in back-lever responding, $F(4, 4) = 66.911$, $p = .001$, and timeout responses, $F(4, 4) = 6.959$, $p = .043$.

Figure 18 contains the dose-effect curves for subject Bup11. There was again significant dose-dependent decreases on the overall response rate ($F(4, 16) = 9.131$, $p = .000$.) and the number of reinforcers ($F(4, 16) = 47.669$, $p = .000$.) for this subject, while there was no significant effect of the drug on the back-lever responding or timeout responses. Figure 19 shows the effects of bupropion on the four dependent measures for subject Bup12. For this subject there was again a significant effect of the drug on the overall response rate and the number of reinforcers obtained, while there was no significance of the drug's effects on back-lever responding or timeout responses. There was a significant rate-decreasing effect of bupropion on the overall response rate, $F(4, 10) = 6.381$, $p = .008$, as well as a drug decreasing effect on the number of reinforcers obtained within a session, $F(4, 16) = 8.877$, $p = .003$.

Figures 20, 21, and 22 contain representative cumulative response records of subject Bup10 from control, saline, and the three different doses of bupropion. The much steeper slope of the lines indicates a higher rate of behavior maintained under the food-

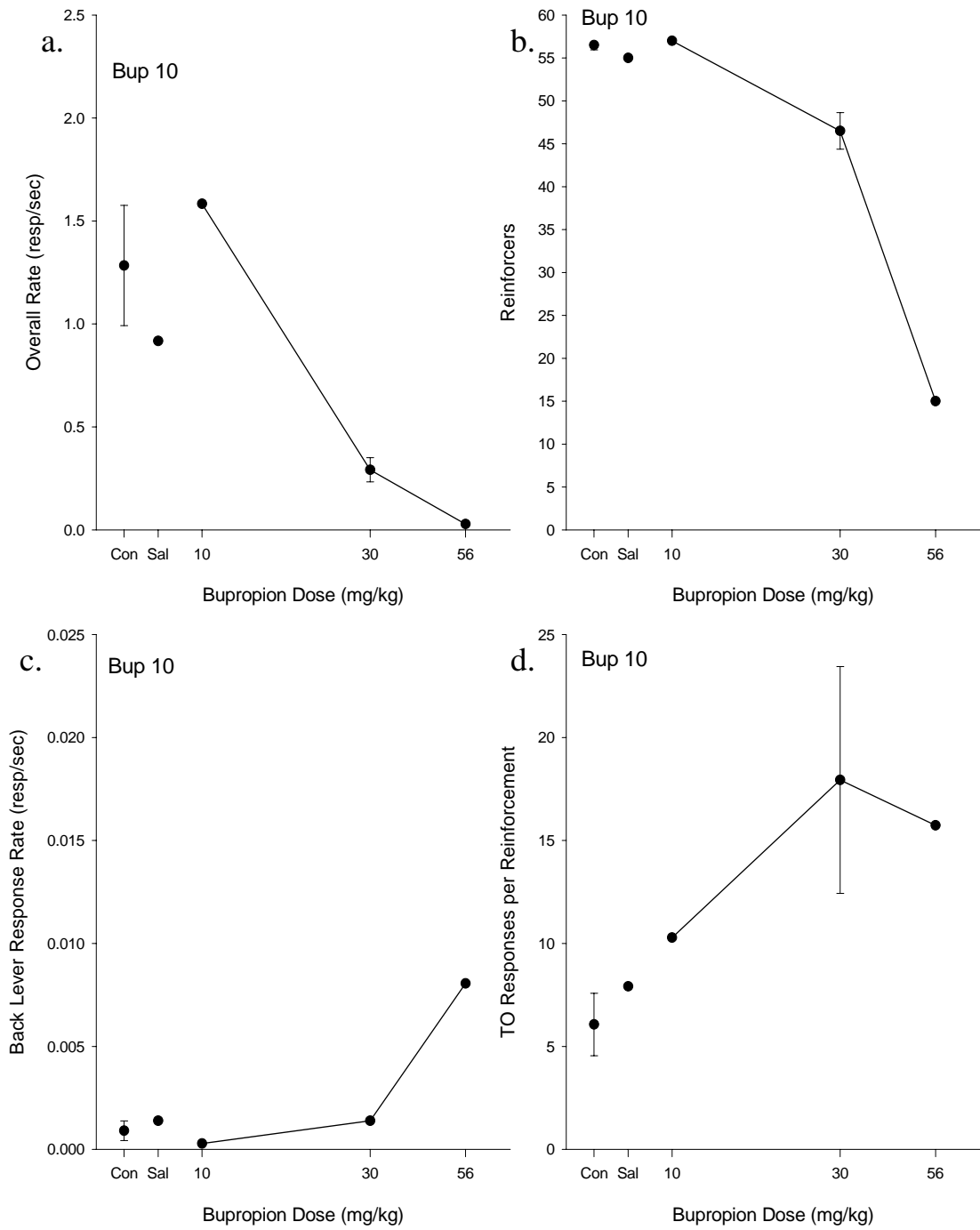


Figure 17. The effects of bupropion (10, 30, 56 mg/kg) on food-maintained behavior under food derivation conditions for subject Bup10. For description of the graph, refer to Figure 1.

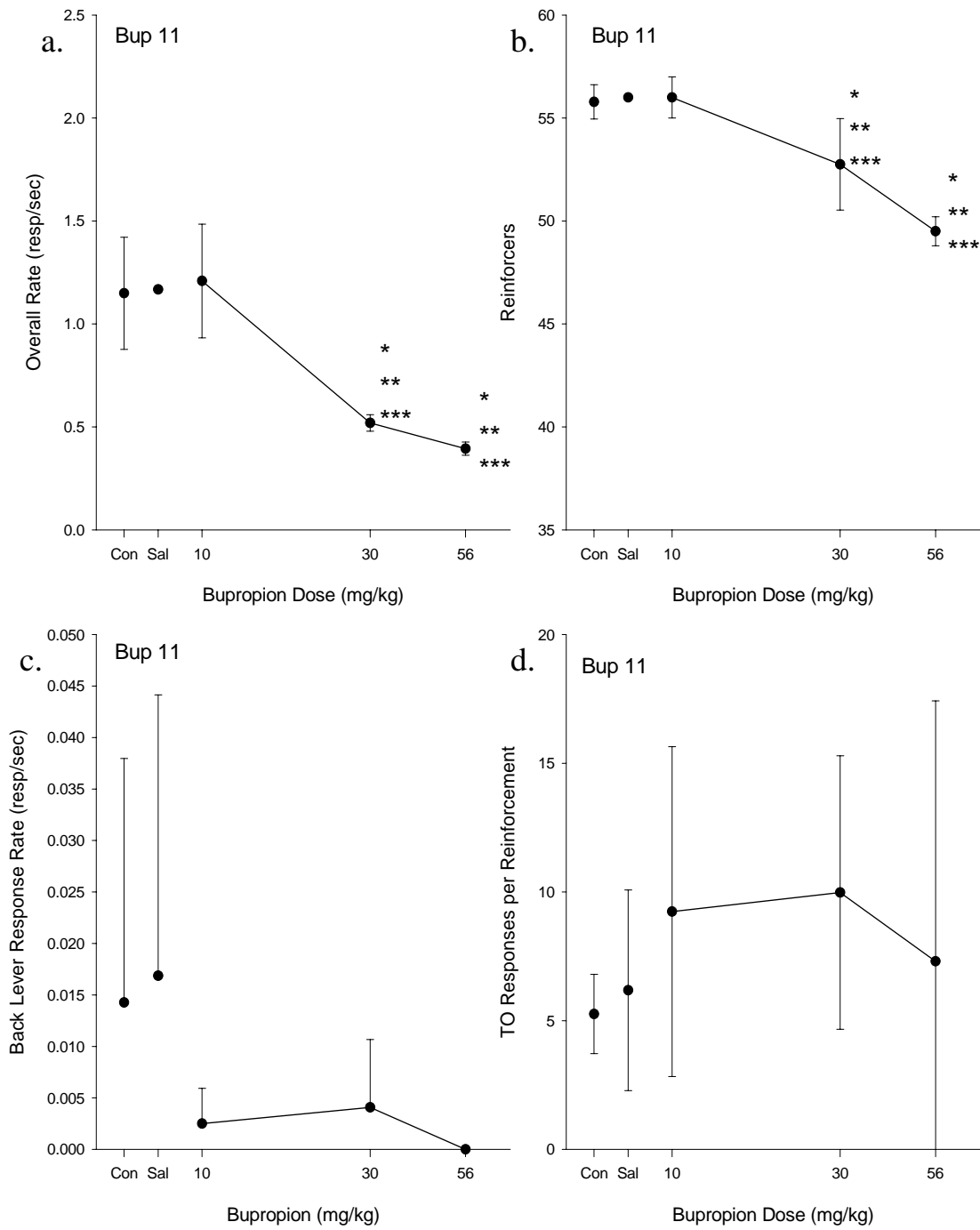


Figure 18. The effects of bupropion (10, 30, 56 mg/kg) on food-maintained behavior under food derivation conditions for subject Bup11. For description of graph, refer to Figure 1.

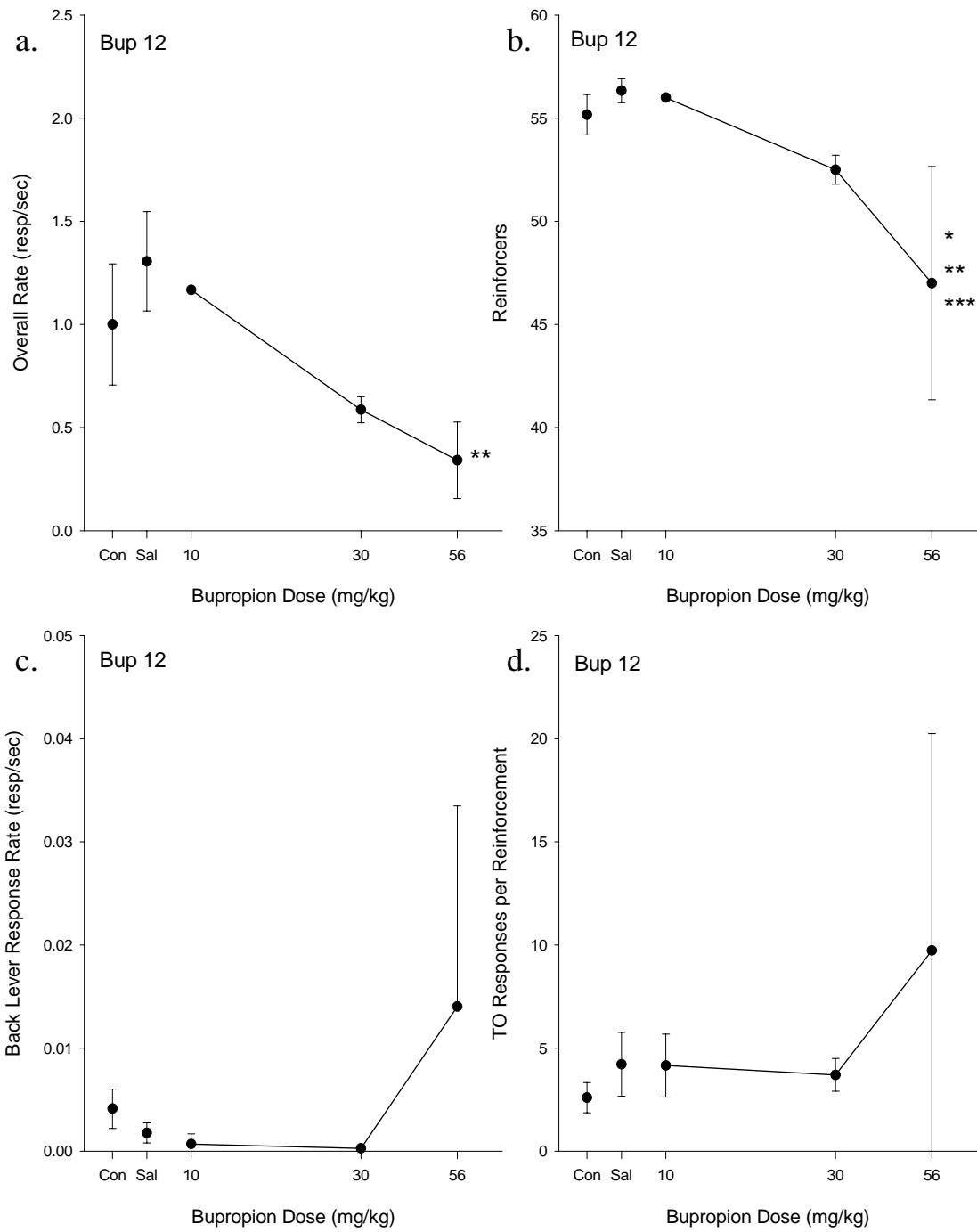


Figure 19. The effects of bupropion (10, 30, 56 mg/kg) on food-maintained behavior under food derivation conditions for subject Bup12. For description of graph, refer to Figure 1.

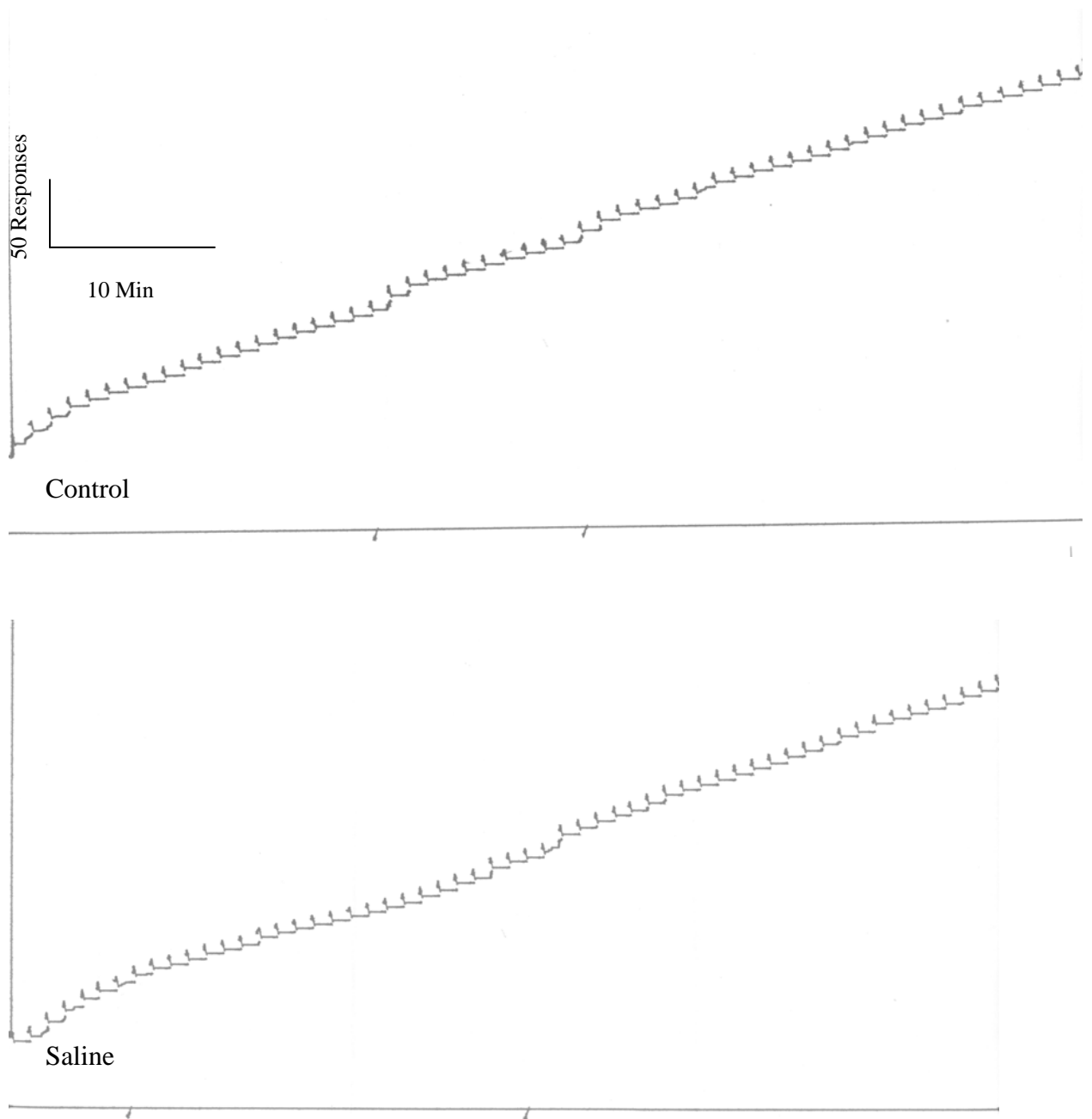


Figure 20. Cumulative response record of a representative subject's (Bup10) behavior on an FR5 60 s TO schedule of food reinforcement under control and saline conditions. Descriptions of the cumulative records are found in Figure 9.

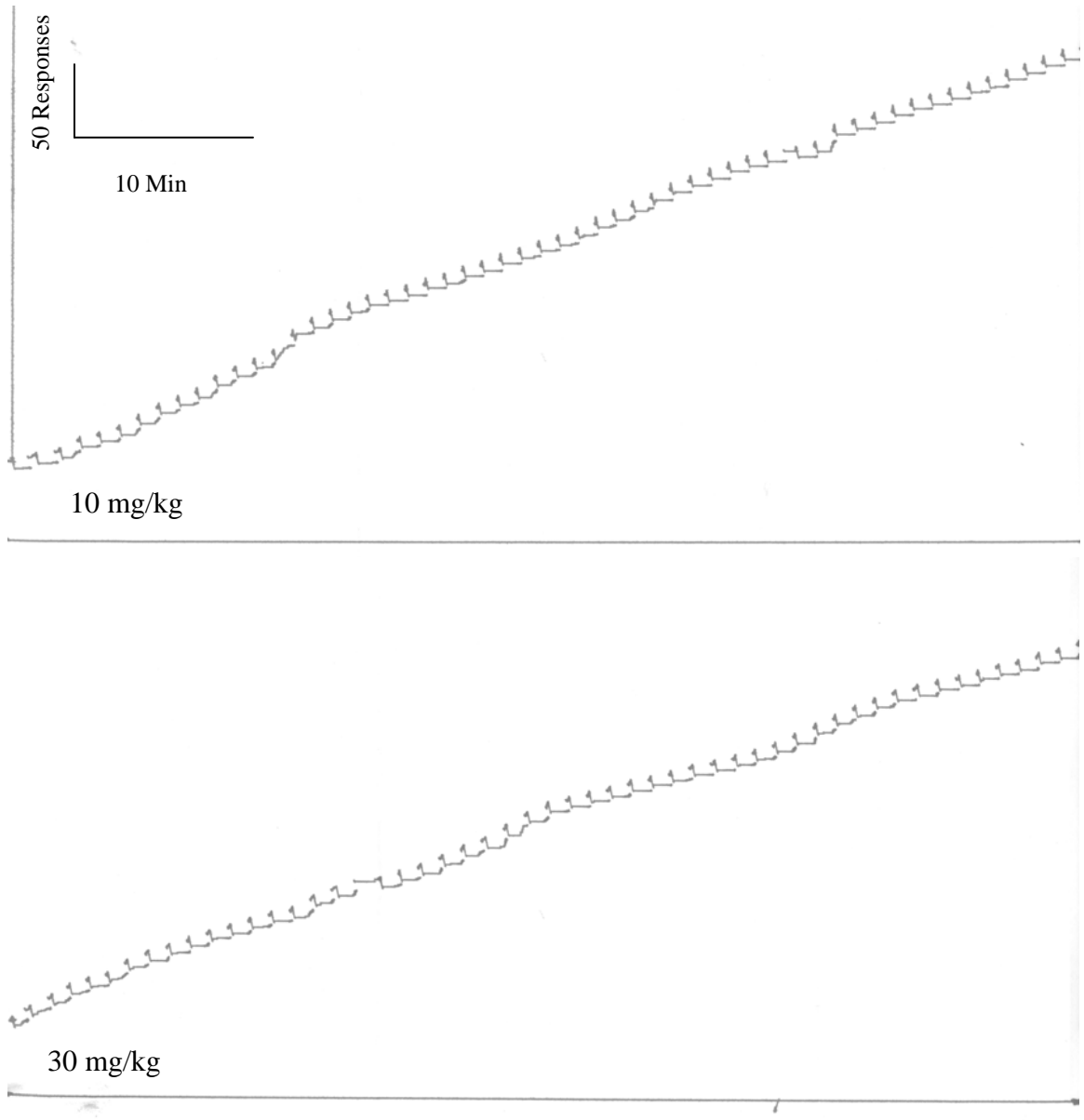


Figure 21. Cumulative response record of a representative animal's (Bup10) behavior on an FR5 60 s TO schedule of food reinforcement under drug conditions. Descriptions of the cumulative records are found in Figure 9.

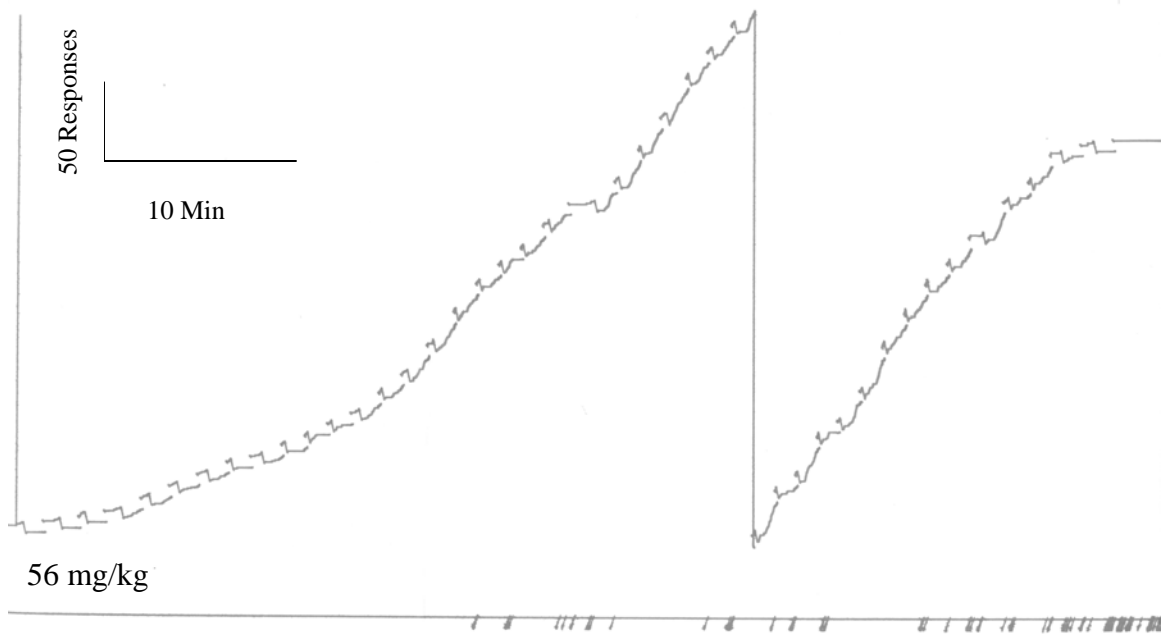


Figure 22. Cumulative response record of a representative animal's (Bup10) behavior on an FR5 60 s TO schedule of food reinforcement following administration of 56 mg/kg dose of bupropion. Descriptions of the cumulative records are found in Figure 9.

deprived conditions compared to the nicotine study. In addition, the behavior was fairly consistent across the low and moderate doses. There was a slight disruption in responding at the 30 mg/kg dose of the drug, indicated by a decrease in the slope of the line indicating longer run times compared to control conditions. A small increase in the number of timeout responses is shown by the increase in the slope of the line while the pen is displaced near the end of the timeout periods. At the 56 mg/kg dose (Figure 22) of the drug, a large disruption in responding can be seen. The decrease in the overall response rate is indicated by an increase in the run times and, as a result, a decrease in the slope of the line compared to control levels. The increase in the number of timeout responses is shown by the dramatic increase in the slope of the line while the pen was displaced. The increase in back-lever responding is indicated by the increase in the number of pen displacements on the event line.

The rate-dependency plots for the food-deprived study are shown in Figures 23 and 24. Again, the percent control is plotted on the y-axis against the control rate that is plotted on the x-axis. Figure 23 shows the rate-dependency plots following saline and the 10mg/kg administration of bupropion. Saline and the low dose of bupropion did not result in a rate-dependent effect on behavior; this is illustrated by the majority of points falling around 100 percent. There was very little deviation from control rates although the 10 mg/kg dose of bupropion did tend to decrease back-lever responding. Figure 24 illustrates the rate-dependency plots for the effects of the two highest doses of bupropion on the three behaviors. The moderate dose of bupropion again did not result in any rate-dependent effects as indicated by the relatively flat trend line fit to the data points. The rate dependency plot for the 56 mg/kg dose of bupropion indicates a rate-dependent

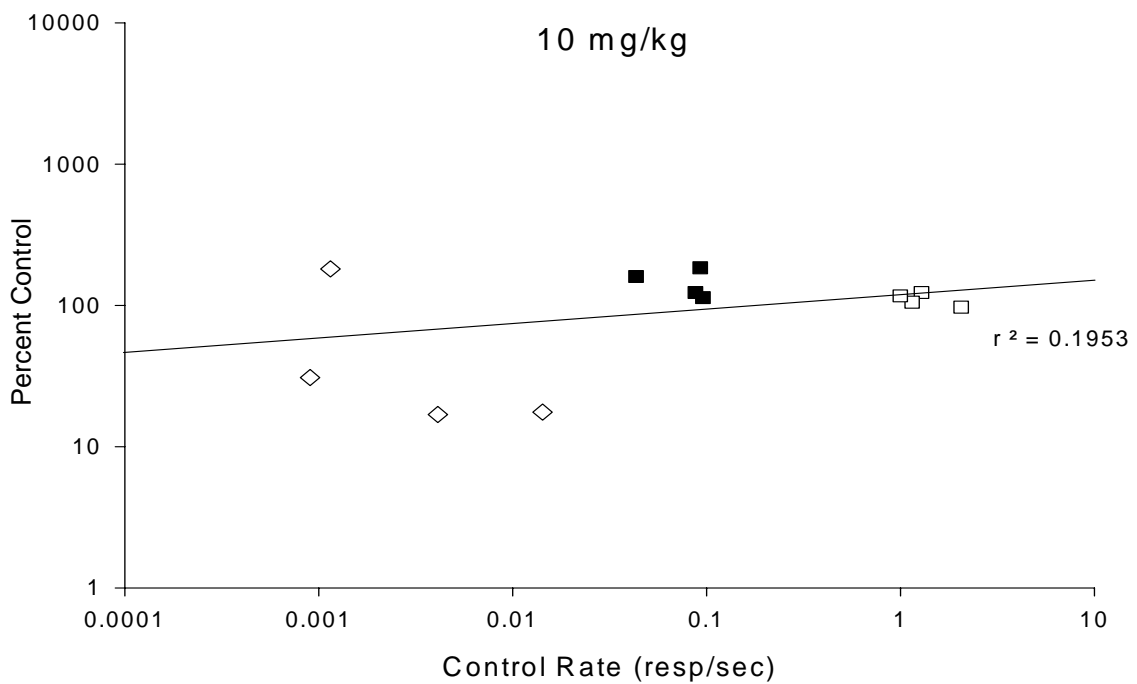
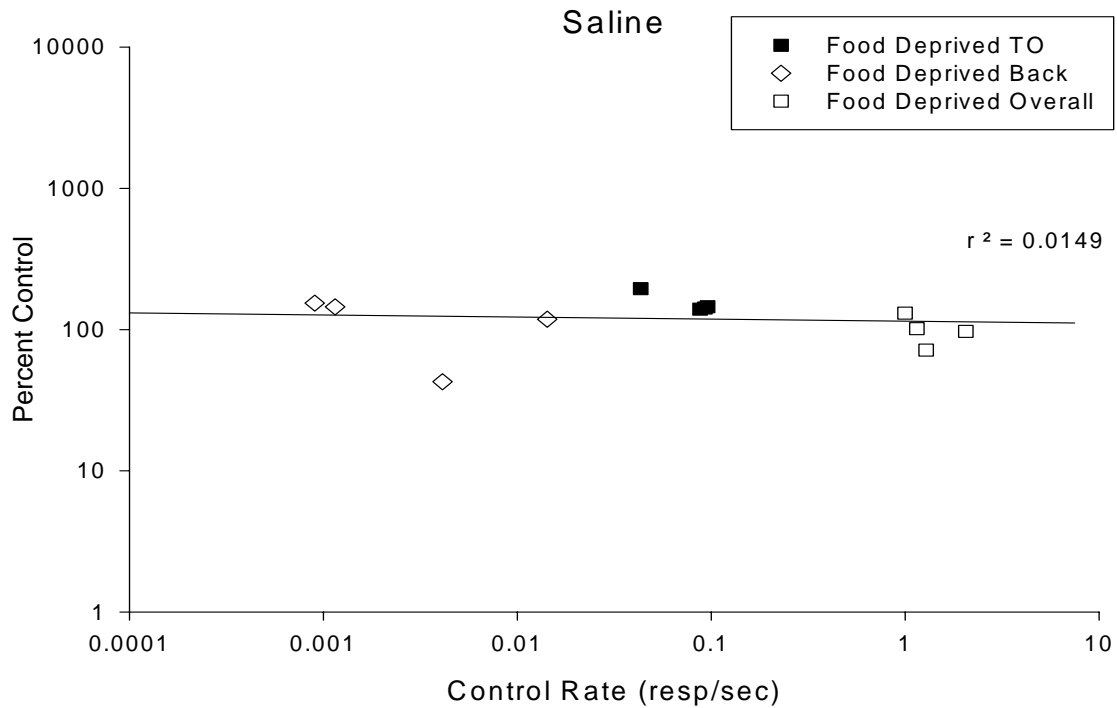


Figure 23. Rate dependency plots of the three behaviors; timeout response rate (Food Deprived TO), back lever response rate (Food Deprived Back), and the overall response rate (Food Deprived Overall). All rates are expressed in terms of the percentage of control plotted against the control rate of the subject. Trend lines were fit to all data points; the r^2 values for the trend lines are illustrated on each graph. The figure illustrates the effects following saline administration and 10 mg/kg dose of bupropion for four rats on an FR5 60 s TO of food reinforcement under deprivation conditions.

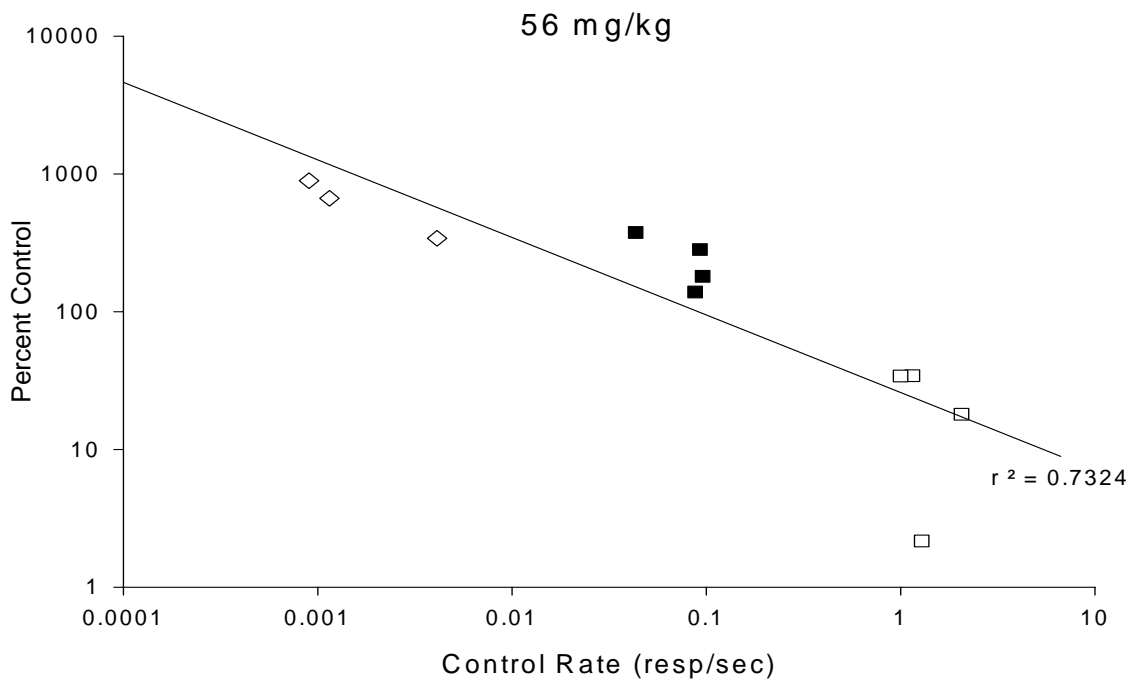
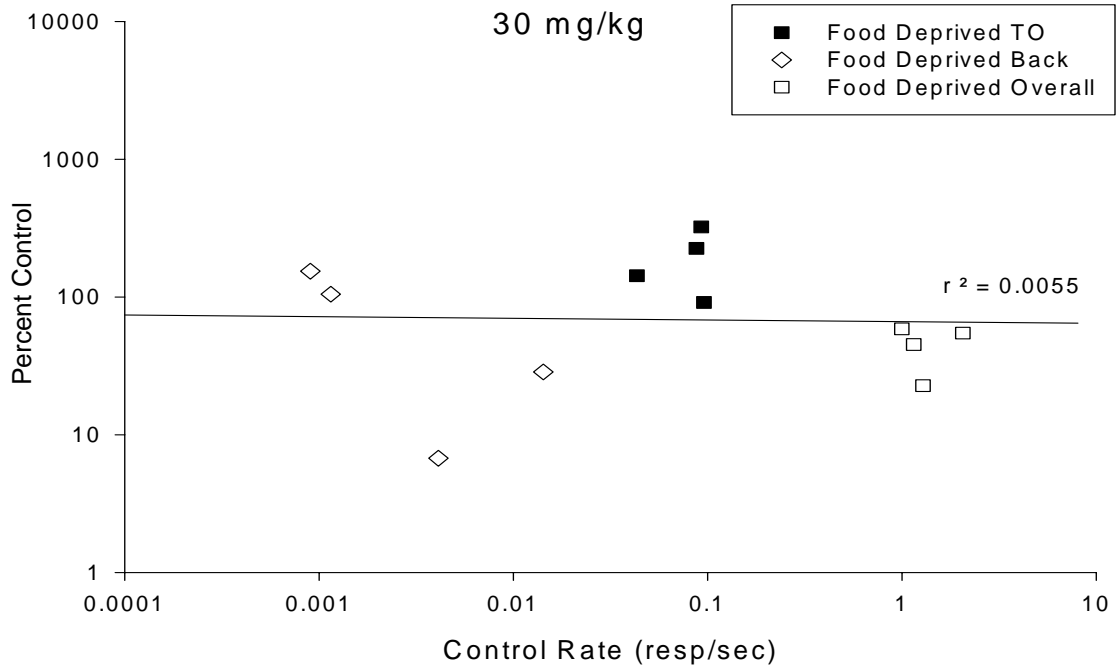


Figure 24. Rate dependency plots for four rats on the FR5 60 s TO schedule of food reinforcement under deprivation conditions, following the administration of 30, and 56 mg/kg doses of bupropion. For description of the graph, refer to Figure 21.

effect of the drug. The rate-dependent effect of the highest dose of the drug is demonstrated by the high amount of variance accounted for by the regression line fit to the data ($r^2 = .7324$). The 56 mg/kg dose of the drug tended to increase the lowest and moderate rates of responding (back-lever responding and timeout responding, respectively), while decreasing the highest rate of responding (overall response rate).

RESULTS-FOOD-SATIATED EXPERIMENT

The group averages for the dependent measures of the four subjects in the food-satiated study are shown in Figure 25. Bupropion tended to slightly increase the overall response rate and the number of reinforcers obtained for the group for both the 10 and 30 mg/kg doses, while the highest dose of 56 mg/kg decreased the overall response rate and the number of reinforcers for the group. The effect of dose on the overall response rate was found to be significant ($F(4, 53) = 2.799, p = .030$). The effect of the drug on the number of reinforcers obtained was also found to be significant ($F(4, 53) = 9.493, p = .000$). Bupropion had no consistent effect on back-lever responding. The number of timeout responses for the group significantly increased at the medium and high doses of the drug, $F(4, 51) = 5.122, p = .002$.

Figure 26 illustrates the effects of bupropion on the four dependent measures for subject Bup60. Bupropion increased both the overall response rate and the number of reinforcers obtained within the session when compared to saline at the 10 and 30 mg/kg doses; these effects were found to be significant, $F(4, 9) = 4.853, p = .023$, and $F(4,9) = 7.599, p = .006$, respectively. The high dose of bupropion tended to increase both the back-lever response rate as well as the number of timeout responses. The effect of the drug on the back-lever response rate was significant ($F(4, 9) = 7.433, p = .006$). The

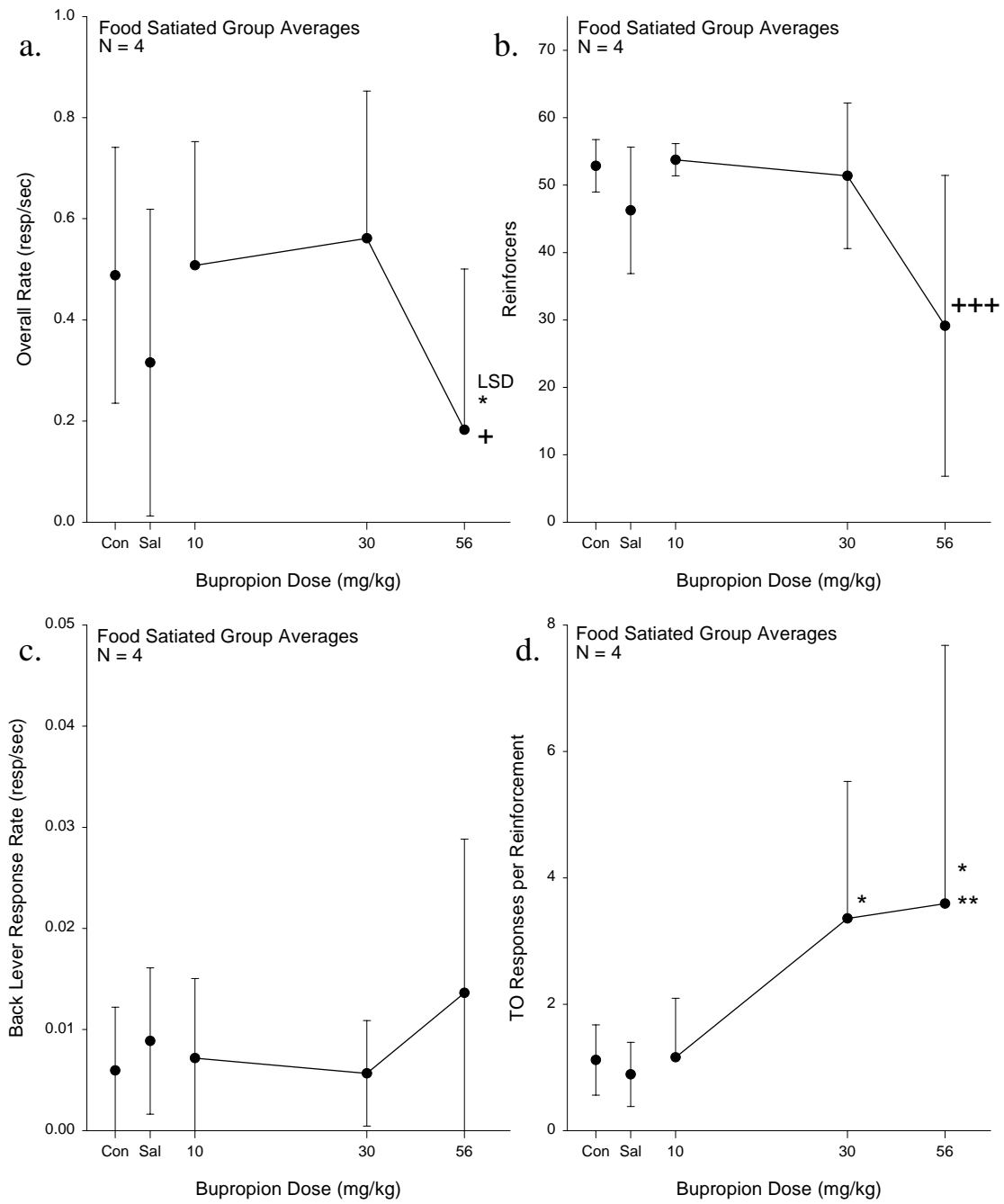


Figure 25. The effects of bupropion (10, 30, 56 mg/kg) on behavior maintained by an FR3 60 s TO schedule of reinforcement in four food satiated animals. The closed circles are averages of four rats, the error bars indicate ± 1 standard deviation of the mean. For further description of the graphs, refer to Figure 1.

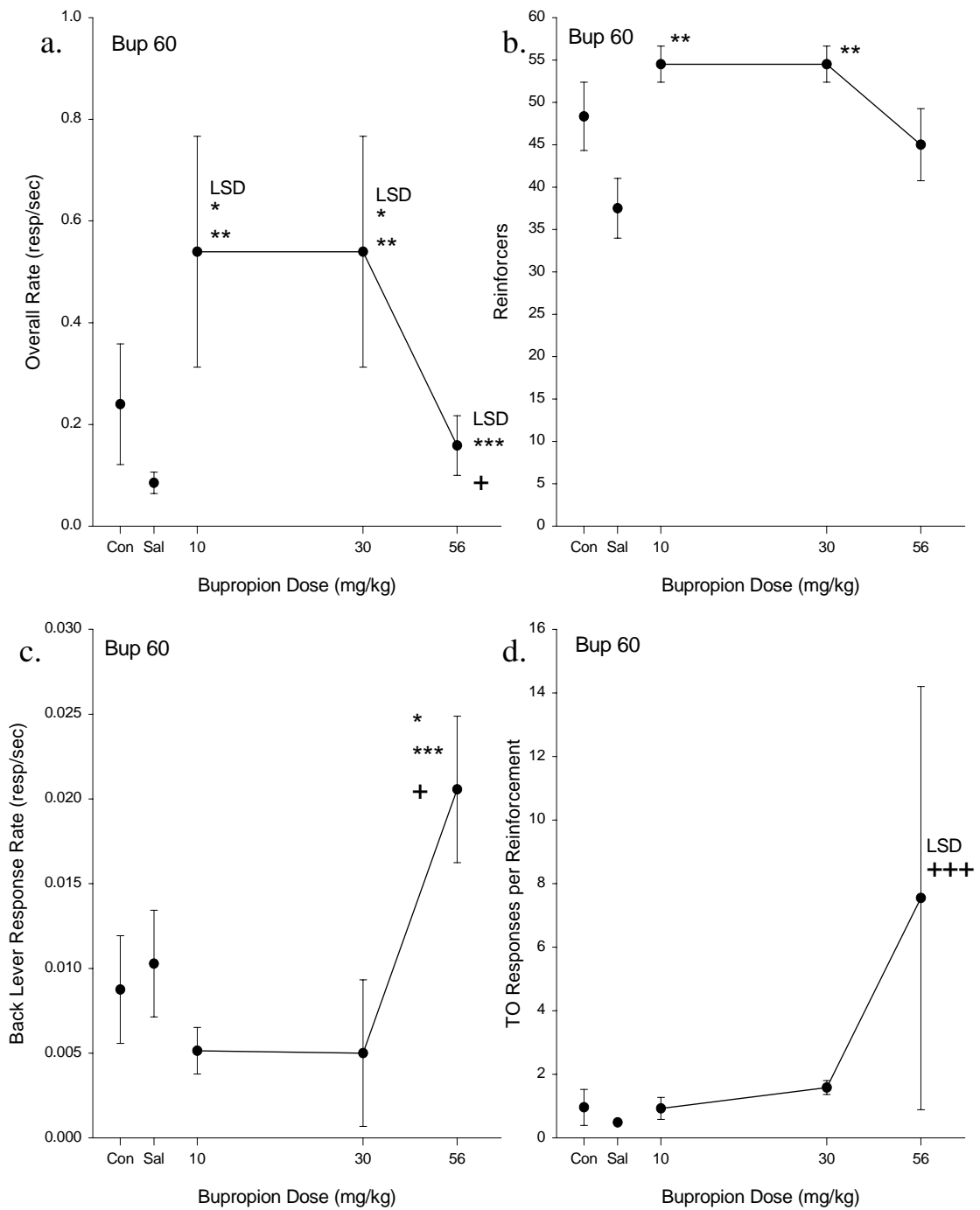


Figure 26. The effects of bupropion on food-maintained behavior under the food satiated condition for subject Bup60. For description of graph, refer to Figure 1.

effect of the drug on the number of timeout responses was also significant ($F(4, 9) = 7.599, p = .006$).

Figure 27 shows the influence of the drug on four dependent variables for subject Bup61. Bupropion increased the overall response rate at the medium dose while the higher dose of the drug decreased response rate. These effects were found to be statistically significant ($F(4, 9) = 4.533, p = .028$). The high dose of bupropion had a significant decreasing effect on the number of reinforcers obtained within session ($F(4, 9) = 8.880, p = .003$). Bupropion increased back-lever responding at the high dose of the drug ($F(4, 9) = 6.589, p = .009$). Bupropion also tended to increase the number of timeout responses per reinforcement at the moderate dose of the drug although this effect was not significant ($F(4, 9) = 2.198, p = .150$).

Figure 28 depicts the effects of the drug for the four dependent measures for subject Bup62. Bupropion had no consistent effects on the overall response rate, number of reinforcers, and the back-lever response rate, although there was a slight decrease in the back-lever response rate at the largest dose of bupropion for subject Bup62, $F(4, 9) = .081, p = .986, F(4, 9) = .509, p = .731, F(4, 9) = .306, p = .867$, respectively. Bupropion did have a dose-dependent increase in the number of timeout responses per reinforcement; this effect was found to be significant, $F(4, 9) = 14.315, p = .001$.

Figure 29 illustrates the effects of bupropion on the four dependent measures for Bup63. Bupropion had no significant effect on the overall response rate, with the exception that the high dose completely suppressed responding for this subject $F(4, 9) = 1.608, p = .254$. Bupropion resulted in a significant dose-dependent decrease in the number of reinforcers obtained within the session ($F(4, 9) = 19.105, p = .000$). The drug

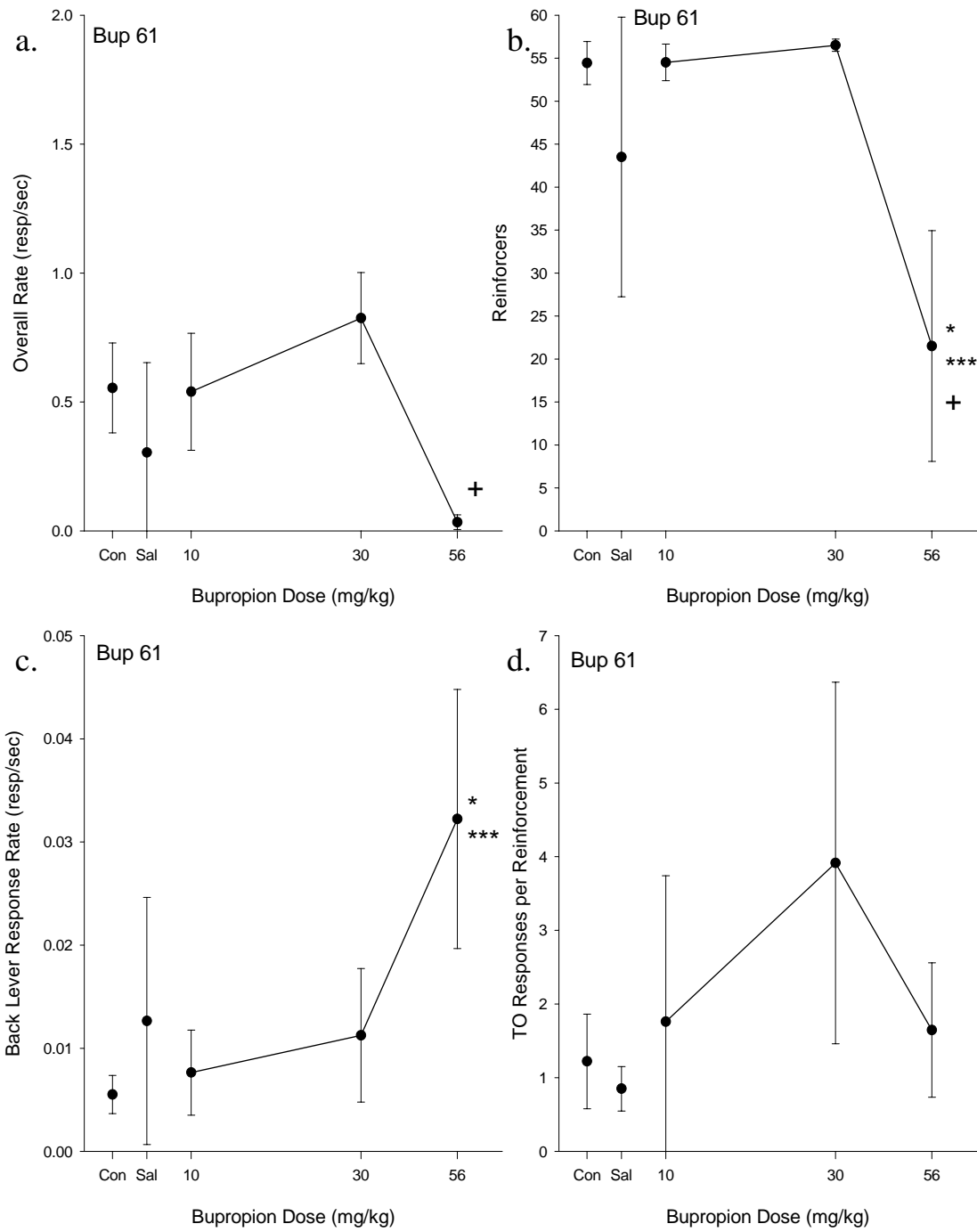


Figure 27. The effects of bupropion (10, 30, 56 mg/kg) on food-maintained behavior under the food satiated condition for subject Bup61. For description of graph, refer to Figure 1.

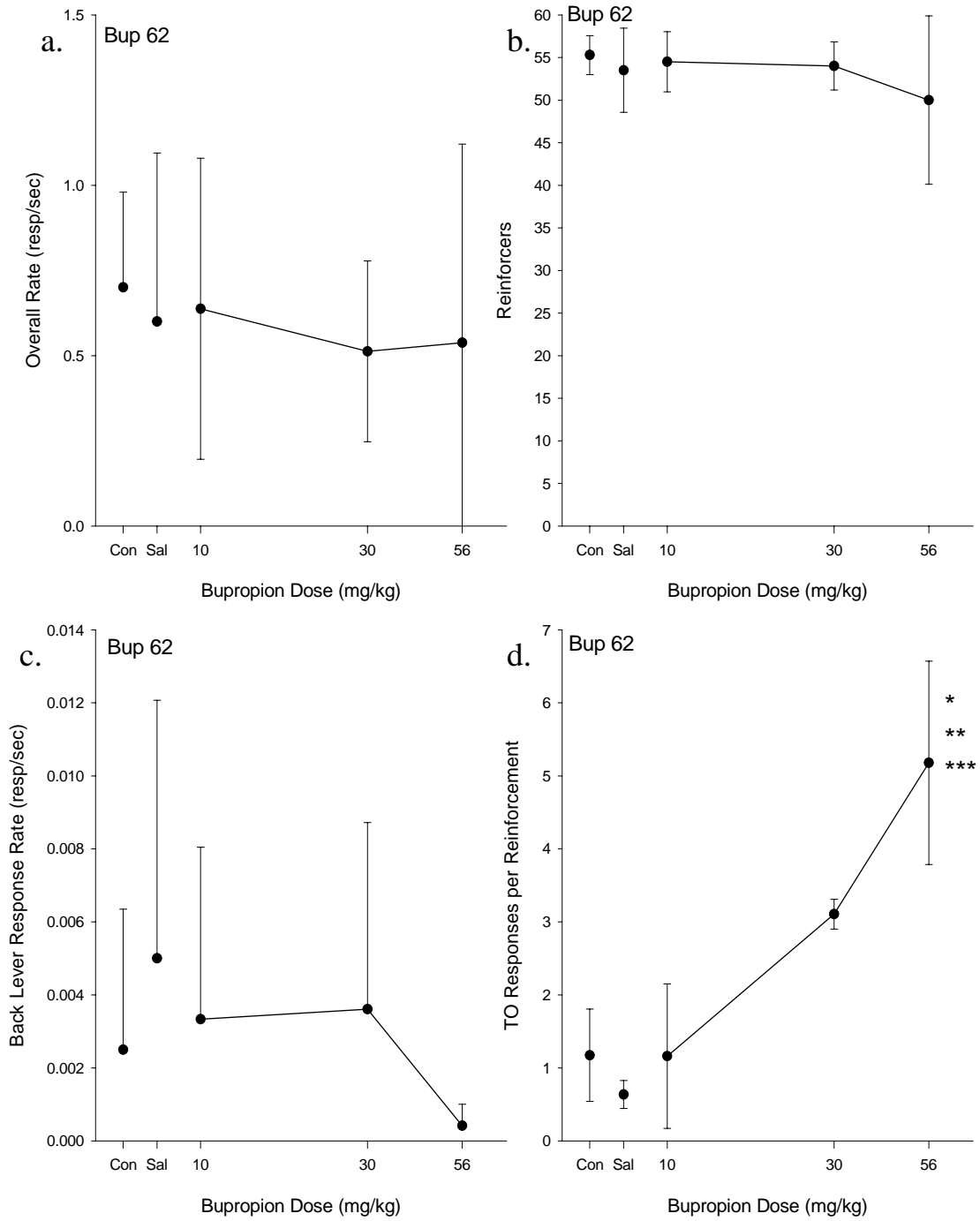


Figure 28. The effects of bupropion (10, 30, 56 mg/kg) on food-maintained behavior under the food satiated condition for subject Bup62. For description of graph, refer to Figure 1.

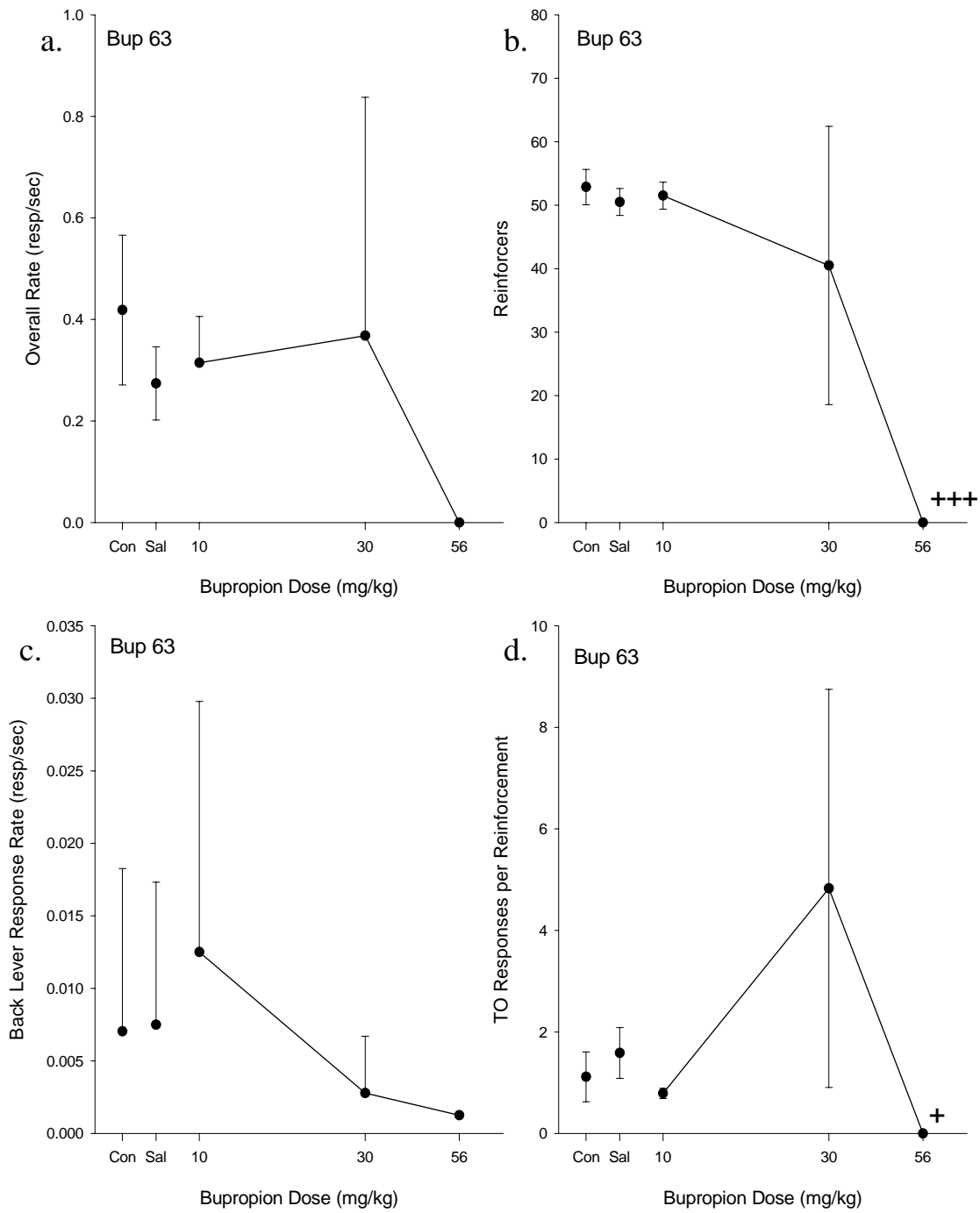


Figure 29. The effects of bupropion (10, 30, 56 mg/kg) on food-maintained behavior under food satiated conditions for subject Bup61. For description of graph, refer to Figure 1.

did not have consistent effects on back-lever responding. Bupropion resulted in an inverted U-shaped dose-response curve for the number of timeout responses for this subject ($F(4, 9) = 3.814, p = .044$). The behavior under saline and drug conditions for subject Bup60 best represented the group averages, so cumulative response records of this subject are shown in Figures 30 and 31. The increase in overall response rate at the 10 and 30 mg/kg doses is illustrated by the increase in slope seen in the two cumulative response records when compared to saline and control conditions. The increase in timeout responses can also be seen by the increase in the slope of the line while the pen is in the displaced position. The decrease in the overall response rate at the highest dose of bupropion is illustrated by the decrease in the slope of the line near the end of the session.

The rate-dependency plots for the food-satiated group are illustrated in Figures 32 and 33. The rate-dependency plots have the percent control on the y-axis plotted against the control rate plotted on the x-axis. Figure 32 shows the rate-dependency plots under saline and the 10 mg/kg dose of bupropion. The rate-dependency plots in Figure 32 again illustrate that saline and the lowest dose of bupropion are not affecting behavior in a rate-dependent manner, as indicated by points for all behaviors in both graphs falling around 100 percent. Figure 33 contains the rate-dependency plots of the behaviors following the administration of the moderate and highest doses of bupropion. The small r^2 values for the both the 30 and 56 mg/kg doses indicate that bupropion did not have rate-dependent effects. The 30 mg/kg graph shows that at the moderate dose of bupropion tested points continued to stay around 100 percent, with only the timeout responding showing a slight increase from 100 percent. Data following the administration of the 56 mg/kg dose

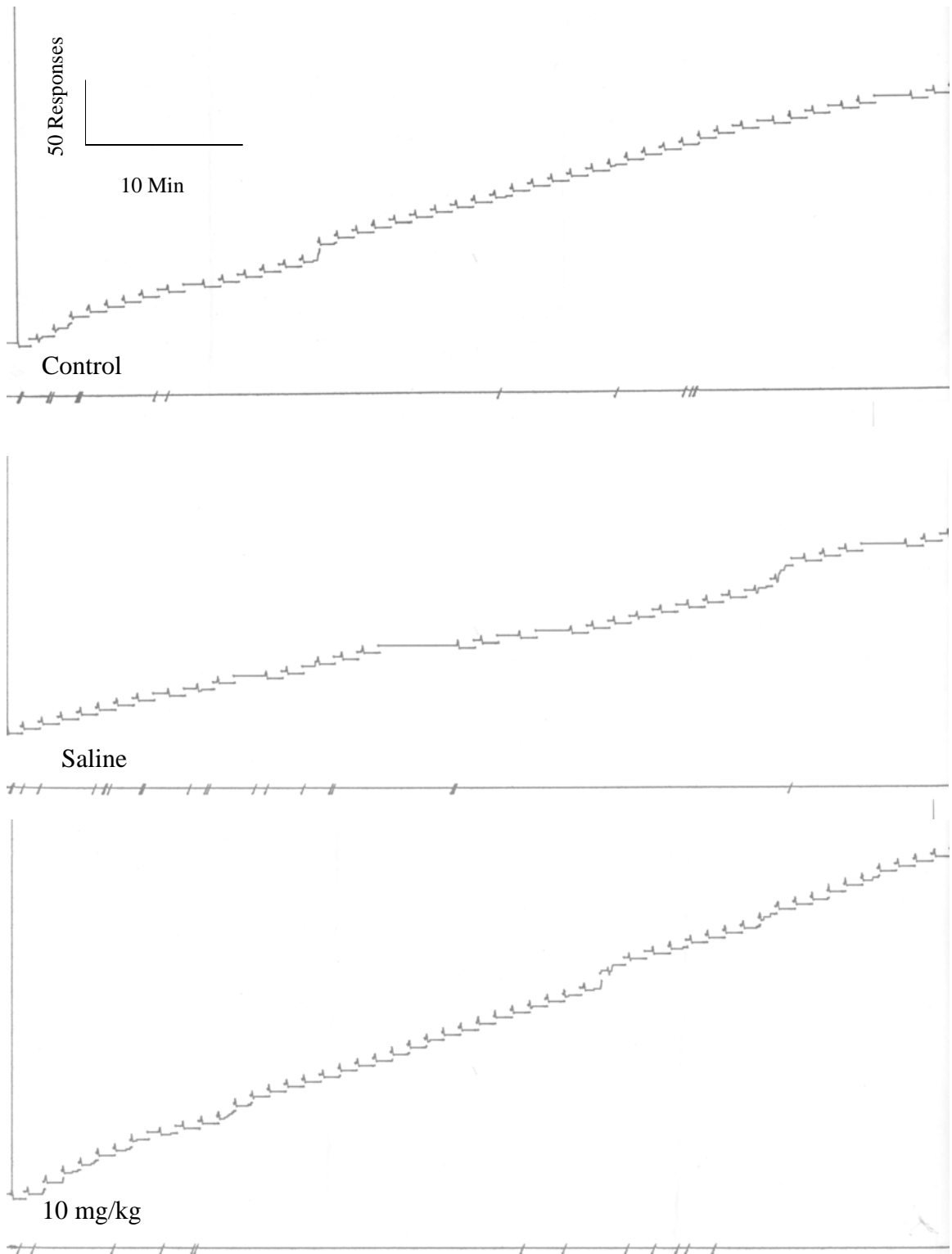


Figure 30. Cumulative response record of subject's Bup60 responding on an FR3 60 s TO schedule of food reinforcement under control, saline, and 10 mg/kg drug conditions. Descriptions of the cumulative records are found in Figure 9.

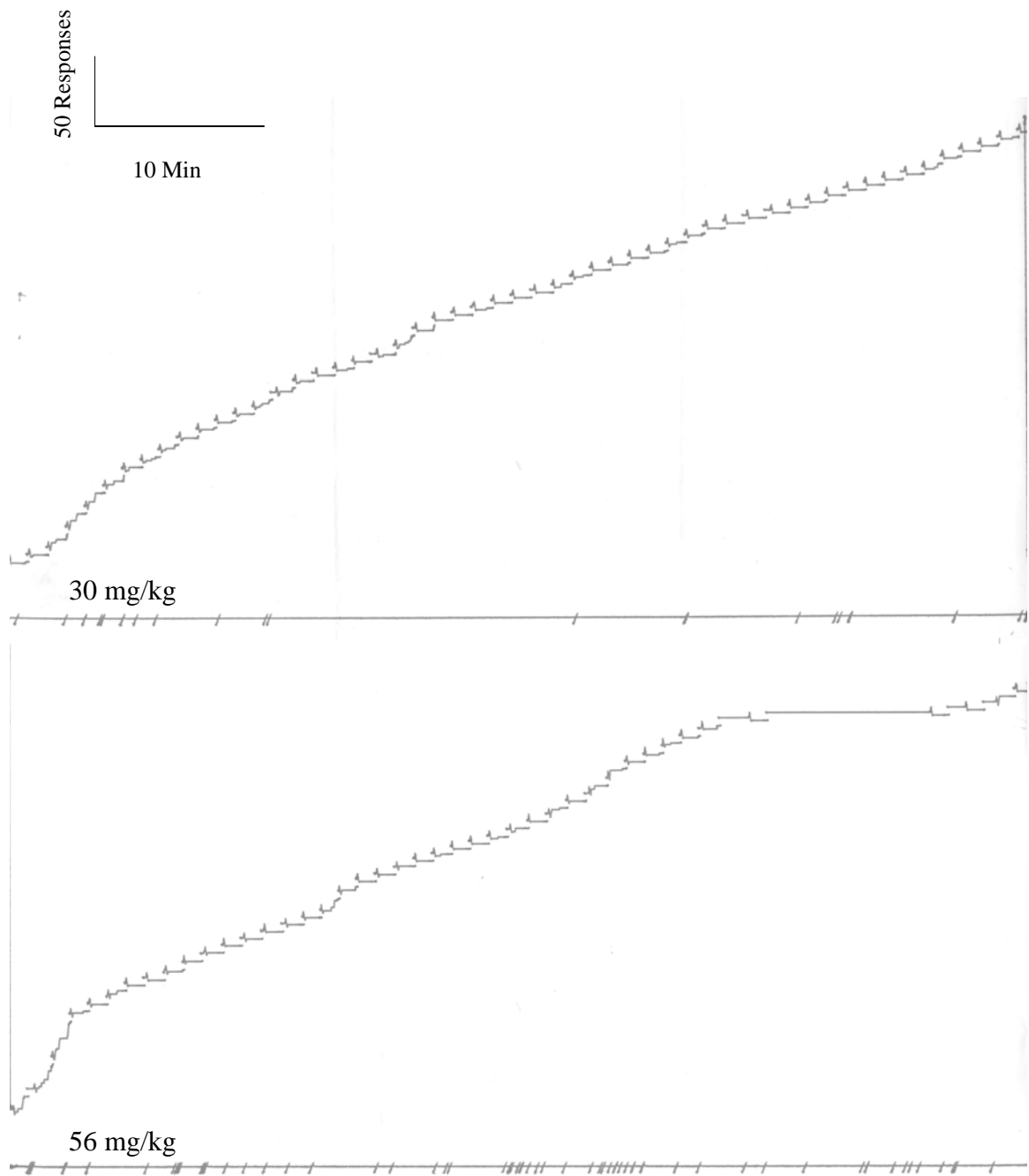


Figure 31. Cumulative response record of subject's Bup60 responding on an FR3 60 s TO schedule of food reinforcement following the administration of 30 and 56 mg/kg doses of bupropion. Descriptions of the cumulative records are found in Figure 9.

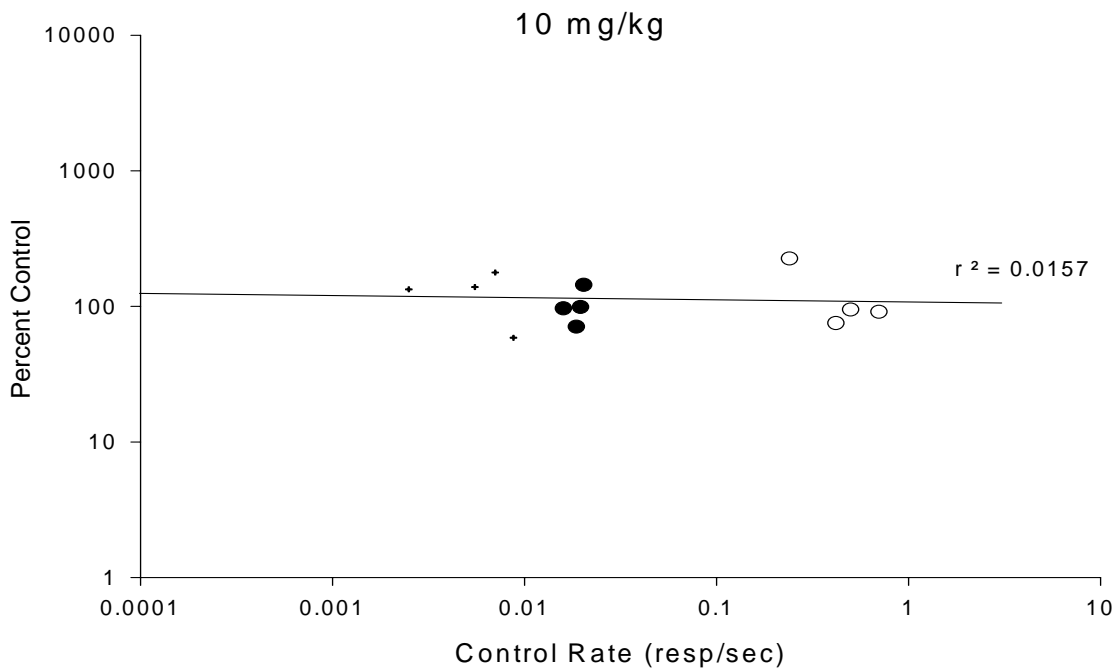
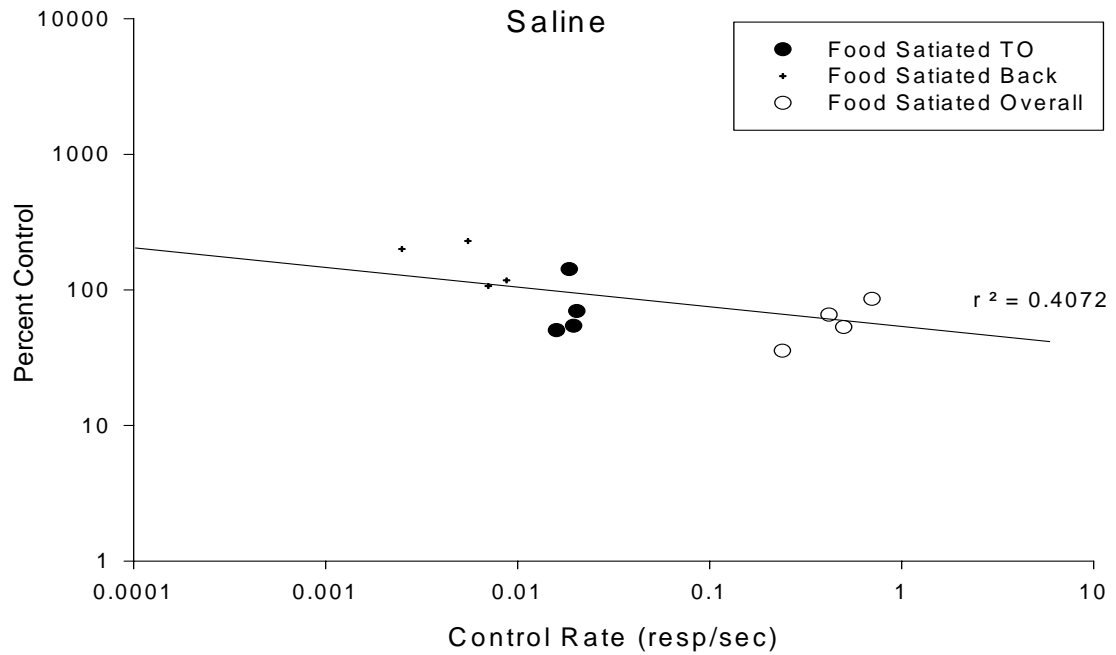


Figure 32. Rate dependency plots of the three behaviors; timeout response rate (Food Satiated TO), back lever response rate (Food Satiated Back), and the overall response rate (Food Satiated Overall). All rates are expressed in terms of the percentage of change from control plotted against the control rate of the subject. Trend lines are fit to all data points; the r^2 values for the trend lines are illustrated on each graph. The figure illustrates the effects following saline administration and 10 mg/kg dose of bupropion for four rats on an FR3 60 s TO of food reinforcement under satiated conditions.

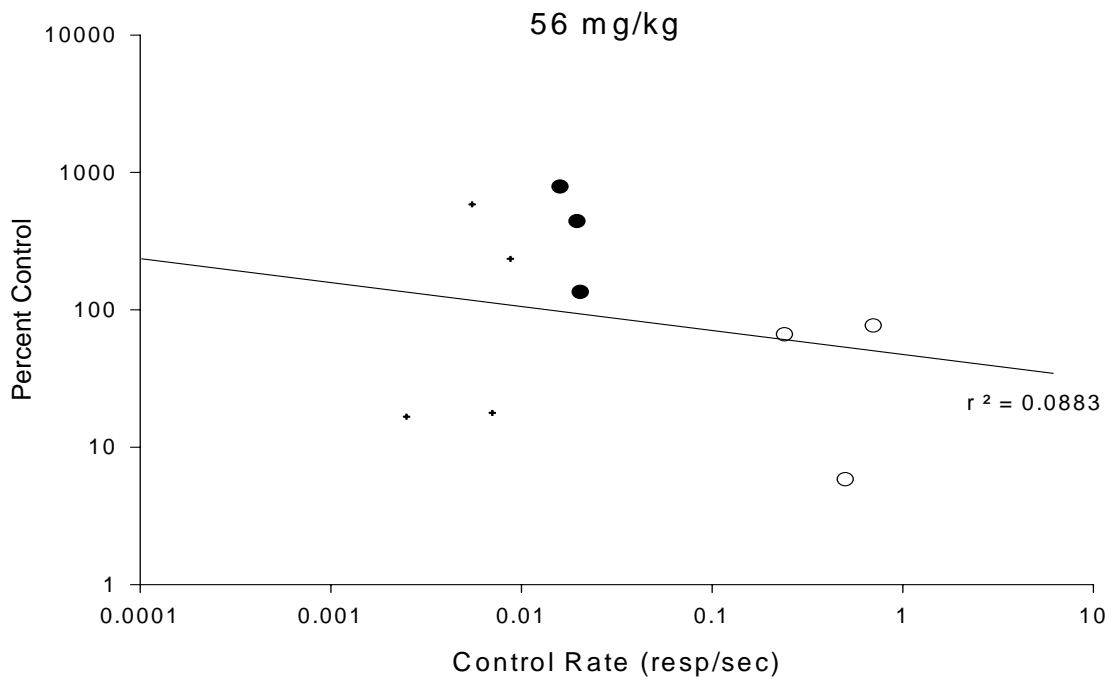
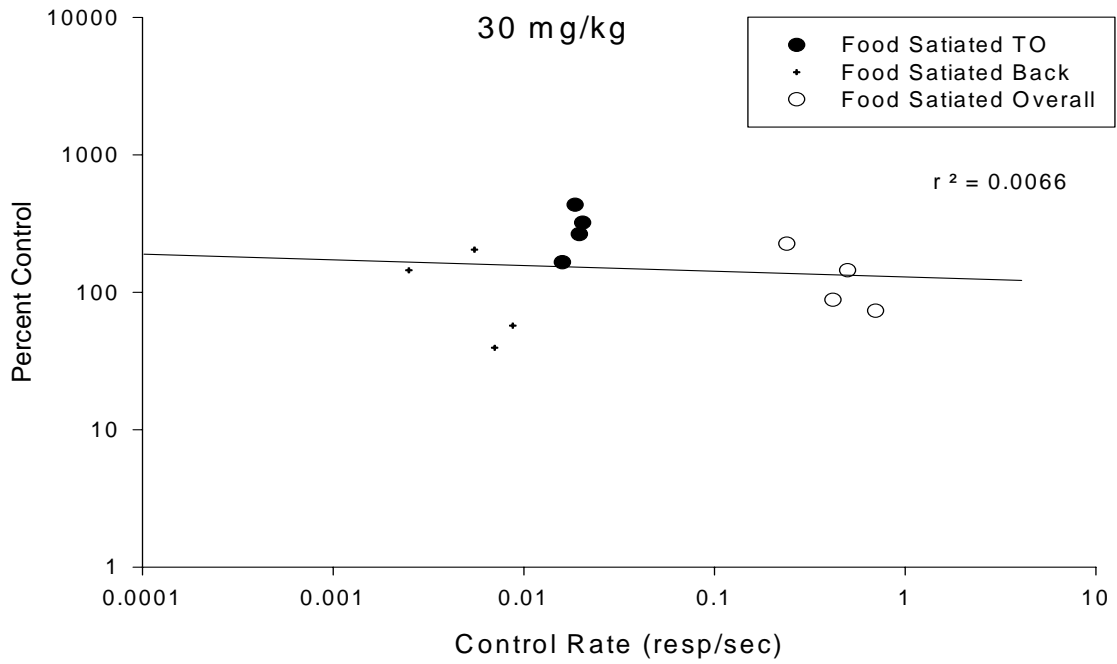


Figure 33. Rate dependency plots for four rats on an FR3 60 s TO of food reinforcement under satiated conditions, following the administration of 30 and 56 mg/kg doses of bupropion. For description of the graph, refer to Figure 30.

indicate that behavior following the administration of this dose was much more variable across animals but no rate-dependent trends in the data were found.

In order to make comparisons across the three different studies, the overall response rates for each group of animals, following the administration of saline and the doses of bupropion (10, 30, 56 mg/kg), were converted into percent control and are displayed in Figure 34. For graphs in Figure 34 an increase above 100 indicates that the drug increased overall response rates above control levels, while points plotted below 100 illustrate that the drug had a decreasing effect on these rates. Figure 34 shows that the 30 mg/kg dose of bupropion increased the mean overall response rate (average control rate, 0.012 resp/sec) maintained by nicotine self-administration ($F(3, 24) = 3.037, p = .049$). There was also a non-significant trend for the moderate dose of bupropion to increase behavior maintained by food-reinforcement when the animals' overall response rates were decreased through food satiation (average control rate, 0.488 resp/sec), $F(3, 12) = 2.970, p = .074$. However, this effect was not as pronounced as the effect on nicotine. Figure 34 also revealed that when bupropion was administered to subjects on a similar food reinforcement schedule but under deprived condition (i.e. resulting in higher response rate, average control rate 1.377 resp/sec), the 30 mg/kg dose of bupropion resulted in rate-decreasing effects, $F(3, 12) = 23.876, p = .000$.

In order to determine whether there were any differences in the effects of bupropion between the three different studies, analyses were conducted on the percent control of the overall response rate. Oneway ANOVAs were conducted on each dose of bupropion between the different studies. Analysis of the 30 mg/kg dose revealed a significant effect between studies, $F(2, 12) = 5.676, p = .018$; no effects were found

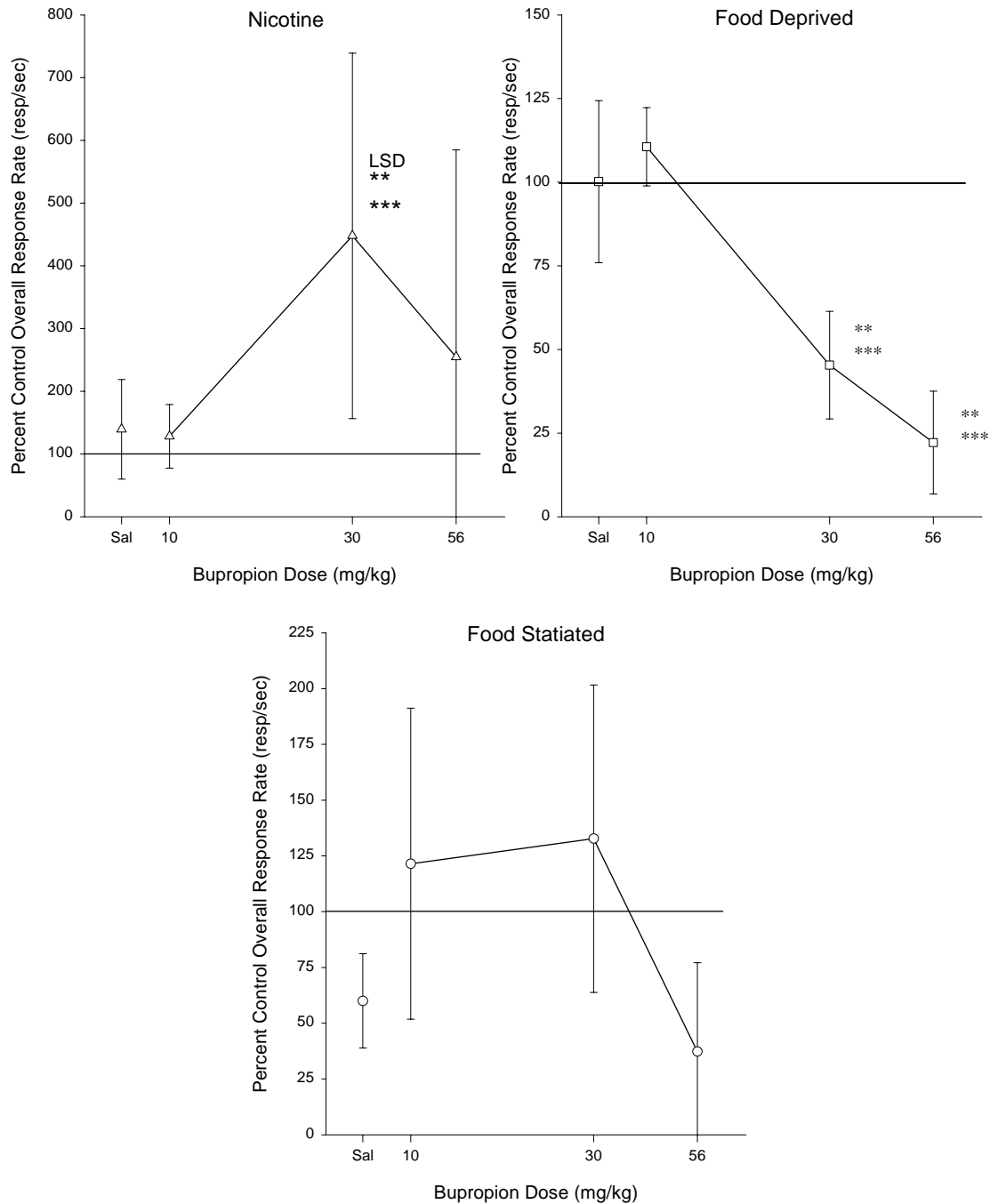


Figure 34. The percentage of change in the overall response rate from control rates following the administration of doses of bupropion and saline, for the three studies. The open triangles in the nicotine graph are the average of seven data points at each dose (one for each rat). The open circles in the food-satiated graph are the average of four data points at each dose (one for each rat). The open squares in the food-deprived graph are also the average of four data points at each dose (one for each rat). The error bars on all three graphs are one standard deviation of the mean. For description of the symbols, refer to Figure 1.

between studies for any other doses. A Bonferroni post hoc test revealed that the increase in the overall response rate in the nicotine study following the administration of the 30 mg/kg dose of bupropion had a significantly different effect from the effect on overall response rate in the food-deprived study. The increasing effect on the overall response rate in the nicotine study was not significantly different than from the increase seen in the food-satiated study.

Rate-dependency plots for the three behaviors for all three studies are depicted in Figures 35 and 36. Figure 35 shows the rate-dependency graphs for saline administration and 10 mg/kg dose of bupropion. Again the low r^2 values for saline and the 10 mg/kg dose of bupropion indicate that the low dose of the drug did not have rate-dependent effects. The rate-dependency plots for the 30 and 56 mg/kg doses, found in Figure 36, reveal that the highest dose of bupropion had rate-dependent effects on behavior. Bupropion at the highest dose appeared to increase low to medium rates of behavior and decreased the higher rates of behavior. A fair amount of variance can be accounted for by the regression line plotted to the data in the 56 mg/kg graph in Figure 36 ($r^2 = .3507$).

An even more striking correlation can be seen when just the overall response rates for the three different studies are presented using rate-dependency plots. Figure 37 shows that there are no rate-dependent effects on the overall response rates following the administration of saline or the 10 mg/kg dose of bupropion. Again, for both saline and the low dose of the drug, data remained around 100 percent resulting in a straight trend line. Figure 38 strongly indicates that the overall response rate under control conditions

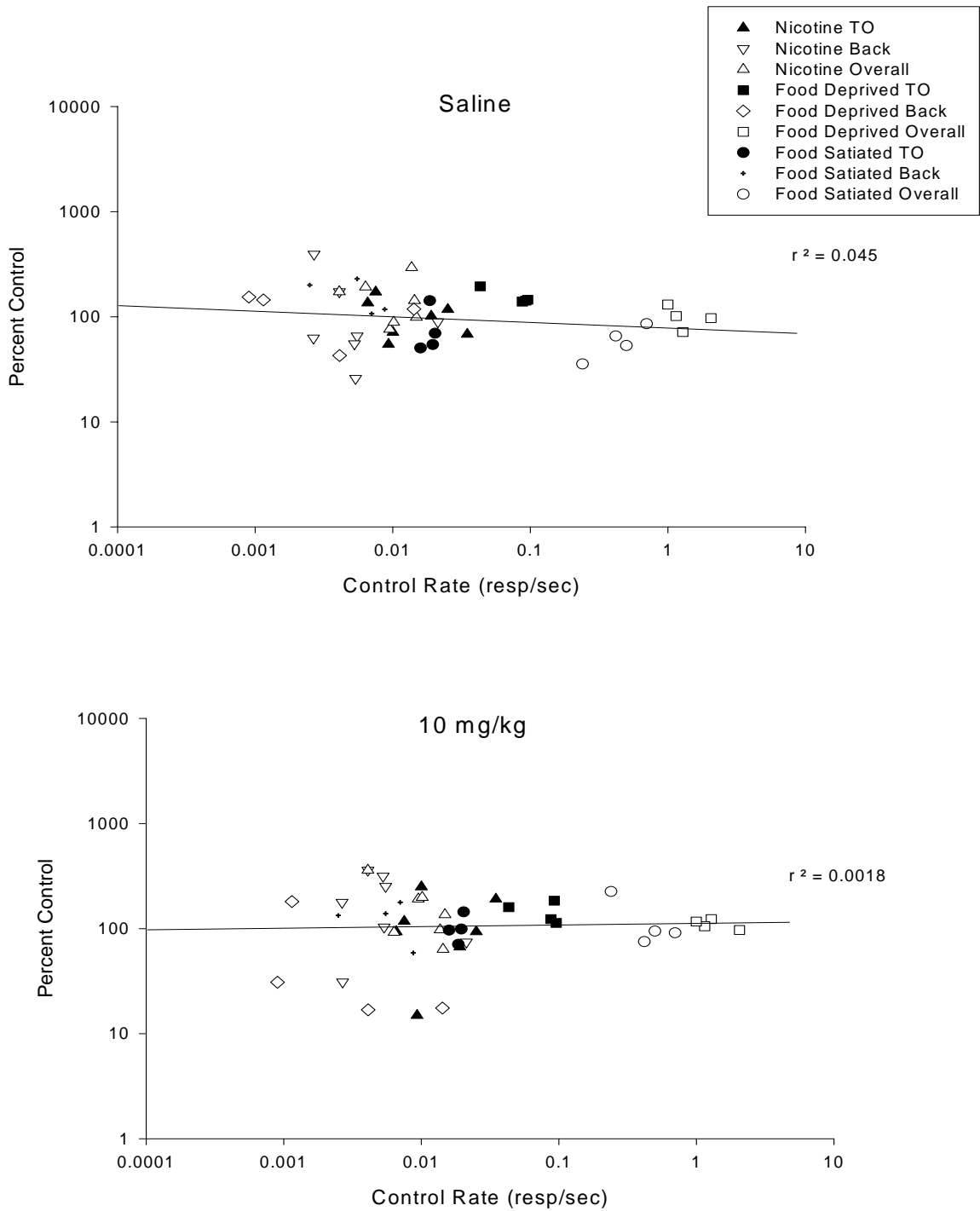


Figure 35. Rate dependency plots of the three behaviors for all three studies. The symbols and descriptions of the graphs are the same as previously described in Figures 11, 21, and 30. The figure illustrates the effects following saline administration and 10 mg/kg dose of bupropion for all three studies.

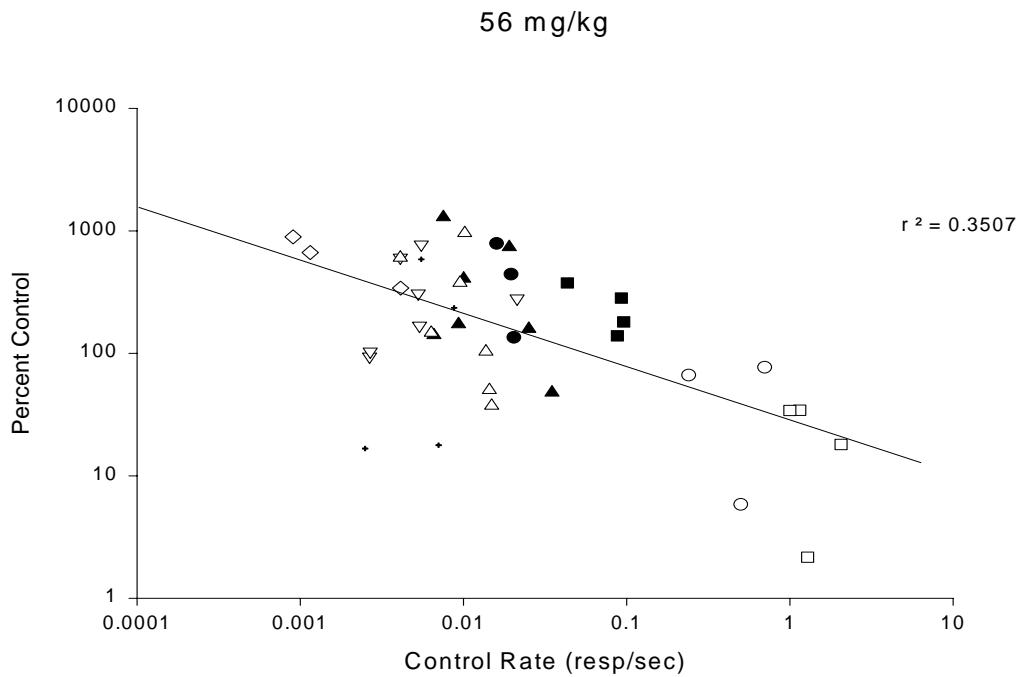
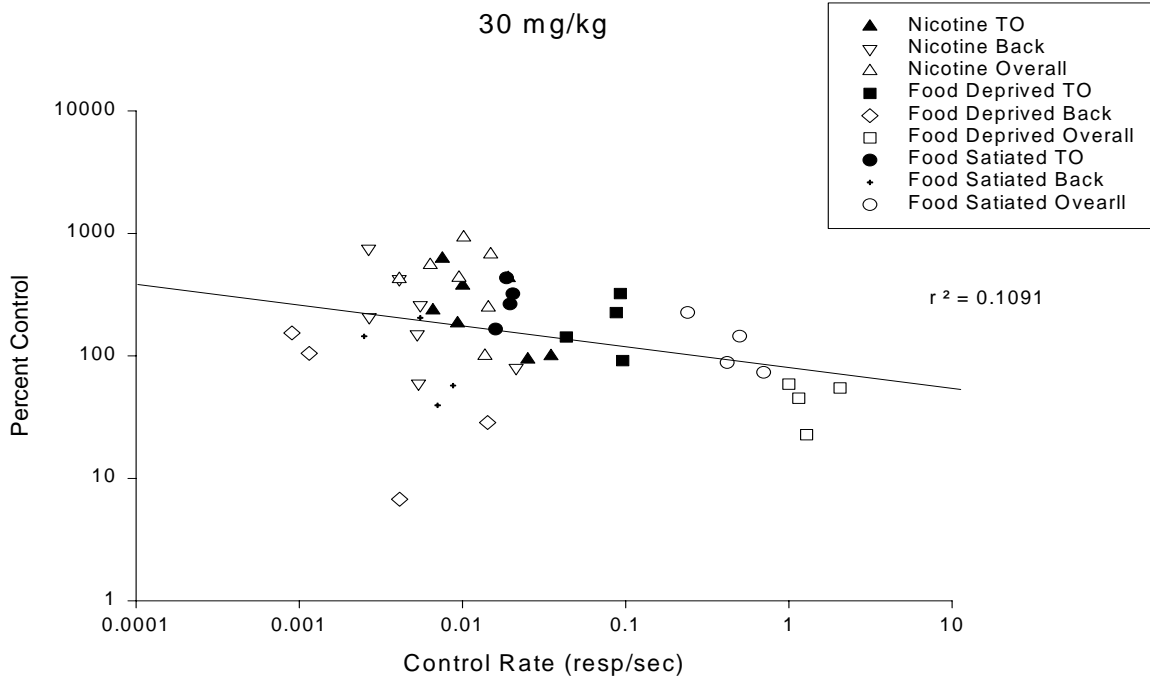


Figure 36. Rate dependency plots of the three behaviors for all three studies. The symbols and descriptions of the graphs are the same as previously described in Figures 11, 21, and 30. The figure illustrates the effects following the administration of 30 and 56 mg/kg doses of bupropion for all three studies.

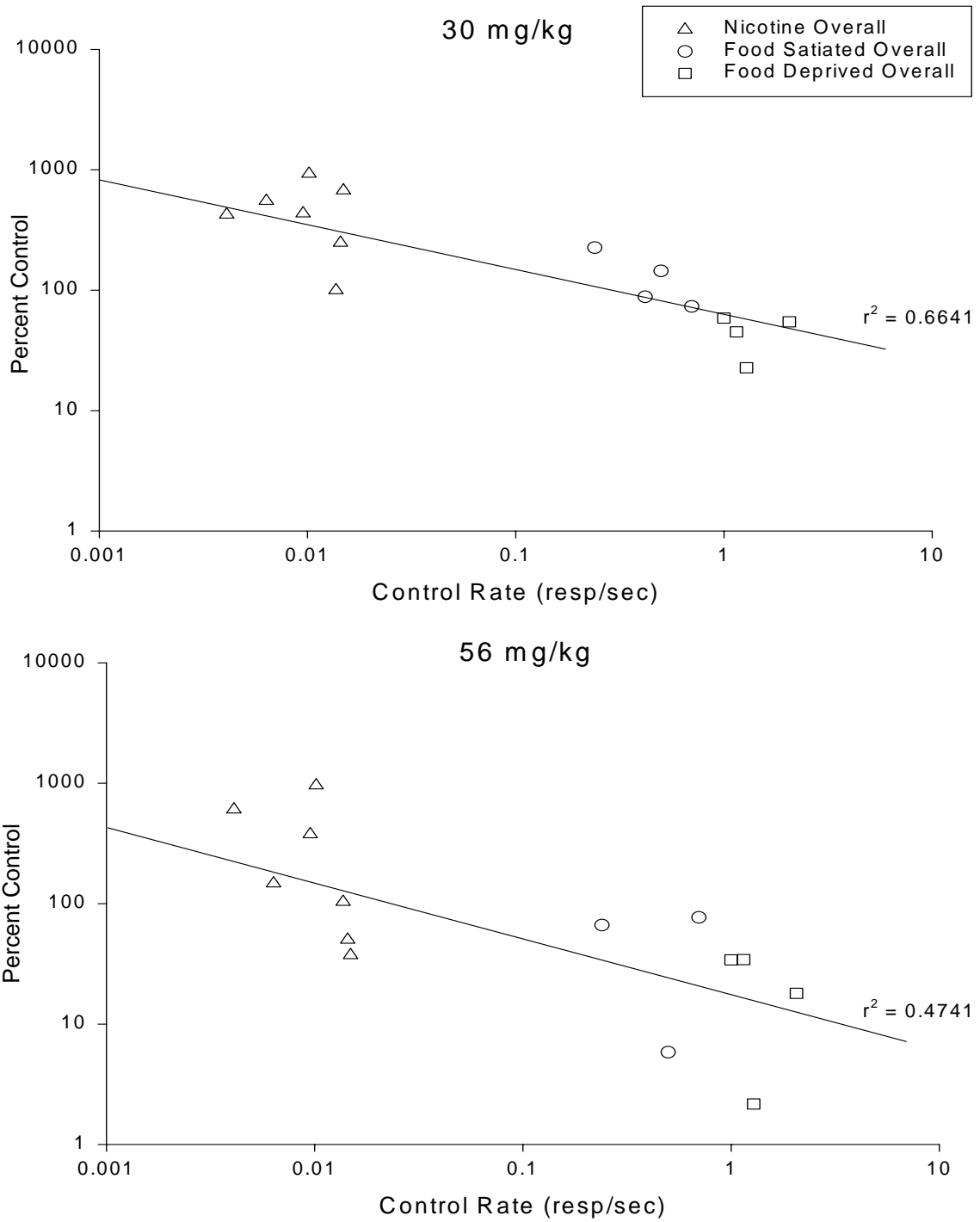


Figure 38. Rate dependency plots of the overall response rates of the three different studies. The symbols and descriptions of the graphs are the same as previously described in Figures 11, 21, and 30. The figure illustrates the effects on the overall response rate following the administration of 30 and 56 mg/kg doses of bupropion for all three studies.

was a determinant for effects of the drug following the administration of the two highest doses of bupropion. When the three overall response rates were plotted against percent control for the 30 mg/kg dose a high r^2 was found ($r^2 = 0.6641$). The 56 mg/kg dose of bupropion also indicated a large amount of variance that could be accounted for by the regression line ($r^2 = 0.4741$). Bupropion at the 30 mg/kg dose tended to increase the lowest overall response rate found in the nicotine study while resulting in a slight increase in the moderate response rate found in the food-satiated study. The 30 mg/kg dose of bupropion resulted in a decrease in the highest overall response rate found in the food-deprived study. The 56 mg/kg dose of bupropion had similar effects on the overall response rates to that of the moderate dose, yet the results were more variable.

DISCUSSION

In the nicotine study, the significant increases in the overall response rate resulted in a corresponding significant increase in the number of reinforcers with the apex of the dose-effect curve occurring at the 30 mg/kg dose of bupropion. Administration of bupropion in the nicotine study resulted in a dose-dependent increase in timeout responding with the significant increase occurring following the administration of the highest dose of the drug. The highest dose of bupropion also resulted in a significant increase in back-lever responding in the nicotine study. The effects of bupropion on the three rate measures in the nicotine study did not appear to be dependent on the control rate of responding, which was indicated by the flat trend lines in the nicotine rate dependency plots.

The effects of bupropion on food-maintained behavior in food-deprived subjects resulted in dose-dependent decreases in both the overall response rate and the number of

reinforcers. For both the overall response rate and the number of reinforcers the significant decreasing effects of the drug were found to be statistically significant following the administration of the highest dose. The effects of bupropion on the timeout responding in the food-deprived study resulted in dose-dependent increases, with significant effects resulting from the administration of both the moderate and highest dose of the drug. Bupropion did not have an effect on back-lever responding in the food-deprived study. The effects of the highest dose of bupropion on the three rate measures in the food-deprived study appear to be a function of the control rate of the behavior. Bupropion tended to increase the low and moderate rates of behavior in the food-deprived subjects while decreasing the highest rate of behavior.

When food-maintained behavior occurred at a more moderate rate (i.e. food-satiated study), bupropion tended to increase the overall rate of response at the low and moderate dose of the drug, while only the highest dose of the drug decreased overall response rate. Only the highest dose of bupropion resulted in a decrease in the number of reinforcers obtained in session for the food-satiated group. Bupropion tended to dose-dependently increase timeout responding with the significant effect resulting from the administration of the moderate and highest doses of the drug in the food-satiated study. Bupropion failed to have an effect on back-lever responding in the food-satiated study. The effects of bupropion on the three rate measures in the food-satiated study appear not to be dependent on the control rate of the behavior at the time that the drug is administered. This is evident from the relatively flat trend line in the food-satiated rate-dependency plots.

Bupropion tended to increase the overall response rate maintained by nicotine self-administration, with the peak effect following the administration of the 30 mg/kg dose. While an increase in nicotine self-administration was found, bupropion in the food-deprived study resulted in a dose-dependent decrease in the overall response rate when the rates were considerably different. By satiating the animals, a lower response rate was achieved which allowed for the comparisons of the drug's effects on two more comparable rates of responding (i.e., nicotine overall response rate and food-satiated overall response rate). When bupropion was administered to a more comparable rate of behavior maintained by food to the rate of nicotine-maintained behavior, the drug resulted in similar effects with both reinforcers. The peak increase in the overall response rate in the food-satiated group again resulted after the administration of the 30 mg/kg dose of bupropion. When the overall response rates for the different studies were investigated to determine whether bupropion was having rate-dependent effects, the 30 and 56 mg/kg doses of the drug indicated that the effect of the drug was a function of the control rate of responding.

A striking result from the current studies is the fact that bupropion resulted in an increase in nicotine self-administration. These results would not be suspected from a drug that has been shown to have clinical efficacy in furthering smoking cessation (Hurt et al., 1997; Jorenby et al., 1999). The results from the current study are congruent with recent study conducted by Rauhut, Neugebauer, Dwoskin, and Bardo, (2003). In the Rauhut et. al. study, bupropion was also found to increase nicotine self-administration in rats while decreasing responding maintained by sucrose pellets. In another recent study by Shoaib, Sidhpura, and Shafait (2003), a 30 mg/kg dose of bupropion given chronically

to rats for 28 days resulted in an increase in nicotine intake. The increase in nicotine self-administration in the Shoaib, et. al. study persisted through the 28 days of treatment.

A possible explanation for discrepancy between the results from the clinical studies (Hurt et al., 1997; Jorenby et al., 1999) and the current study is in the difference in species used. This does not appear to be a viable explanation for the discrepancy between the animal studies and the clinical trial results because it has recently been found that acute doses of bupropion, when administered to humans, resulted in an increase in the number of cigarettes smoked (Cousins, Stamat, & de Wit, 2001). The increase in cigarette smoking following administration of bupropion was similar to the increase in the number of cigarettes smoked following the administration of another stimulant, d-amphetamine (Cousins et al.). The results from the current study and Cousins et al. indicate that the difference in the dosing regimen of bupropion may have contributed to the difference between the current study and the clinical studies.

A possible reason for the increase in nicotine self-administration following administration of bupropion could be that the drug, a dopamine reuptake inhibitor (Cooper et al., 1980; Ferris, Maxwell, Cooper, & Soroko, 1982), is having a priming effect on nicotine self-administration. That is, bupropion may be blocking the reuptake of dopamine in the nucleus accumbens, causing increased levels of extracellular dopamine and priming the substrates that are involved in drug reward. It has been shown that animals will self-administer drugs to maintain particular levels of dopamine in the nucleus accumbens (Wise et al., 1995). If bupropion was resulting in an increase in the levels of extracellular dopamine in the NA, the subjects could be increasing nicotine self-administration in an attempt to reach a particular level of dopamine. A priming

interpretation for the increase in nicotine self-administration may not be a viable explanation since the administration of bupropion did not result in an increase in amphetamine self-administration in the Rauhut et. al. (2003) study. If bupropion was increasing nicotine self administration from priming through the drug's dopamine reuptake mechanism, it would be suspected that the drug would also prime responding that was maintained through other reinforcers that result in increase in DA levels in the NA.

Another possibility is that bupropion may be acting as a nicotinic antagonist. Recently, bupropion has been found to be a noncompetitive nicotinic antagonist (Fryer & Lukas, 1999; Slemmer et al., 2000). Bupropion blocked the $\alpha 4\beta 2$, $\alpha 3\beta 2$, and the $\alpha 7$ nicotinic acetylcholine receptors (Slemmer et al., 2000). A recent study by Miller, Sumithran, and Dwoskin (2002) found that bupropion inhibited nicotine-evoked dopamine overflow through the drug's antagonistic effects at the $\alpha 3\beta 4$ and the $\alpha 3\beta 2$ nicotinic receptors. Bupropion could be binding to the nicotinic receptors in the VTA and blocking the receptors; this would result in a decrease in the amount of dopamine released in the nucleus accumbens. Thus, bupropion may be blocking the reinforcing effects of nicotine and the increase in drug intake is an extinction burst, or the animal's were attempting to override the antagonistic effects of the drug. If bupropion were affecting nicotine self-administration through this mechanism, it would be the first antagonist to the author's knowledge that resulted in an increase in nicotine self-administration using the rodent model.

A third possible interpretation of the results of this study is that bupropion may not be altering any reinforcing effects of nicotine. The increase in nicotine self-

administration could be a behavioral effect of the drug (i.e., rate dependency) not related to changes in the reinforcing efficacy of nicotine. Little research has been conducted investigating the effects of bupropion on schedule-controlled behavior. In one study investigating the effects of bupropion on behavior maintained by a multiple FI FR schedule, it was found that bupropion increased responding in the FI component (lower rate of behavior) and had little to no effect on the FR component of the schedule (McKearney, 1982). In another study, bupropion was found to increase low rates of responding under a fixed-interval schedule of reinforcement (Spealman, Madras, & Bergman, 1989).

The results from the current studies seem to indicate that bupropion was having rate-dependent effects. The rate-dependency plots of the overall response rates (Figure 36) for the different groups of animals indicates that the 30 mg/kg and the 56 mg/kg doses of bupropion are showing a strong tendency to increase the lower rates found in the nicotine study. The 30 mg/kg dose of bupropion also slightly increased the moderate rates found with the food-satiated study, while decreasing the higher rates of behavior found in the food-deprived study. Also, when looking only at the food-deprived group, the rate-dependency plot for the 56 mg/kg dose (Figure 22) shows that the largest dose of bupropion increased the low and moderate rates of behavior (back response rate and timeout response rate, respectively), while decreasing the highest rate of behavior (overall response rate). Also, by visually examining the cumulative record for the 56 mg/kg dose of bupropion of Bup10 (Figure 20), the decrease in overall response rate can be seen with the longer run times as well as the increasing number of timeout responses and back-lever responses compared to that of control (Figure 18).

The apparent rate-dependent effects of bupropion on nicotine-maintained behavior and food-maintained behavior in the current studies are most likely due to the response rate rather than the difference in the maintaining event. The effects of stimulants on schedule-controlled behavior have been shown to be a function of the rate of response rather than the maintaining event. In a study by Branch (1979), it was found that the effects of cocaine and d-amphetamine were not dependent of the type of event maintaining behavior. In a three-component multiple schedule of food presentation, electric shock presentation, and escape responding, Branch found that the acute administration of either cocaine or d-amphetamine affected responding in a similar manner across all three components. McKearney (1974) conducted a study that also shows that the primary determinant of a stimulant's effect on schedule-controlled behavior is the ongoing rate of behavior rather than the consequent event. In the study by McKearney, similar rates of behavior were maintained on a FI schedules of shock presentation and food presentation, as well as on a multiple schedule of food and shock presentation. The administration of d-amphetamine resulted in similar rate-dependent effects for behavior that was maintained by shock presentation and food presentation under single FI schedules as well as the two schedules in a multiple schedule paradigm.

The data from the current studies indicate that the increasing effects of bupropion on nicotine self-administration may not have resulted from the drug's effects on the nicotinic substrates but rather were influenced by the control rate of responding. Although the data indicate a rate-dependent effect of the drug, a more conclusive understanding of rate-dependent effects of bupropion could be achieved by looking at the drug on a multiple schedule of positive reinforcement.

Bupropion may be increasing nicotine self-administration in the current study by decreasing the averseness of nicotine. This interpretation seems unlikely, considering that bupropion failed to alter the aversive stimulus effects of nicotine in a conditioned taste aversion procedure (Shoaib et al., 2003). A fifth possible explanation for the increase in nicotine self-administration could be that bupropion resulted in a general increase in locomotor activity. Bupropion has been shown to increase locomotor activity (Cooper et al., 1980), and in the current nicotine study, a dose-dependent increase in back-lever response rate (Figure 1) was seen. Even though bupropion resulted in an increase in back-lever response rates, there was a large amount of variability between doses, and the effect was not consistent across all animals in the nicotine study. Also, an increase in back-lever response rate was not seen in either of the two food studies. This indicates that the increase in nicotine self-administration may not be a result of a general increase in locomotor activity. If bupropion was having antagonistic effects on nicotinic substrates, then the increase in the back-lever response rate in the nicotine study could be a result of the animal experiencing extinction on the active lever. For example, if bupropion was acting as a nicotinic antagonist and decreasing the reinforcing efficacy of nicotine by blocking the release of DA in the NA, then the increase in the overall response rate on the active lever could be viewed as an extinction burst. At the present time, it is unclear why bupropion resulted in an increase in the back lever response rate specific only to nicotine self-administration. Further research in this area may aid in a better understanding of this effect of the drug.

An important aspect to consider when testing potential pharmacotherapeutics for nicotine addiction is the effect that the drug may have on conditioned reinforcers that

become paired with the delivery of the drug. Conditioned reinforcers have been found to be important in the maintenance and acquisition of nicotine self-administration both in the animal (Caggiula, Donny, Chaudhri et al., 2002; Caggiula et al., 2001; Caggiula, Donny, White et al., 2002) and human (Rose et al., 1999; Westman, Behm, & Rose, 1996) self-administration paradigms. The increase in timeout responding seen in all three studies may be the drug affecting the conditioned reinforcers (i.e. lights, tones, and sound of the drug pump or the pellet dispenser) that were paired with the nicotine infusion or the food pellet. It has been shown that stimulants and more specifically monoamine reuptake inhibitors increase responding maintained through conditioned reinforcement (Robbins, Watson, Gaskin, & Ennis, 1983). The increase in the number of timeout responses could be a result of bupropion's ability to block the reuptake of DA or even NE. It has been shown that cues can reinstate nicotine responding (Caggiula et al., 2001) and that dopaminergic mechanisms are involved in nicotine abuse (Dani & Heinemann, 1996) and relapse of abused drugs (Spealman, Barrett-Larimore, Rowlett, Platt, & Khroyan, 1999). Perhaps bupropion's effects on conditioned cues through dopaminergic activity may play a role in its clinical effectiveness in smoking cessation.

Results from the current study indicate that bupropion is not having reinforcer-specific effects on nicotine self-administration. Rather, the drug is having qualitatively similar effects on behavior regardless of the maintaining event when rates of responding are somewhat comparable. Results from the food-satiated study indicate that bupropion is still increasing behavior maintained by food reinforcement, but the effect is not as pronounced. When the rates of behavior are extremely different, the drug resulted in qualitatively different effects. The qualitatively different effects can be seen when

comparing the increasing effects of bupropion on nicotine self-administration to the decreasing effects of the drug on food-maintained responding under food deprivation conditions.

The current studies indicate that bupropion is affecting smoking cessation through some mechanism other than the nicotine in the cigarette. Perhaps the effectiveness of bupropion as a smoking cessation adjunct could be improved by taking into consideration the drug's rate-dependent effects. It may be important to consider the number of cigarettes the individual smokes each day when prescribing bupropion as a pharmacological aid in smoking cessation. The two clinical trials (Hurt et al., 1997; Jorenby et al., 1999) kept the number of cigarettes smoked per day relatively constant across all groups receiving placebo and doses of bupropion so it is impossible to determine what effect level of smoking had on the drug's ability to increase smoking abstinence. The individual's rate of smoking may determine whether or not bupropion will benefit or hinder their attempts at smoking cessation.

Despite the fact that bupropion doesn't appear to be acting specifically on nicotinic substrates, its clinical efficacy as a pharmaceutical aid in smoking cessation cannot be ignored. Future studies in both the human and animal self-administration paradigms may elucidate how bupropion is affecting smoking cessation. Although it is extremely beneficial for a nicotinic pharmacotherapeutics to act on the specific neural nicotinic substrates, it may be helpful to test potential pharmacotherapeutic's effects on the conditioned cues associated with nicotine delivery. With continued use of the current procedures and with the addition of a procedure to test drug's effects on conditioned

cues, perhaps a more effective pharmacotherapeutic can be found that will assist in nicotine addiction.

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