EFFECTS OF D-AMPHETAMINE ON CHOICE BEHAVIOR

UNDER MIXED CONCURRENT SCHEDULES

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EFFECTS OF D-AMPHETAMINE ON CHOICE BEHAVIOR UNDER MIXED CONCURRENT SCHEDULES

Phyllis A. Reile

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Phyllis A. Reile

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VITA

Phyllis Ann Reile, daughter of Frederick John and Janet (Bartosiewicz) Reile, was born December 13, 1964, in Plainview, New York. She graduated from Brentwood Ross High School, Brentwood, New York in 1981 and attended Binghamton University. After receiving her bachelor's degree, she worked as a behavior therapist with children with developmental disabilities, where she met her husband, James Marcus Williams, Jr. (Marc). They entered graduate school at Auburn University and married in September 1991. Phyllis received her M.S. in Psychology in 1994. She is most proud of Marc, who graduated with his Ph.D. in 1998, and their longed-for son, Logan Reile Williams, born the same year.

DISSERTATION ABSTRACT

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Phyllis A. Reile

Doctor of Philosophy, August 4, 2007
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The goals of this dissertation were to conduct detailed analyses of behavior in transition in response to changes in reinforcement contingencies by using mixed concurrent Random Interval-Random Interval (conc RI RI) schedules of reinforcement and to examine the effects of *d*-amphetamine on behavior in transition. A mixed conc RI RI schedule of reinforcement (MCS) procedure was used with rats to arrange reinforcers for responding across two independent levers. Subjects could vary responding between the two levers. During the initial 30 min of a 3-hour session, the contingencies were equal, after which they changed during some of the sessions. For

one-third of sessions, the probability of reinforcement for left lever responding was four times greater than for responding on the right lever. For one-third of sessions, the probability of reinforcement for right lever responding was four times greater than for responding on the left lever. For the remaining one-third of sessions, the probability of reinforcement for responding remained equal across both levers. Terminal reinforcer ratios (left: right) used were 4:1, 1:1, and 1:4. Once responding during transition sessions stabilized over several sessions, saline or *d*-amphetamine (0.1 - 6.0 mg/kg) was administered IP 30 min prior to some of the experimental sessions.

Dose-response curves for all rats showed no significant differences in reinforcers obtained before transitions between control, saline, and *d*-amphetamine sessions, except for at the highest dose of *d*-amphetamine for which there was typically a decrease. Tabular data revealed a slight peak in reinforcers that corresponded with the dose that increased total reinforcers for that rat. Microanalytic data further revealed more rapid transitions in response proportions after the programmed changes under low to moderate doses, an increase in total responses and visits at low to moderate doses due to more changeovers, and a decrease in response rate and some perseverative responding at higher doses of *d*-amphetamine, which disrupted performance and resulted in fewer reinforcers.

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I would like to dedicate this work to the loved ones I lost prematurely over the past five years, my mother and best friend, Janet Reile, who showed me how to laugh in spite of it all, my brother and only sibling, Freddy Reile, who was my e-mail buddy, and my very close friend from childhood, Josephine Laneville, who showed me how to appreciate each moment and how to accept fate gracefully. I miss all of them dearly.

I am eternally grateful to my husband, Marc, and my father, Frederick Reile, for their everlasting support through these most challenging years. I also want to express gratitude to my son, Logan, for making me smile every day, and to Carolyn Parisa, my good friend of 28 years. I am also very thankful for all of the encouragement and the wonderful opportunity provided to me by Tina Vazin. Finally, my utmost gratitude goes to my dissertation committee, Lewis Barker, Peter Harzem, and Bill Buskist, and the department chair, Barry Burkhart, for their faith in me and for nudging me to pick myself up and trek onward. You all have my sincerest thanks for all you have done and for being such generous advocates, sources of inspiration, and for encouraging me in this academic endeavor.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

I. INTRODUCTION

Most research on acquisition has gravitated toward examining, experimenter-defined, relatively discrete, and somewhat static steady-states, behavioral events that occur before and after an arranged treatment. Contrary to this fact, behavior is continuous and fluid and its change consists not only of initial and final steady-states. Steady-states surround transient-states, periods during which behavior may be quite variable. The focus of studies to identify the behavioral mechanisms underlying a drug's effect has typically been on performance rather than on learning. There are likely several reasons for the focus on performance including logistical constraints and the limitations of a supporting literature (Reile, 2000). Despite the difficulties, several studies qualify as exemplary attempts at examining transient-states (e.g., Boren, 1963; Cohn, MacPhail, & Paule, 1996; Cohn & Paule, 1995; DeCarlo, 1985; Dreyfus, DePorto-Callan, & Pesillo, 1993; LeSage, Byrne, & Poling, 1996; Newland, Reile, & Langston, 2004; Newland, Yezhou, Logdberg, & Berlin, 1994; Thompson & Moerschbaecher, 1979a, 1979b). These studies have demonstrated the advantages of using operant methods for identifying mechanisms underlying drug and toxicant effects on learning.

For the purposes of this dissertation, *learning* is the change in behavior from one steady-state to another in response to an environmental event. This comprehensive

account includes relatively rapid behavior change at the level of the individual (e.g., habituation, respondent conditioning, and operant conditioning) as well as protracted behavior change that occurs over generations through the course of natural selection (e.g., reproduction and foraging). Thus, *learning* cannot be considered a single type of event (Newland & Reile, 1999). The primary focus of this dissertation is on the transition from one steady-state to another of schedule-controlled free-operant choice behavior as it adapts to changes in reinforcement schedules.

Acquisition of Operant Behavior

An enormous body of research has been directed at the examination of steady-state behavior under concurrent time-based schedules (e.g., DeCarlo, 1985; Heyman & Tanz, 1995; Shurtleff & Silberberg, 1990; Wearden, 1980). Because of the wealth of work in this area, the reader is directed to de Villiers (1977) and Davison and McCarthy (1988) for more comprehensive reviews. Research, most notably, by Herrnstein (e.g., 1961, 1970) led to the extensive analysis of performance under concurrent schedules typically referred to as matching. Known as the strict matching law, Herrnstein's original equation is as follows:

$$\frac{B_1}{(B_1 + B_2)} = \frac{R_1}{(R_1 + R_2)} \quad .$$

Thus, the relative proportion of responses allocated to each alternative is a function of the relative proportion of reinforcers obtained under each alternative.

The equation can be modified to describe a single response under the VI schedule occurring in a context of all other activities and their reinforcers considered

collectively (Herrnstein, 1970, 1974):

$$B_1 = \frac{kR_1}{R_1 + R_e}$$

.

This equation is based on two assumptions. First, Herrnstein proposed that the overall rate of all responses made by an organism is a constant, *k*. Herrnstein assumed that the organism was always responding to a concurrent schedule of sorts even if the experimenter only arranged reinforcement for a single response class (R_1). Thus, he argued that reinforcement contingencies not programmed by the experimenter (R_e) might maintain behavior other than that the arranged schedule(s). Second, the amount of behavior allocated to each schedule (B_1) lies in proportion to the reinforcers obtained on each schedule. Therefore, Herrnstein's (1970) equations predict that the relative proportion of responses (and time) allocated to each alternative will strictly match the relative proportion of reinforcers acquired by each alternative on concurrent VI VI schedules (Baum, 1974).

In fact, many investigators have reported systematic deviations from strict matching (e.g., Lobb & Davison, 1975; Myers & Myers, 1977). In general, under concurrent VI VI schedules, response allocation does not adhere to strict matching whereas time allocation tends to approximate closely matching. Thus, Baum (1974) proposed a modified relation, referred more to as the “generalized matching law,” described by the following equation:

$$\frac{B_1}{B_2} = a\left(\frac{R_1}{R_2}\right)^b$$

,

where B_1/B_2 is the ratio of behavior (responses, response rate, or time spent on the alternatives) between two alternatives and R_1/R_2 is the ratio of reinforcers obtained between the two alternatives and *a* and *b* are free parameters. When plotted on log-log coordinates, the equation forms a straight line with an intercept of log *a* and a slope of *b*. Baum (1974) considered *b* to be indicative of sensitivity to reinforcement. A slope >1 indicates greater sensitivity and is described "as 'overmatching,' whereas a slope <1 indicates less sensitivity and is described as 'undermatching.' If '*a*' is positive, then bias is toward B_1. If '*a*' is zero, then the regression line passes through the origin. Finally, if '*a*' is negative, then bias is toward B_2 (1974).

Previous views of bias have been that it indicates partiality toward one position or stimulus (Baum, 1974). Baum, Schwendiman, and Bell (1999), however, confirmed the model of choice behavior in Houston and McNamara's foraging theory (e.g., Houston & McNamara, 1981; Houston, Sumida, & McNamara, 1987), that suggests a different view of bias. This view considers choice behavior in the context of rich and lean alternatives rather than in terms of location of alternatives or stimuli as in the generalized matching law. Previous models of choice were proposed to explain matching (e.g., Herrnstein & Vaughan, 1980; Hinson & Staddon, 1983; Myerson & Miezin, 1980; Rachlin, 1978; Shimp, 1966), but failed to explain undermatching and overmatching. Foraging theory views bias toward the rich or lean alternative as driving choice behavior. Thus, undermatching is a result of bias to the lean alternative and overmatching is a result of bias to the rich alternative.

Baum et al. (1999) found that the changeover delay (COD) decreased changeover rates and increased the number of responses on the lean alternative. They

found matching to be a function of the frequency of visits to the lean alternative, which was directly proportional to the relative reinforcement on the lean alternative. For this reason, they characterized concurrent performance as "responding on the rich alternative interrupted at some frequency, depending on the relative reinforcement there, by brief visits to the lean alternative" (p. 370). This conception contradicts models such as melioration (Herrnstein & Vaughan, 1980) and the kinetic model (Myerson & Miezin, 1980), which assume that responding adjusts equally at both alternatives. Although Baum et al. did not examine equal ratio schedules, they studied a wide range of ratios, and from that, noted that when reinforcement on the two alternatives approaches equality, responding approaches indifference, and visit durations on both alternatives decrease. Moreover, Davidson and Baum (2003) found that pigeons' were more sensitive to rate of reinforcement ratios across response alternatives than to the magnitude of reinforcement ratios across response alternatives with increasing numbers of reinforcers in components.

Research has found response matching across different types of response classes such as key pecking and lever pressing (Davison & McCarthy, 1988; de Villiers, 1977), treadle pressing (McSweeney, 1975), and even scanning eye movement rates (Schroeder & Holland, 1969). The general finding has also been extended to several species including pigeons and rats (Davison & McCarthy, 1988; de Villiers, 1977), humans (Horne & Lowe, 1993) and across reinforcers such as food (Davison & McCarthy, 1988; de Villiers, 1977), brain stimulation (Shull & Pliskoff, 1967) and points (Kollins, Newland, & Critchfield, 1997).

There are only a few models of transitional choice behavior worth reviewing. The discovery of an appropriate model of transitional choice behavior will involve grappling with some key issues. One problem is whether molar or molecular approaches are appropriate for studying behavior change. From this perspective, another question that arises is whether it is best to handle behavior change as a continuous or discrete variable. The term *change* implies that it is logical to handle it as if fluid, although in practice it is much easier to record discrete events. Other issues involve whether a model should treat behavior change as a linear or nonlinear event, and as a stochastic or deterministic occurrence (Marr, 1992).

A debate about the usefulness of molar or molecular approaches has been around for some time (e.g., Baum, 1989, 2002; Bickel & Etzel, 1985; Dreyfus et al., 1993; Galbicka & Platt, 1989; Marr, 1992; Nevin, 1982; Shimp, 1966; Shimp, Fremouw, Ingebritsen, & Long, 1994). Anger's (1956) demonstration that interresponse times (IRTs) are selected by consequences spawned interest in molecular variables. Herrnstein's (1961) description of matching consequently redirected attention toward molar events. Recently, Baum (2002) argued that the more traditional molecular view considered evidence of molar choice performance as overreaching whereas the more contemporary molar view perceives momentary responses as abstractions. Controversy has centered on the following questions: What constitute the relevant behavioral units? For example, is response rate (molar units) more pertinent than interresponse times (IRTs; molecular units)? Is behavior primarily influenced by local variables (moment-by-moment changes in reinforcement density) or by global variables (overall rate of reinforcement)?

Both molar and molecular behavioral units have orderly relations with reinforcement, however, molar analyses alone leave out the detail necessary to characterize local variables involved in behavior change. Some researchers have argued that orderliness at the molar level is just an aggregate of molecular events (e.g., Hinson & Staddon, 1983; Shimp, 1966; Shimp et al., 1994; Staddon & Cerutti, 2003) and on the other end, other researchers have argued that molecular events have no clear sequential structure relevant to a molar account (e.g., Baum, 1989; Blough, 1963; Nevin, 1982). It would be imprudent to deny the evidence or reject the use of either approach because each approach is asking different questions about behavior.

A related issue involves whether behavior should be considered as a continuous event or as discrete events (Marr, 1992). An experimenter's perspective of behavior will ultimately select the types of experimental questions asked and, therefore, will determine the characteristics of behavior to study. A free-operant procedure such as the MCS procedure offers the opportunity to examine the continuity in behavior change whereas a discrete-trials procedure limits the examination to change that occurs from trial to trial, ignoring that which occurs in between trials. For example, interest in changes in lever-press responding may facilitate use of a free-operant procedure whereas interest in changing performance on a matching-to-sample task may prompt use of a discrete trial procedure. Yet unknown is the extent to which behavior occurring between discrete trials is relevant to responding that occurs during trials. Whether contiguous behavior influences behavior during discrete trials will likely determine the extent to which discrete trial procedures are useful in examining the transitional process.

Other considerations are whether a model that is stochastic versus deterministic and linear versus dynamic best describes behavior change. Stochastic models suggest the involvement of random variables. On the other hand, deterministic models do not allow for random events; there are antecedent causes for all events. Linear models suggest an output (i.e., behavior) that is directly proportional to the input (i.e., controlling variables) whereas a nonlinear model implies that the relationship is not a constant. The linear-operator model (Bush & Mosteller, 1955) predicts that "each reinforcement increments response probability on one alternative by an amount that is a constant fraction of the difference between the current probability and maximum probability" and "nonreinforcement acts in the same way, reducing response probability by a fraction…" (Staddon & Horner, 1989, p. 57). The effects depend, however, on the baseline response probability. The ratio-invariance model (Horner & Staddon, 1987; Staddon & Horner, 1989) is different from the above model in that it predicts that the magnitudes of the reinforced effects, *a*, and nonreinforced effects, *b*, are the same for both responses ("source independence"). Where *s* is the probability of a response to one alternative in a two-choice situation, the ratio $a(s)/b(s)$ is constant. Both models predict slightly slower transitions with the difference between two response probabilities is larger (Mazur, 1992). Myerson's kinetic model (Myerson & Hale, 1988; Myerson & Miezin, 1980) predicts that "each reinforcement on one schedule decreases the rate of switching to the alternative by some proportion, *k* and the sum of the local rates of switching back and forth is a constant, *c*" (Myerson & Hale, 1988, p. 291). Melioration theory (Herrnstein & Vaughan, 1980) predicts that local reinforcement rates determine the relevant dependent variable, the amount of time spent responding to each

alternative. The kinetic and melioration models predict that the transition rates will be the same in all conditions with equal values of differences between two response probabilities (Mazur, 1992). Ultimately, however, Mazur and colleagues (Bailey & Mazur, 1990; Mazur, 1991, 1992, 1995a, 1995b, 1997) examined the above proposed mathematical models and demonstrated that each of the above models of behavior change fall short in some of their predictions. They have found, however, that the hyperbolic and exponential equations fit nicely to transitional data when averages are taken over relatively short periods such as 30-min sessions (e.g., Mazur, 1992, 1997).

With that in mind, and the idea that a more molecular analysis would perhaps be better suited for revealing behavioral mechanisms, Newland devised a new method for examining behavior in transition and has tested it under a variety of conditions with colleagues (Newland et al., 2004; Newland, Warfvinge, & Berlin, 1996; Newland et al., 1994).

Initial investigations began with an interest in quantifying behavior change to examine prenatal and long-term consequences of lead, methylmercury, or mercury vapor in primates (Newland et al., 2004; Newland et al., 1996; Newland et al., 1994). With 5-6 year-old squirrel monkeys, Newland and his colleagues (1994) examined transitions over several comparatively short sessions. After several sessions of stable steady-state responding under conc RI RI schedules operating independently on two levers, a behavioral transition occurred when the proportion of reinforcers allocated between the two levers changed. Control monkeys tracked changes in contingencies while monkeys exposed to higher doses of methylmercury or lead were much less sensitive to changes in reinforcement density. The researchers observed that behavior

either changed more slowly, not at all, or was directed at the leaner alternative. When an intervention was applied such that reinforcement came solely from one response alternative, the monkeys finally began to track the changes in reinforcement density. This study demonstrated the sensitivity of such a procedure for identifying a possible behavioral mechanism for lead and methylmercury exposure, namely reduced sensitivity to changes in reinforcement contingencies. Such effects would not be apparent from a simple examination of steady-state behavior alone.

With a modified procedure, Newland et al. (2004) examined behavioral transitions with rodents exposed prenatally to methylmercury. Unlike the above studies, however, Newland et al. described a way for transitions to occur within a single session. Pregnant Long-Evans rats received 0, 0.5, or 6.4 ppm methylmercury in their drinking water. The offspring later responded under conc RI RI schedules of reinforcement in daily 3 hr sessions and transitions occurred 30 min into the session. When behavioral testing began, one group of offspring was 1.7 years-old and the other was 2.3 years-old. As with the present study, the first 30 min of the session arranged equal probabilities of reinforcement. Transitions to the left or right occurred pseudo-randomly and no-transition, left-transition, right-transition sessions each composed 33% of the total sessions. Reinforcer ratios (left: right) set up at 30 min included: 9:1, 4:1, 3:1, 1:1, 1:3, 1:4, and 1:9. The computer recorded moment-by-moment response rates across the two levers throughout each session. For the 1.7 year-old offspring, reinforcer rates, but not methylmercury, influenced response rates and changeover rates in a manner reflecting sensitivity to reinforcement rates throughout the session. For the 2.3 year-old offspring, however, reinforcer rates did not influence changeover rates. Moreover, the exposed

rats in this group required twice as many reinforcers than the control rats in this group to complete 50% of the transitions to the 9:1 and 4:1 reinforcer ratios, reflecting a decreased sensitivity to changes in reinforcement rates. Thus, this study found that prenatal methylmercury exposure impaired acquisition in offspring as they aged.

Based on earlier work in Newland's laboratory, Newland and Reile (1999) recommended examining behavioral transitions with mixed concurrent schedules of reinforcement and fitting a logistic equation to the data generated from each transition session. The logistic equation parameters were found to be helpful for examining the molecular transition data of the large group of subjects exposed to methylmercury in the Newland et al. study. Because behavior often does not change until well after the reinforcement contingencies have changed, Newland and Reile (1999) reported that the logistic equation appears best suited for examining transition data. The Gompertz equation was found to be similar, but less ideal. Both s-shaped functions, the logistic and Gompertz equations estimated comparable initial and final steady states. However, the difference was in the shape of the curve revealing the rate of behavior change. The logistic equation assumes symmetry around the midpoint whereas the Gompertz equation estimates asymmetrical rates of change around the midpoint suggesting that the departure from the initial steady-state occurs more or less rapidly than the approach to the final steady-state. The logistic equation better fit the data from Newland's laboratory. Finally, Newland and Reile (1999) argued that the hyperbolic and exponential equations were unsuitable for describing behavior change because both lack a parameter to describe the steady-state either before (hyperbolic) or after (exponential) the transition.

When graphically examining molecular transition data there is much variability from visit to visit. Therefore, a LOWESS smoothing algorithm, which also smoothes large fluctuations in variability, further enhanced the interpretation of the data, because it revealed trends in behavior. Moreover, when used with molecular transition data, the LOWESS equation, had little effect on the logistic equation parameters (see Newland & Reile, 1999).

Many of the graphical analyses in the present study include fits of a LOWESS smoothing algorithm. The current study did not use a logistic equation because it is likely to be informative with only four subjects than more conventional graphical analyses. The logistic equation parameters are more useful for comparing data from a larger group of subjects (see Newland et al., 2004) or when comparing a larger group of repeated-measures with a single-subject design.

Dopamine, reinforcement, and learning

Over the past decade, the dopaminergic system has become of interest to behavioral psychologists because it appears to be a major factor in regulating reinforcement processes. The relation between the dopaminergic system and reinforcement processes is pertinent to an analysis of behavior in transition because reinforcement selects behavior under changing environmental conditions. Thus, reduced or increased sensitivity to reinforcement will alter acquisition patterns. Two primary classes of drugs that act on the dopaminergic system are stimulants and neuroleptics.

Amphetamine is a stimulant that can take on two stereochemical isomeric forms. The *d*-isomer has been known to be much more potent than the *l*-isomer (K. M. Taylor & Snyder, 1970). Stimulants such as *d*-amphetamine, methylphenidate (Ritalin® and

Methylin®), and *l*-amphetamine (Adderall®) are agonists that, to different degrees, potentiate the action of dopamine, norepinephrine, and to a smaller degree, serotonin by releasing central stores of and blocking reuptake (Sotak, Hnasko, Robinson, Kremer, & Palmiter, 2005). Amphetamine also inhibits monoamine oxidase (MAO), an enzyme that breaks down catecholamines (Nichols, 1994). Amphetamine and its analogs are prototypical stimulants. Many disorders including attention deficit hyperactivity disorder (ADHD), narcolepsy, and obesity are treated with stimulants. Depending on dose, dopaminergic agonists have generally been characterized as producing such effects as *increased* blood pressure, heart rate, rate of respiration, alertness, euphoria, excitement, mood, rate of speech, and motor activity (Julien, 1998).

Conversely, traditional neuroleptics (antipsychotics) such as chlorpromazine (Thorazine®), thioridazine (Mellaril®), and haloperidol (Haldol®) are antagonists that to different degrees nonselectively block the action of dopamine as well as acetylcholine, serotonin, histamine, and norepinephrine. Haloperidol is a neuroleptic traditionally used to treat psychoses. It is a prototypical high-potency D2 dopamine receptor blocker (Hyttel, Larsen, Christensen, & Arnt, 1985), although it does have some anticholinergic effects (Rammsayer, Rodewald, & Groh, 2000). Depending on dose and specificity, antagonists engender such effects as *decreased* psychomotor activity, attention to sensory stimuli, emotional responses, paranoia, agitation, delusions, and hallucinations. Thus, these drugs are often referred to as major tranquilizers (Julien, 1998). Subchronic treatment with traditional neuroleptics results in fewer electrically active dopaminergic neurons in the ventral tegmental area (VTA) and the substantia nigra. However, administration of newer and more selective

antipsychotics such as clozapine results in fewer electrically active dopamine neurons in the VTA alone (Chiodo & Bunney, 1983).

Despite wide therapeutic use of many of the drugs listed above, research efforts tend to focus on behavior that is well established and usually referred to as *performance*. The research focus on performance may have come from the use of the drugs to treat problematic behavior patterns rather than problems associated with learning. A focus on performance, however, rather than on learning might have tangible consequences for individuals taking dopamine agonists or antagonists. Some drugs have been found to affect learning at doses that do not affect performance (Bickel, Higgins, & Hughes, 1991; Thompson & Moerschbaecher, 1979a). *Safe* dosing based on performance data, may inadvertently compromise a person's ability to learn. For this reason, it is crucial that we understand the behavioral and physiological mechanisms by which dopaminergic drugs interact with other environmental variables to influence learning.

Dopaminergic agonists and antagonists have been found to affect performance by increasing or decreasing motor activity (e.g., Agrawal, Tilson, & Bondy, 1981; Cagiano et al., 1990; Dorman et al., 2000; Hitchcott & Phillips, 1998; Ikemoto & Panksepp, 1999; Smith-Roe & Kelley, 2000; Solanto, 1998; K. M. Taylor & Snyder, 1970; Thiruchelvam, Richfield, Goodman, Baggs, & Cory-Slechta, 2002). In addition, dopaminergic agonists and antagonists alter stimulus control (Solanto, 1998; Wyvell & Berridge, 2000; Yin, Zhuang, & Balleine, 2006), and modify the reinforcement process (Daw, Kakade, & Dayan, 2002; Dayan & Balleine, 2002; Di Chiara, 1999; Suri, 2002; Wise, 2002; Wyvell & Berridge, 2000).

Behavioral studies that have examined the effects of dopaminergic agonists and antagonists on learning largely comprise discrete-trials procedures that have been conducted with a variety of species including humans (Sprague, Barnes, & Werry, 1970; Ward, Kelly, Foltin, & Fischman, 1997), monkeys (Schultz, Apicella, & Ljungberg, 1993; Thompson & Moerschbaecher, 1979b), pigeons (Evans & Wenger, 1990), squirrel monkeys (Evans & Wenger, 1992), and rats (Mayorga, Popke, Fogle, & Paule, 2000).

Generally, dopamine antagonists disrupt learning (e.g., Bedard et al., 2000; Dickinson, Smith, & Mirenowicz, 2000; Ploeger, Spruijt, & Cools, 1994; Poling, Cleary, Berens, & Thompson, 1990). Other studies examining acquisition have demonstrated that dopamine agonists also have disruptive effects, especially at higher doses (Bartus, 1979; Mayorga, et al., 2000; Thompson, 1974, 1976). Chuhan and Taukulis (2006) stated that fewer studies have examined methylphenidate (the dopamine agonist commonly used to treat ADHD) than *d*-amphetamine. Methylphenidate studies have largely examined effects on attention rather than on acquisition because it is often presumed that learning and memory are enhanced as a function of improved attention. Two studies reported enhanced acquisition of the stimulus-reward association with intra-amygdala microinjections of *d*-amphetamine and have concluded that the D3 dopamine receptor subtype modulates this effect (Hitchcott, Bonardi, & Phillips, 1997; Hitchcott, Harmer, & Phillips, 1997).

Discrete-trials procedures used with dopaminergic compounds include tests such as the incremental repeated acquisition (IRA) of behavioral chains procedure (Evans & Wenger, 1992; Mayorga, et al., 2000; Poling, et al., 1990; Schrot & Thomas, 1983;

Schulze & Paule, 1990; Thompson, 1974; Ward, Kelly, Foltin, & Fischman, 1997), object discrimination reversal learning (Ridley, Haystead, & Baker, 1981), reaction time (Mayfield, Randall, Spirduso, & Wilcox, 1993a, 1993b), maze learning (Jaenicke, Jaenicke, Schulze, & Coper, 1990), list-learning memory tasks with humans (Kern et al., 1999; Legangneux et al., 2000), motor learning tasks (Kern et al., 1999), acquisition of conditioned place preference (e.g., Leri & Franklin, 2000; Tirelli, Tambour, & Michel, 2003) and conditioned avoidance (e.g., Bean, Elgin, Cooper, & Martin, 1987; Linner, Wiker, Wadenberg, Schalling, & Svensson, 2002; White & Rebec, 1994). Comparatively few investigators have examined variables that influence free-operant response acquisition, a problem also noted by other investigators (Branch, 1977; Commons, Woodford, Boitano, Ducheney, & Peck, 1982; Dickinson, Watt, & Griffiths, 1992; Evans & Wenger, 1992; Lattal & Gleeson, 1990; LeSage et al., 1996). Other than the MCS procedure used in Newland's laboratory, few procedures for examining acquisition of free-operant behavior have been developed. A few free-operant procedures worth noting include acquisition of FR schedule performance (Byrne, Lesage, & Poling, 1997) and lever-press acquisition (Stolerman, 1971a, 1971b).

Because the RA procedure is a common behavioral test for the effects of pharmacological and toxicological agents on learning, it is worth comparing with the MCS procedure used in this dissertation. First described by Boren (1963), the RA procedure generally requires subjects to learn a different sequence of behavioral responses during each experimental session and each response in the sequence can be paired with a particular stimulus condition. With an incremental RA procedure, the difficulty level of the trial following successful responding can be increased based on

the capabilities of the subject (e.g., Paule & McMillan, 1984). This procedure has proven very useful in identifying behavioral mechanisms underlying drug and toxicant effects (Cohn & Cory-Slechta, 1994; Cohn, Cox, & Cory-Slechta, 1993; Cohn, Ziriax, Cox, & Cory-Slechta, 1992; Paule & McMillan, 1984).

Discrete-trials procedures and free-operant procedures for examining learning are fundamentally different for obvious reasons. However, they also focus on different portions of the 3-term contingency, albeit not mutually exclusively. The RA procedure focuses on how behavior is controlled by discriminative stimuli, whereas the MCS procedure focuses on how behavior organizes around its consequences (Newland & Reile, 1999). Therefore, the RA procedure can offer more detailed information about effects other than overall accuracy (Cohn, et al., 1993; Cohn & Paule, 1995) and it is likely to be more sensitive for detecting subtle effects on discrimination because it allows for the arrangement of several discriminative stimuli. The MCS procedure, as used by Newland et al. (2004), allows for one opportunity each session, when the schedules change, to arrange discriminative stimuli. This procedure does not preclude, however, the arrangement of several transitions within one session as done, for example, by Dreyfus (1985), which provides more of an opportunity to study the role of discriminative stimuli under mixed concurrent schedules.

The MCS procedure is likely to be more sensitive for detecting subtle effects on the response-consequence portion of the 3-term contingency. Furthermore, the MCS procedure is more likely to detect subtle motor effects because it is does not limit responding as does the RA procedure (Newland & Reile, 1999). Donahoe, Burgos, and Palmer (1993) contended that different behavioral functions are mediated by different

neuronal structures. Thus, in testing drugs or toxicants, selection of the procedure should be based on known information about the probability that the compound will alter stimulus control or the reinforcement process. An examination of both relations is ideal. However, the use of one procedure does not exclude the possibility of obtaining information about the relation not typically emphasized.

Mesolimbic and mesocortical neurotransmitters

A great deal of attention in recent years has been devoted to the mesolimbic and mesocortical dopamine systems (Nichols, 1994; Segal, 1994). The mesolimbic system consists of dopaminergic cells projecting from the VTA to structures of the limbic system (at the base of the cerebral hemispheres) including the nucleus accumbens, the amygdala, the septal area, and the hippocampus. The mesocortical system consists of dopaminergic cells projecting from the VTA to the nucleus accumbens, olfactory tubercle, and frontal cortex. The neurons projecting to the nucleus accumbens and the frontal cortex appear to be the primary players in the reinforcement process (Wise, 2002) although emphasis has largely been on the mesolimbic system (e.g., Berridge & Robinson, 1998; Bozarth, 1991; Di Chiara & Imperator, 1988; Spanagel & Weiss, 1999; Wightman & Robinson, 2002; Wise, 2002; You, Chen, & Wise, 2001).

Interest in the neuroanatomical structures involved in the reinforcement process largely began when Olds and Milner (1954) discovered that electrical stimulation of the septal area (a cluster of nuclei that separates the anterior horns of the lateral ventricles) in rats' brains functioned as a reinforcer. Shortly thereafter, Sidman et al. (1955) examined lever pressing under various schedules of reinforcement maintained by intracranial self-stimulation. Dews (1955a, 1955b, 1956, 1958) and Dews and Morse

(1961) began examining drug effects on responding under simple schedules of reinforcement. Several investigators later began examining more closely the behavioral effects of stimulants such as the amphetamines (e.g., Barrett, Katz, & Glowa, 1981; Bhagat & Wheeler, 1973; Dews & Morse, 1958; Dews & Wenger, 1977; Downs & Braude, 1977; Johanson, Aigner, Seiden, & Schuster, 1979; McMillan, 1969; Paule & McMillan, 1984; Schrot & Thomas, 1983; K. M. Taylor & Snyder, 1970; Thompson, 1974; Weiss & Gott, 1972; Weiss & Laties, 1962, 1964). Dews and Wenger (1977) found that the behavioral effects of amphetamine were dependent on the ongoing rate of responding. Specifically, amphetamine increased low rate behavior and decreased high rate behavior. In addition, many investigators noted that amphetamines were readily self-administered by a variety of species (e.g., Griffiths, Brady, & Bradford, 1977; Grove & Schuster, 1974; Haug & Gotestam, 1980; Johanson, Balster, & Bonese, 1976; Thompson, 1968; Thompson & Pickens, 1970; Wilson & Schuster, 1973). This observation culminated in the idea that addictions to drugs such as stimulants, opiates, nicotine, caffeine, barbiturates, alcohol, benzodiazepines, cannabis shared a common mechanism involving the dopaminergic pathways (Wise, 1980, 1982; Wise & Bozarth, 1987; Wise & Rompre, 1989).

A stream of research directed at examining drugs as reinforcers followed. Di Chiara and Imperato (1988) proposed that the activation of the mesolimbic dopaminergic system is involved in the reinforcing properties of drugs. Berridge and Robinson (1998) reviewed the literature and asserted that the dopaminergic system does not mediate learning of likes and dislikes, but instead mediates the incentive value of stimuli. Spanagel and Weiss (1999) reviewed the literature examining the dopamine

hypothesis for reward and concluded that mesolimbic dopaminergic neurons play a significant role in the acquisition of behavior by mediating the development of associations between salient contextual stimuli and internal reinforcing or aversive events (see also Ikemoto & Panksepp, 1999).

Recent progress in measuring dopamine transmission indicates that phasic (intermittent) as opposed to tonic (persistent) firing of the dopaminergic neurons coincides with reinforcing or signaling stimuli (Schultz, 2002; Wightman & Robinson, 2002). Schultz (2002) noted that the significance of the rapid neuronal discharge is in signaling the difference between actual and predicted rewards and thus plays a critical role in learning. Wightman and Robinson (2002) suggested that researchers remain unsure of the exact role within the network for processing reinforcers. Phillips, Stuber, Heien, Wightman, and Carelli (2003) reported that electrophysiological data did not reveal the difference between dopamine release associated with "reward-prediction error" and that associated with "reward-seeking" or operant behavior. This prompted Montague et al. (2004) to measure fluctuations in dopamine of freely moving rats with fast-scan cyclic voltammetry every 100 msec during patterns of electrical stimulation via a microelectrode to the striatum. They found that electrochemical analyses were able to reveal all measured oscillations in dopamine delivery. They ultimately proposed a three-component dynamic model in which dopamine release is controlled by mechanisms of plasticity inherent exclusively to the dopaminergic neuronal terminal without changes in uptake parameters. Montague et al. noted that future research is required to test further this model.

Given that *d*-amphetamine potentiates dopaminergic activity (Sotak, Hnasko, Robinson, Kremer, & Palmiter, 2005), it is not surprising that researchers have uncovered a variety of findings with respect to its effects on behavior in general and on the process of reinforcement and learning. Most of what we know about the effects of dopaminergic agonists and antagonists on learning comes from studies emphasizing the stimulus-response relation. As one might expect from a stimulant, *d*-amphetamine increases motor behavior, but contrary to what might be expected, it does not always increase operant response rates although some studies have found *d*-amphetamine reliably increases operant response rates (e.g., Fletcher & Korth, 1999; Fletcher, Korth, & Chambers, 1999; Ward, Kelly, Foltin, & Fischman, 1997). When appetitive stimuli were used as reinforcers, however, *d*-amphetamine often did not affect response rates until near doses high enough to disrupt responding by producing competing stereotypical behavior (Mobini, Chiang, Ho, Bradshaw, & Szabadi, 2000; Paule & McMillan, 1984; Schulze & Paule, 1990). Ziriax, Synder, Newland, and Weiss (1993) found dose-related decreases in responding due to increases in interresponse times (IRTs) and visit durations. Reilly (2003) used a five-component multiple fixed-ratio schedule with discriminative stimuli to examine effects of *d*-amphetamine and found that rate-decreasing effects of *d*-amphetamine (0.32 to 3.2 mg/kg) were due primarily to motor impairment and secondarily to increased impulsivity. Reilly suggested that the highest doses might have decreased the reinforcing effect of food.

Using a free-operant procedure with non-resetting and resetting-delay conditioning, LeSage et al. (1996) did not find an effect of *d*-amphetamine on acquisition until rats were administered doses that produced general behavioral

disruption. O'Tuathaigh and Moran (2002) found that *d*-amphetamine disrupts overshadowing in rats. The dopaminergic D2 receptor antagonists, haloperidol and raclopride, did not reverse the effect but the selective dopaminergic D1 antagonist, SCH 23390 did. Moreover, the partial D1 agonist SKF 38393 eliminated overshadowing when administered alone suggesting that *d*-amphetamine disrupts overshadowing perhaps by interacting with D1 receptors. Considering Montague et al.'s (2004) model and the disruptive effects of *d*-amphetamine, the increased release of dopamine may be the neuronal mechanism primarily underlying *d*-amphetamine's effects on learning. Likewise, d-amphetamine's blockade of the reuptake of dopamine may be the neuronal mechanism underlying *d*-amphetamine's effects on motor activity.

The types of tasks and analyses used probably account for some of the differences found as is evident from a study in which Schulze and Paule (1990) used an operant test battery to examine acquisition and performance of monkeys exposed to *d*-amphetamine. They found that some tests in the battery were much more sensitive to *d*-amphetamine's effects and others not very sensitive at all. The operant tasks designed to test ability to learn (such as the IRA procedure) and time perception were more sensitive to the disruptive effects of *d*-amphetamine than were tasks employed to access motivation, short-term memory, and attention. They found the latter tasks, however, to be more sensitive than tasks that model discrimination of color and position.

In addition to task differences, stimulants that act on dopamine such as *d*-amphetamine may differentially act on other neurotransmitter systems at different doses and make it more difficult to interpret results across studies. Kuczenski, Segal, Cho, and Melega (1995) used microdialysis in "behaving" rats to measure dopamine

and serotonin in the caudate and norepinephrine in the hippocampus when either D- or L- isomers of amphetamine or methamphetamine were administered. They found that although both isomers of each drug produced similar levels of stereotypy each produced different magnitudes of response from the dopamine, serotonin, and norepinephrine systems. They suggested that the different magnitudes are likely due to their different levels of potency at the presynaptic uptake sites but that a clear relationship between the neurotransmitter and behavioral profiles was not evident. One caveat worth mentioning is that the animals had continuous access to food and water. It would have been interesting to examine the effects of the drugs on neurotransmitters and behavior when behavior was under the control of a reinforcer arranged by the experimenter because of evidence suggests that dopamine plays a role in the reinforcement process.

Hitchcott, Harmer, and Phillips (1997) examined Pavlovian conditioning with rats using sucrose and found that the group receiving intra-amydala injections of *d*-amphetamine had an increased rate of acquisition of the S-R relation in which a 1-sec light became a conditioned reinforcer after pairing it with sucrose. Afterward, with an operant procedure, they examined acquisition of a novel lever-pressing response using the conditioned reinforcer from the Pavlovian test. They did not find any difference in acquisition. Thus, the efficacy of the conditioned reinforcer for acquisition of an operant response was similar for both *d*-amphetamine and control groups.

Solanto (1998) concluded that stimulants act on motor activity, reinforcement, and rate-dependency (differential effects based on the initial rate of behavior) by interacting with dopaminergic neurons in the nucleus accumbens. She also suggested that stimulants influence delayed responding and working memory by altering

norepinephrine in both the locus coeruleus and prefrontal cortex. Finally, she argued that stimulants appear to increase attention and stimulus control by interacting with both dopamine and norepinephrine and that these effects suggest the possibility that stimulants act at presynaptic inhibitory autoreceptors, resulting in reduced dopaminergic and noradrenergic activity.

Using a conditioned place-preference paradigm, Ventura and colleagues (2003), examined the activity of norepinephrine in the medial prefrontal cortex of mice bred to be sensitive to the reinforcing effects of amphetamine as a result of depleted prefrontal norepinephrine. On the one hand, they found that norepinephrine mediates the motor effects of amphetamine. On the other hand, they concluded that prefrontal norepinephrine is involved in the reinforcing effects of amphetamine to the extent that it enables increased dopamine release in the nucleus accumbens induced by amphetamine.

Some researchers have proposed that the serotonergic system has, to some degree, an inhibitory effect on reinforcement processes potentiated by dopamine (Harrison & Markou, 2001; Kelland & Chiodo, 1996). For example, Fletcher and colleagues (Fletcher & Higgins, 1997; Fletcher & Korth, 1999; Fletcher, Korth, & Chambers, 1999) found that injecting *d*-amphetamine into the nucleus accumbens of rats noticeably increased responding for a conditioned reinforcer. When they additionally injected serotonin to the nucleus accumbens, they found that it diminished the effects of *d*-amphetamine.

Complicating the puzzle further, Cannon and Palmiter (2003) found evidence challenging the assumption that dopamine plays a fundamental role in reinforcement. They found that dopamine-deficient bred mice preferentially responded for sucrose, and

the noncaloric sweetener, saccharin, over water. The deficient mice also demonstrated a greater rate of licking, bout size, and bout length when drinking sweets than control mice. They argued that these data refute the idea that dopamine is a requirement for reinforcement, but they did find that the dopamine-deficient mice had fewer total licks and initiated licking less frequently than control mice.

In summary, researchers have yet to identify conclusively the specific roles neurotransmitters play in the process of reinforcement, although it appears that the evidence is mounting in favor of all playing some role. Dopamine appears to be the main player, yet by itself, it does not explain the findings. Norepinephrine and serotonin may play more of an indirect role by modulating dopaminergic activity in the mesolimbic system. When dopamine is absent, it may be that norepinephrine plays a more pivotal role (Cannon & Palmiter, 2003). Even so, it is likely that a variety of variables including procedural differences for examining performance and acquisition of behavior, drug specificity, dosage, and subject variables, such as age interact with this process.

Research objectives

The goals of the current study were to examine acquisition of behavior in transition using a mixed concurrent RI RI schedules procedure to evaluate whether microanalytic data could reveal any behavioral mechanisms underlying changes in behavior that are not readily apparent with molar analyses (e.g. Baron & Leinenweber, 1994; Ziriax et al., 1993). A second goal was to examine the effects of *d*-amphetamine on learning under this procedure.

II. METHODS

Subjects

The subjects were four Long-Evans male rats purchased from Harlan, maintained at approximately 85% of their free-feeding weight on a standard rodent chow diet, and provided tap water *ad libitum*. They were housed individually in an environmentally controlled colony room with a 12-hr light-dark cycle. Animal protocols were approved by the Institutional Animal Care and Use Committee. The experiment began when the rats were approximately 1.5 years old. The rats previously served as control subjects in a previous study using mixed concurrent schedules (Newland et al., 2004).

Apparatus

Sessions were conducted in conventional experimental chambers during the animals' light cycle from approximately 1 to 4 pm, Monday through Friday. Each chamber was enclosed in a sound-attenuating cubicle and outfitted with two response paddles (2.5 x 2.5 x 0.16 cm) separated by 14.5 cm on one wall approximately 5 cm from the bottom of a grid floor. Food pellets (45 mg, Noyes) were delivered through a 3.8 cm^2 opening centered between the two levers. White noise was generated from a speaker 7.2 cm above the food dispenser. Reinforcement contingencies and data collections occurred with 0.01-sec resolution using a Digital Equipment Corporation PDP 11/73 computer running SKED11 software (State Systems).

Training

Autoshaping was used to train subjects to lever press during the previous experiment (Newland et al., 2004). Rats were placed in a chamber overnight in which food was delivered under a conc fixed-ratio 1 fixed-time 60-sec schedule of food reinforcement. Every 60 sec, a stimulus light over the lever was illuminated for 5 sec before a food pellet was delivered. Simultaneously, any lever press resulted in food reinforcement. After 10 presses of the left lever, the free food was terminated and a fixed-ratio 1 schedule remained in place until 100 lever presses occurred on the left lever.

Then, pressing the left lever no longer produced a reinforcer and a fixed-ratio 1 schedule was established on the other lever until 100 reinforced presses occurred on that lever, usually within one or two 30-min sessions. Lever pressing was then reinforced under a concurrent random-interval 60-sec random-interval 60-sec (Conc RI 60 RI 60) schedule of reinforcement. Under this schedule, a press on either lever produced a food pellet about once every 60 sec, on average, but the exact interreinforcer interval was unpredictable. For example, as the animal responded on the right lever, the timer for the left lever continued to operate, potentially setting up a reinforcer to follow the next eligible left-lever press. Thus, under a Conc RI 60 RI 60 schedule an animal could receive two reinforcers per min from the two levers combined. This schedule was continued for approximately thirty 1-hr sessions. Then the schedule changed to a Conc RI 180 RI 180, and when behavior under this schedule was stable, the session length was increased to 3 hr. Following common practice, a changeover delay of 2 sec was imposed in order to reduce rapid switching between levers and to enhance the

sensitivity of behavior to differences in the reinforcement rate between the two levers. That is, no reinforcer was delivered following a changeover from one lever to the other until at least the first response after 2 sec elapsed.

Behavioral tests

Because training occurred in a previous experiment, the subjects began this study on a mixed concurrent random-interval t_1 random-interval t_2 (CONC RI t_1 RI t_2) schedules in which t_1 and t_2 were both equal to 2 min. During the experimental sessions of this study, the rats responded to the independent schedules of reinforcement with a 2-sec COD in 3-hr sessions. CONC RI 2' RI 2' schedules were always active for the first 30 min of the session. After 30 min elapsed, the schedules were arranged on an equal, but pseudo-random basis such that the schedules either remained at CONC RI 2' RI 2' or changed to CONC RI 1' RI 4' (left-lever became rich) or CONC RI 4' RI 1' (right-lever became rich). Figure 1 depicts the experimental arrangement described above. Terminal reinforce ratios (left: right) used were 4:1, 1:1, and 1:4. Table 1 describes reinforcement rates and ratios. The arrangement allowed for the possibility of 150 reinforcers during no-transition sessions and 187.5 reinforcers during transition sessions in order to increase the salience of the transition. The houselight was on during these sessions and the transition progress was monitored on a visit-by-visit basis. Each time the animal changed levers (i.e., terminated a visit), the number of responses on that visit, the duration of the visit, and the number of reinforcers delivered were recorded.

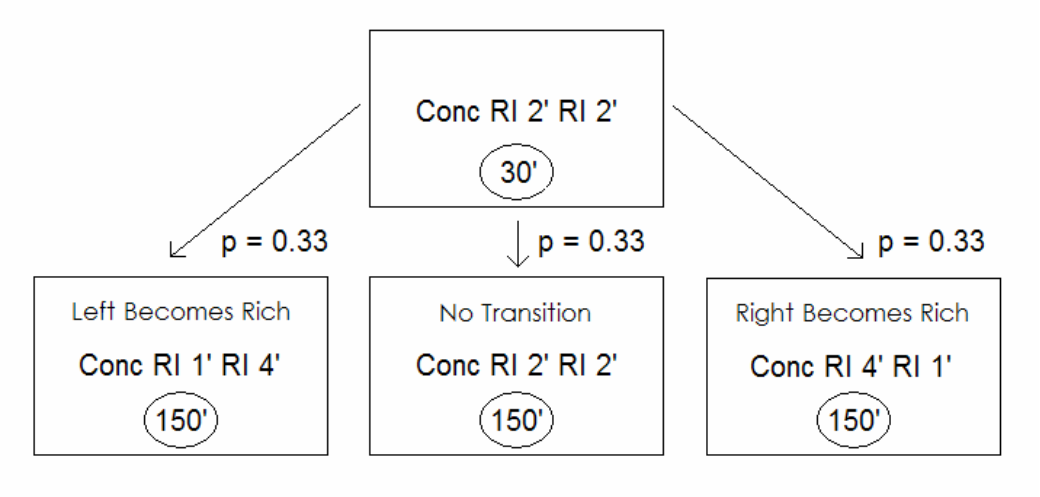

Figure 1. The mixed concurrent random-interval t_1 random-interval t_2 arrangement.

Reinforcement Schedule	Left : Right Reinforcer Ratio 30' - 180'	Reinforcers per Minute			Possible Reinforcers (Before + After Transition)		Total Possible Reinforcers	
		Left	Right	Total	Left	Right	1st 30'	30' - 180'
if after 1st 30' it ***remains*** at **Conc RI 2' RI 2'**	1 : 1	0.5	0.5	1.0	(15 + 75)	(15 + 75)	30	150.0
if after 1st 30' it ***changes*** to **Conc RI 1' RI 4'**	4 : 1	1.0	0.25	1.25	(15 + 150)	(15 + 37.5)	30	187.5
if after 1st 30' it ***changes*** to **Conc RI 4' RI 1'**	1 : 4	0.25	1.0	1.25	(15 + 37.5)	(15 + 150)	30	187.5

Table 1. Reinforcer ratios, rates, and quantity possible under the three types of schedules.

Drug Challenges

After several transitions were analyzed and it was determined that behavior stabilized under these conditions (i.e., there were no trends in session data over 15 consecutive sessions under each of the terminal reinforcer ratios), acute doses of *d*-amphetamine (0.1, 0.3, 1.0, 3.0, and 6.0 mg/kg) dissolved in saline were administered

IP 30 min before Tuesday and Friday sessions. Mondays and Wednesdays were non-drug control days. Vehicle (saline) was injected on Thursdays. It took 6 months to administer the doses in an ascending then descending fashion (instead of testing all three terminal ratios on the descending run, only 1:1 and 1:4 were tested because there was no apparent difference between 4:1 and 1:4 on the ascending run).

Data Analyses

Brooks RS/Client 2.1.2 for Windows and RS/1 Version 6.1 for Windows software was used for storing data, data analyses, and graphical analyses of data. Session data were analyzed in terms of global dependent measures such as total reinforcers, visits to each lever, and overall response, time, and reinforcer proportions and ratios across levers, before and after the transition. In addition, by examining sessions on a visit-by-visit basis, microanalyses were performed to examine the transitions more closely. For example, proportion of newly-rich lever responses or proportion of time on the newly-rich lever was examined as a function of cumulative reinforcers delivered by the newly rich lever. A LOWESS smoothing algorithm was used to refine the appearance of the session data. A smoothing parameter of 9 was used meaning that a particular data point represents a weighted mean of that data point plus four to the left and four to the right, with weights becoming smaller for more distal points (see Chambers, Cleveland, Kleiner, & Tukey, 1983). Data from control, saline, and drug days were compared in a within-subject manner (i.e., the same animal's responding under drug conditions was compared with its own responding under control conditions), although similarities and differences were also noted across subjects.

III. RESULTS

Summary Data

Summary data for all subjects are presented in Tables 2 and 3 and Figures 2 through 6. Group averages are presented in Table 2 and individual averages are presented in Table 3. Averages were calculated by taking the most recent sessions for control, saline, and all doses of d-AMP. Included was one session from each subject for each of the different programmed ratios (i.e., 4:1, 1:1, and 1:4). Group average of responses on the left and right levers peaked at an average of 4376 responses in the 1.0 mg/kg d-AMP condition (see Table 2). Total responses dropped off at 6.0 mg/kg d-AMP; however, a greater portion of that drop was in responding on the left lever. Although not revealed by the table, this bias largely came from one subject. Average time spent on the left and right levers shows a preference for the right lever. This bias becomes much more apparent at 6.0 mg/kg d-AMP. Finally, Table 2 shows little change in total reinforcers obtained until dropping approximately 10% under the 3.0 mg/kg d-AMP dose and approximately 46% under the 6.0 mg/kg d-AMP doses.

Table 3 presents averages of individual subjects for each dose. The figures with the thick borders reveal peak total responses and peak total reinforcers. Two interesting points are that the figures occur at the same dose and that they are greater than under control conditions, however, not always greater than vehicle sessions. Table 3 also shows total responses declining during the 6.0 mg/kg d-AMP sessions and along with that decline, there was a decrement in total reinforcers.

DOSE	LEFT RESPONSES	RIGHT RESPONSES	TOTAL RESPONSES	LEFT TIME	RIGHT TIME	LEFT REINFORCERS	RIGHT REINFORCERS	TOTAL REINFORCERS
Control	1956	1896	3852	4369	5705	84	84	168
Saline	1783	1687	3470	4614	5495	86	86	172
0.1 mg/kg	2208	1934	4142	4668	5362	84	83	168
0.3 mg/kg	2150	2064	4214	4619	5314	83	82	165
1.0 mg/kg	2398	1978	4376	4712	5214	85	84	169
3.0 mg/kg	2135	2158	4293	3798	5967	73	84	157
6.0 mg/kg	849	1215	2064	1752	6695	25	54	79

Table 2. Group response, time, and reinforcer averages.

SUBJECT	DOSE	LEFT RESPONSES	RIGHT RESPONSES	TOTAL RESPONSES	LEFT TIME	RIGHT TIME	LEFT REINFORCERS	RIGHT REINFORCERS	TOTAL REINFORCERS
111	Control	1718	2409	4128	4392	5670	85	81	166
111	Saline	1328	2261	3589	4593	5549	82	86	168
111	0.1 mg/kg	1924	2688	4612	5067	4910	80	73	153
111	0.3 mg/kg	1713	2534	4246	4941	5038	87	78	165
111	1.0 mg/kg	2402	2737	5139	4849	5084	86	88	174
111	3.0 mg/kg	1956	2826	4782	3106	6734	61	90	151
111	6.0 mg/kg	298	2362	2660	688	9829	13	80	93
121	Control	1573	888	2461	4396	5866	79	76	156
121	Saline	2013	880	2893	4998	5211	85	84	168
121	0.1 mg/kg	1989	942	2932	4787	5436	87	82	169
121	0.3 mg/kg	1433	895	2328	4645	5440	79	77	156
121	1.0 mg/kg	1682	955	2637	5118	5036	77	79	156
121	3.0 mg/kg	3027	1645	4672	5331	4125	94	79	173
121	6.0 mg/kg	1892	1339	3231	3364	6201	46	60	106
131	Control	2653	2204	4857	4793	5113	81	87	168
131	Saline	1907	1759	3665	4728	5300	88	86	174
131	0.1 mg/kg	2647	2179	4826	4508	5416	84	85	169
131	0.3 mg/kg	3325	2763	6088	4371	5340	84	90	174
131	1.0 mg/kg	3213	2369	5583	5265	4477	85	77	162
131	3.0 mg/kg	2093	2032	4125	3989	5731	73	82	155
131	6.0 mg/kg	770	686	1456	1699	5856	22	45	66
141	Control	1879	2084	3963	3895	6173	91	90	182
141	Saline	1885	1847	3732	4138	5919	91	87	178
141	0.1 mg/kg	2273	1925	4198	4309	5687	87	93	181
141	0.3 mg/kg	2130	2065	4195	4519	5437	83	83	167
141	1.0 mg/kg	2295	1850	4145	3616	6258	91	92	183
141	3.0 mg/kg	1463	2130	3593	2764	7276	63	86	149
141	6.0 mg/kg	437	474	911	1257	4895	21	30	51

Table 3. Individual response, time, and reinforcer averages.

The shape of the dose-effect curves revealing reinforcers obtained during control, saline, and *d*-amphetamine (d-AMP on figures) transition and no-transition sessions are similar for all rats (see Figure 2). In these figures, all rats showed no difference in reinforcers obtained before transitions among control, saline, and d-AMP sessions, except for at the highest dose of d-AMP for which there was typically a decrease. They also showed no difference in reinforcers obtained after transitions among control, saline, and low-moderate doses of d-AMP. When administered 3.0 mg/kg of d-AMP, Subject 141 showed a decline in reinforcers obtained after the transition during transition sessions only. When administered 6.0 mg/kg of d-AMP, all rats showed a substantial decrease in reinforcers obtained, especially after the transition. All subjects obtained more reinforcers/session during transition sessions than during no-transition sessions because there were more programmed reinforcers available during transition sessions (see Table 1).

Figure 3 illustrates lean reinforcers obtained during control, saline, and d-AMP transition and no-transition sessions. Lean reinforcers are those obtained for responding on the lever associated with the leaner schedule of reinforcement. Again, the dose-effect curves for all four rats are similar. As with total reinforcers, all rats showed no difference in lean reinforcers obtained before transitions among control, saline, and d-AMP sessions, except for at the highest dose of d-AMP for which there was sometimes a decrease. They also showed no difference in lean reinforcers obtained after transitions among control, saline, and low-moderate doses of d-AMP. When administered 6.0 mg/kg of d-AMP, all rats showed a substantial decrease in lean

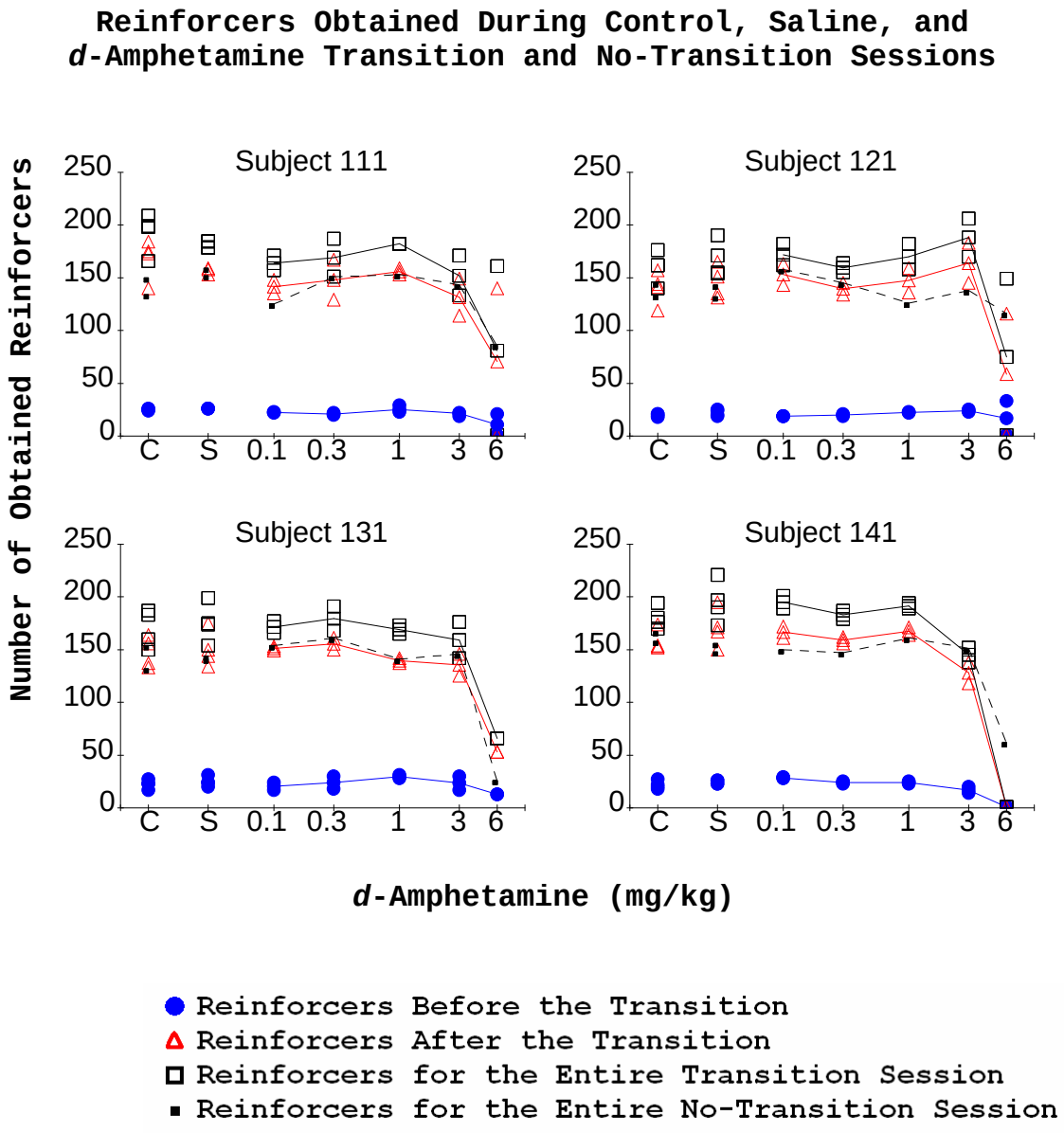

Figure 2. Reinforcers obtained during control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions. See text for details.

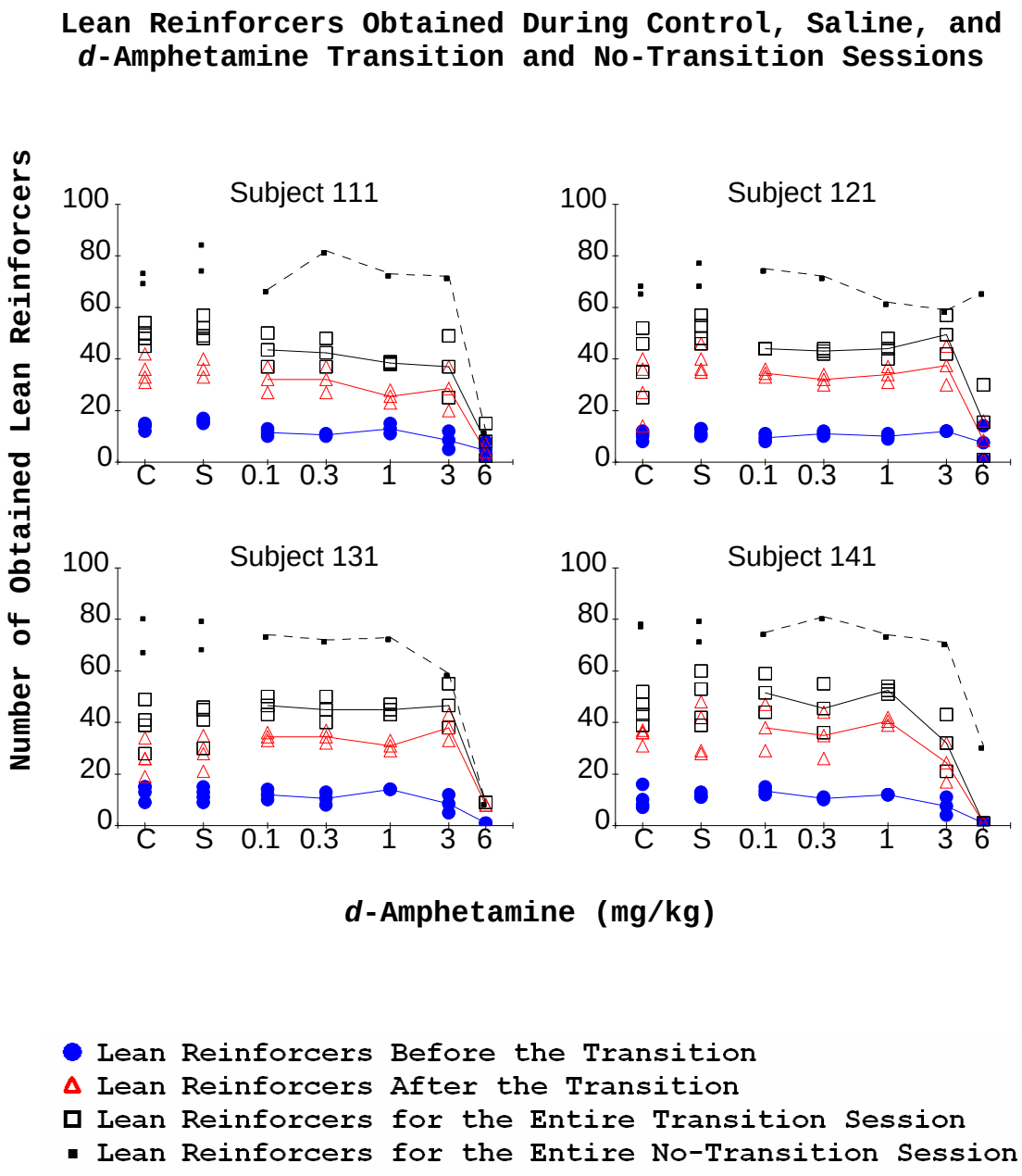

Figure 3. Lean reinforcers obtained during control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions. See text for details.

reinforcers obtained after the transition. They obtained more lean reinforcers per session during no-transition sessions than during transition sessions.

Figure 4 shows rich reinforcers obtained during control, saline, and d-AMP transition and no-transition sessions. Rich reinforcers are those obtained for responding on the lever associated with the richer schedule of reinforcement. Again, the dose-effect curves for all four rats are similar. As with total reinforcers, all rats showed no difference in rich reinforcers obtained before transitions among control, saline, and d-AMP sessions, except for at the highest dose of d-AMP for which there was sometimes a decrease. They also showed no difference in rich reinforcers obtained after transitions among control, saline, and low-moderate doses of d-AMP. When administered 6.0 mg/kg of d-AMP, all rats showed a substantial decrease in rich reinforcers obtained after the transition. Overall, they obtained more rich reinforcers per transition session than during no-transition sessions.

Figure 5 depicts visits made during control, saline, and d-AMP transition and no-transition sessions. Again, a visit began with the first response on one lever and ended with a response on the other lever. The shape of the dose-effect curves for visits made for the entire session for Subjects 111, 131, and 141 were similar: there were no differences among control, saline, and 0.1 – 3.0 mg/kg d-AMP sessions, whereas, there was a decrease in visits at 6 mg/kg d-AMP, especially for Subject 141. Subject 121 showed no differences until an increase in visits during 3.0 and 6.0 mg/kg d-AMP sessions. Subjects 111, 121, and 131 showed dose-dependent decreases in the number of visits before transitions. All rats showed no differences in visits made during transition and no-transition sessions.

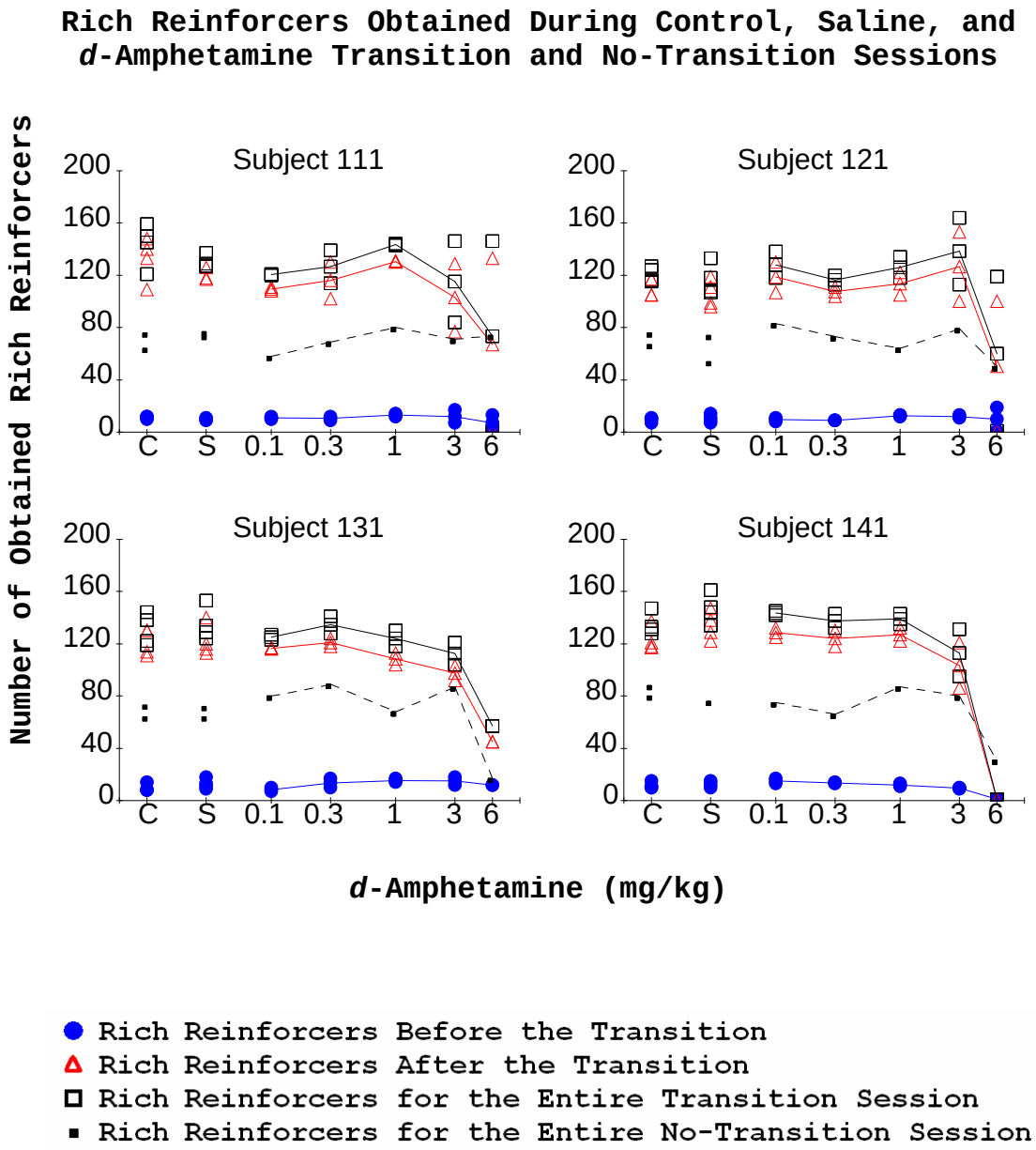

Figure 4. Rich reinforcers obtained during control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions. See text for details.

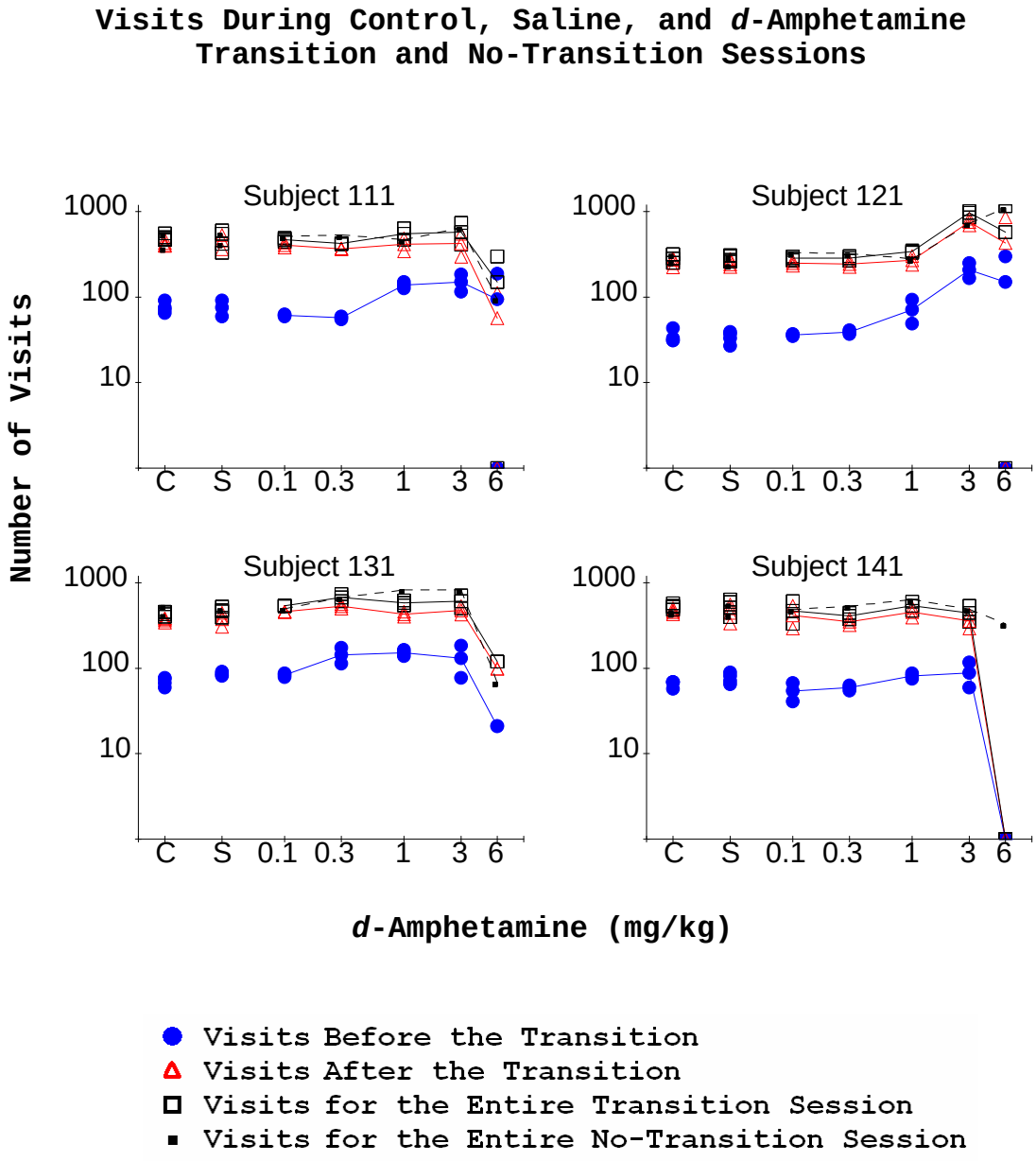

Figure 5. Visits during control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions. See text for details.

Reinforcers per visit were calculated and plotted for control, saline, and d-AMP transition and no-transition sessions (see Figure 6). In general, there was little difference in reinforcers/visit for control, saline, low doses of d-AMP. At moderate and high doses of d-AMP, there was generally a substantial decrease in reinforcers per visit except for Subject 131 and sometimes Subject 111, which showed a substantial increase in reinforcers per visit under 6 mg/kg d-AMP, during transition sessions. The increase in reinforcers per visit under 6 mg/kg d-AMP was a result of a few very long visits under this dose. There were generally more reinforcers per visit obtained for transition than no-transition sessions.

Microanalytic data

The general pattern observed in the microanalytic data is comparable across subjects. Similarly, responding to the right lever was similar to the pattern of responding to the left lever. Because the microanalytic data consist of visit-by-visit recordings of events during 3-hr sessions, there is a plethora of data plotted in each of the following figures and each figure presents seven graphs, one each for control, saline, and each of the doses of d-AMP. Therefore, the data reported below in Figures 7 through 19 are for Subject 111. All figures are arranged similarly such that control, saline, and each dose of d-AMP are in a similar location on the page across all figures enabling a comparison of dose-effect for each of the measures. The data for left lever-responding for Subject 111 as well as all of the same figures for Subjects 121, 131, and 141 can be found in the Appendix.

The proportions of responses, time, and reinforcers to the lever on the right side of the testbox during each visit of no-transition sessions are plotted in Figure 7. The thin

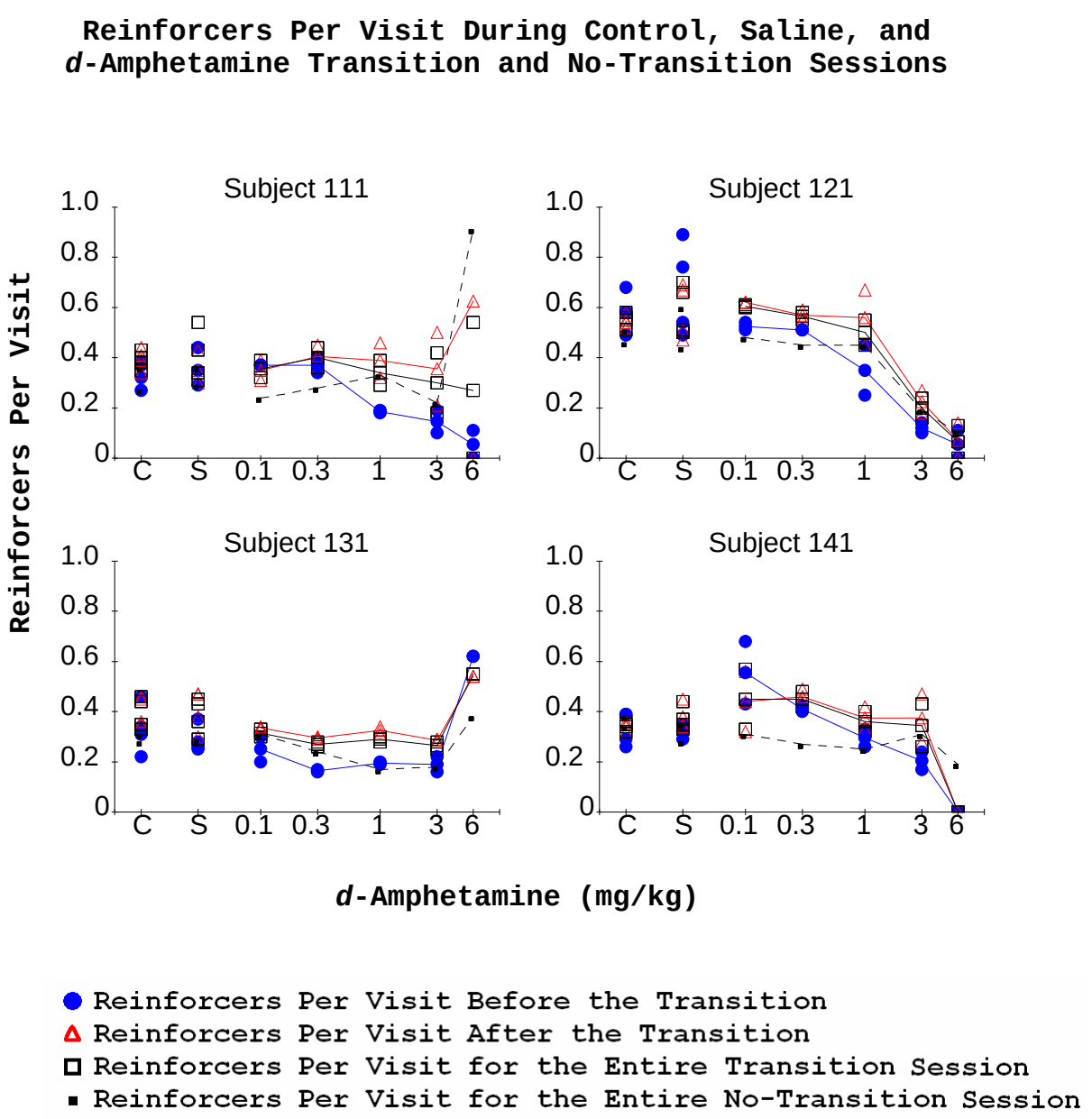

Figure 6. Reinforcers per visit during control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions. See text for details.

double line shows the programmed proportion of reinforcers across the two available levers. The black dots (sometimes so close together that they appear to be a thick black line) are proportions of right obtained reinforcers during each consecutive pair of visits. The red circles are proportions of right responses made during each consecutive pair of visits and the blue dots are proportions of right time spent during each consecutive pair of visits. A Lowess smoothing algorithm was fit to the data in order to see more clearly the course of the proportions of responses to the right and proportions of time to the right made through the session. The Lowess fits for proportion of responses and time closely follow the proportion of reinforcers obtained for right-lever responding through the same session. In general, there was less variability during control, saline, and low-doses of d-AMP than at higher doses of d-AMP. In addition, Figure 7 reveals that the number of visits remains stable across the dose effect curve through 1.0 mg/kg of d-AMP. At 3.0 mg/kg, d-AMP there was a marked increase in the number of session visits and, in contrast, a striking decrease in the number of session visits under 6.0 mg/kg d-AMP.

The proportions of rich responses, time, and reinforcers each visit during transition sessions are plotted in Figure 8, again revealing that the Lowess fits proportions of responding to the rich lever and time spent on the rich lever closely follow the proportion of reinforcers obtained for rich lever responding through the same session. In fact, the courses more closely overlap at 0.1, 0.3, and 1.0 mg/kg d-AMP during these transition sessions than they do during the no-transition sessions plotted in Figure 7. In addition, behavior appears to track more closely the transition of programmed proportion of rich reinforcers during 1.0 mg/kg d-AMP session. Finally,

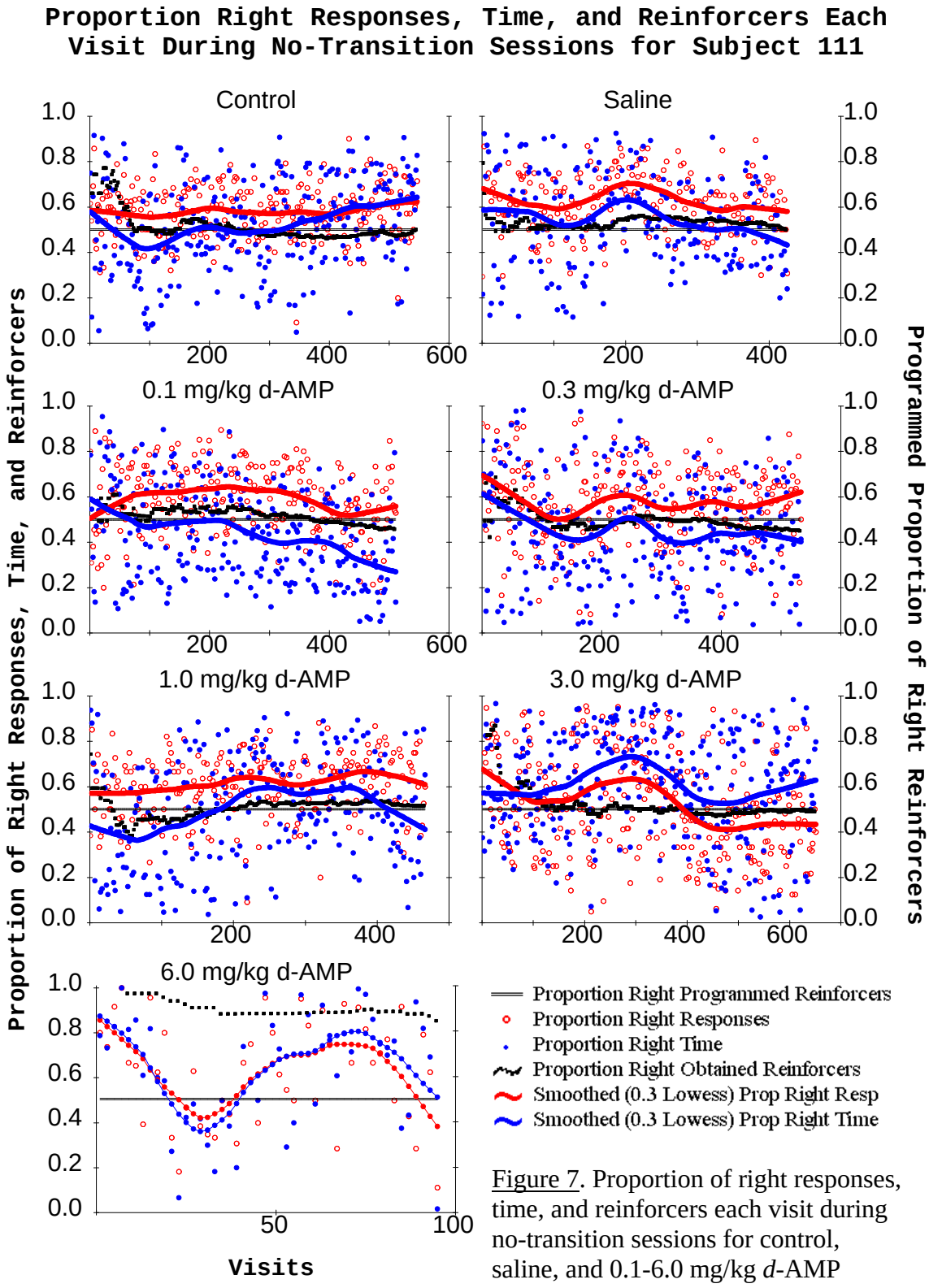

Figure 7. Proportion of right responses, time, and reinforcers each visit during no-transition sessions for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions. See text for details.

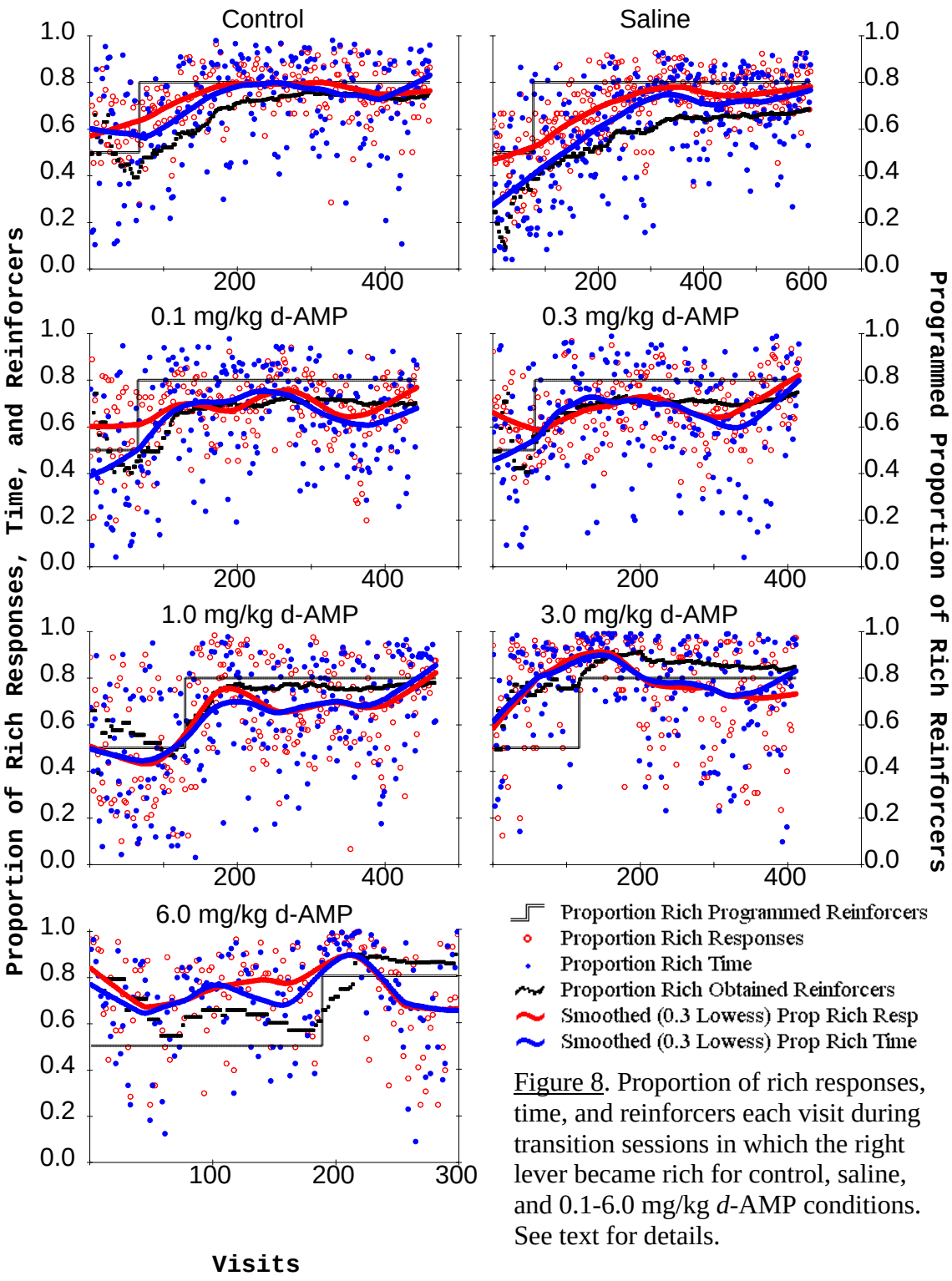

Figure 8. Proportion of rich responses, time, and reinforcers each visit during transition sessions in which the right lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions. See text for details.

3.0 and 6.0 mg/kg d-AMP appears to disrupt the tracking of programmed reinforcer proportions available, especially at the highest dose. In addition, the highest dose, decreased the number of visits by approximately 25%. However, the decrease in the number of visits observed under 6.0 mg/kg was not as marked as the decrease observed under the same dose during the no-transition session plotted in Figure 7.

Visit response rates during no-transition sessions for Subject 111 are shown in Figure 9. With regard to overall response rate, there is little difference among figures for control, saline, 0.1 mg/kg, 0.3 mg/kg, and 1.0 mg/kg d-AMP. There were generally between 0.1 to 2 responses per sec of visit time and approximately 500-550 visits per session. The variability of visit response rates within a session was lower for control and saline than for d-AMP sessions. There were approximately 0.9 responses per sec of right visit time and 0.7 to 0.8 responses per sec of left visit time during control and saline sessions. The left visit response rate decreased under 0.1 mg/kg, 0.3 mg/kg doses of d-AMP, and 1.0 mg/kg. During the 3.0 mg/kg d-AMP session, the left visit response rate increased to approximately 0.9 responses per sec of visit time and the right visit response rate decreased over the session from 0.8 responses to 0.5 responses per sec of visit time. There were also 650 visits during this session, at least 100 visits more than other sessions. Finally, during the 6.0 mg/kg d-AMP session, both left and right responding continued to fluctuate between approximately 0.1 to 2.0 responses per sec, however, visits were substantially reduced to less than 100.

Visit response rates during transition sessions in which the right lever became rich for Subject 111 are shown in Figure 10. With regard to overall response rate, there is little difference among the figures for control, saline, 0.1 mg/kg, 0.3 mg/kg, and

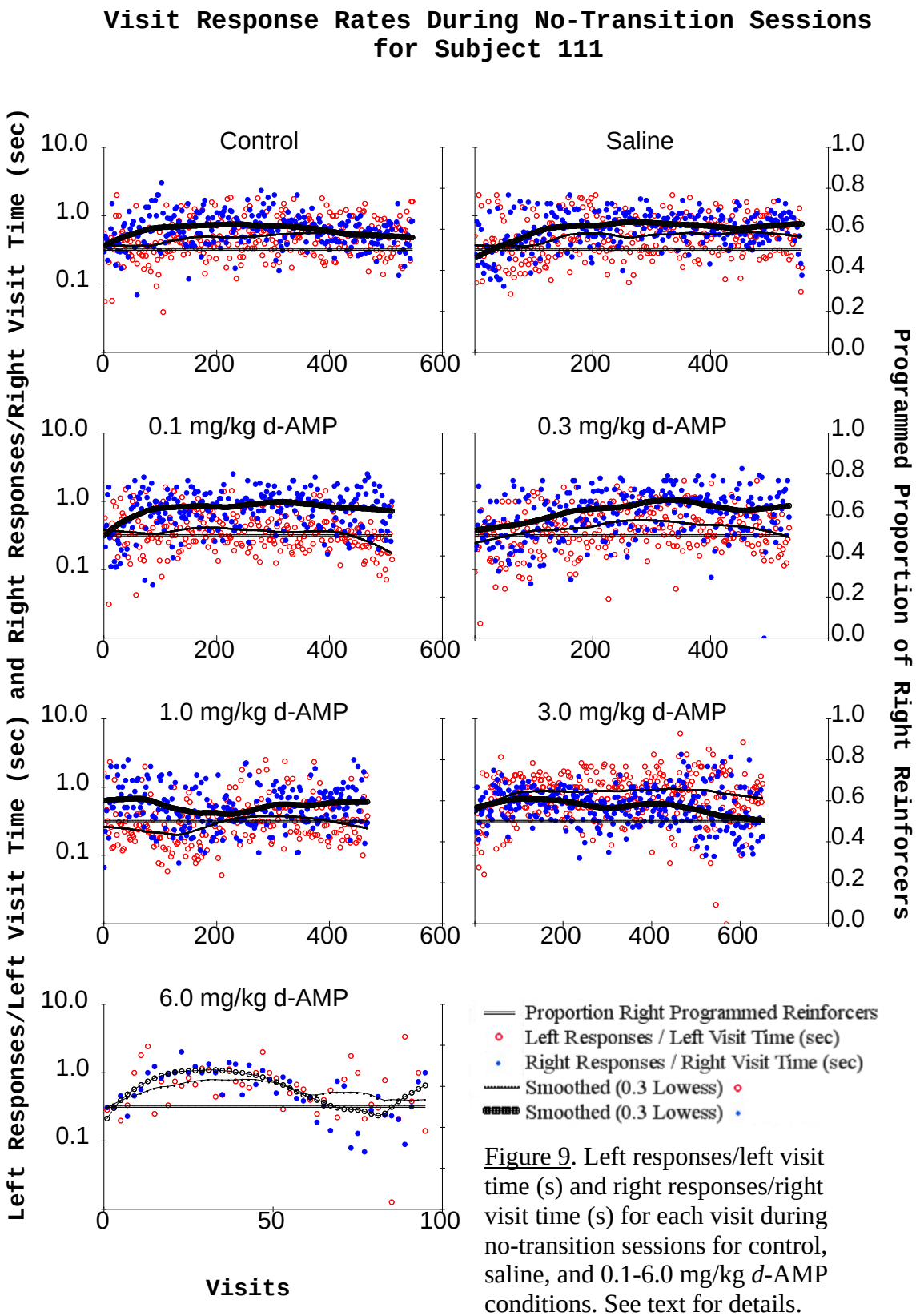

Figure 9. Left responses/left visit time (s) and right responses/right visit time (s) for each visit during no-transition sessions for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions. See text for details.

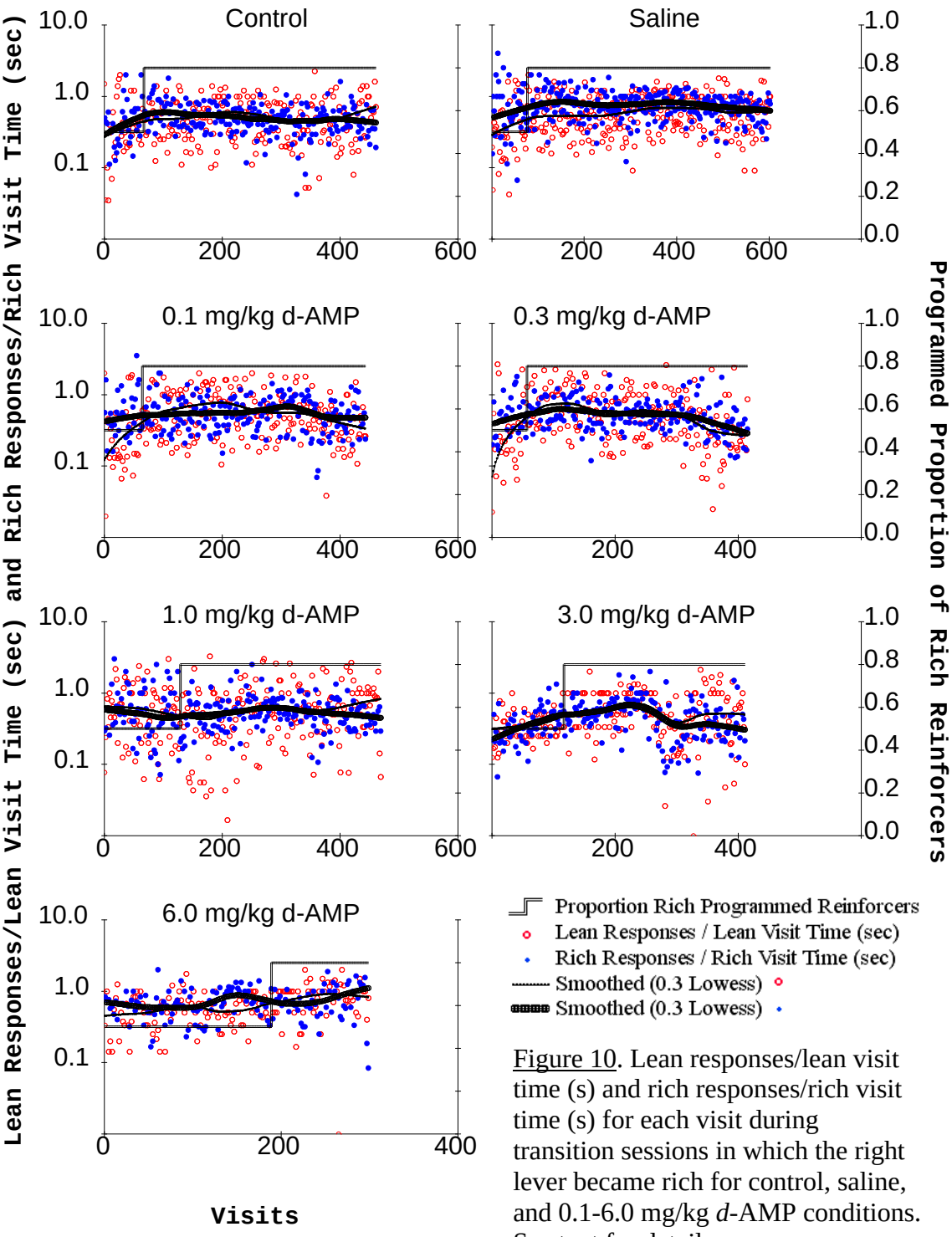

Figure 10. Lean responses/lean visit time (s) and rich responses/rich visit time (s) for each visit during transition sessions in which the right lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions. See text for details.

1.0 mg/kg d-AMP. There were generally between 0.1 to 2 responses per sec of visit time with approximately 500 visits per session (except for 600 during the saline session). The smoothed data show little difference in response rates on the lean versus rich lever. Again, the variability of visit response rates within a session was lower for control and saline than for d-AMP sessions. During the 3.0 mg/kg d-AMP session, the smoothed data reveal more fluctuation in visit response rate than during lower-dose, control, and saline sessions.

Finally, during the 6.0 mg/kg d-AMP session, both lean and rich visit response rates were approximately 0.9 to 1.0 responses per sec of visit time, however, visits were substantially reduced to approximately 300. The step-wise double lined function reveals how many visits occurred before a transition in reinforcer ratios occurred (from 1:1 to 1:4). There were approximately 75 pre-transition visits for control, saline, 0.1 mg/kg, and 0.3 mg/kg d-AMP and 125 pre-transition visits for 1.0 mg/kg, and 3.0 mg/kg d-AMP. Finally, there were almost 200 pre-transition visits for the 6.0 mg/kg d-AMP session indicating a substantial increase in changeovers during the first 30-min of the session.

Responses per visit as a function of cumulative reinforcers in no-transition sessions for Subject 111 are plotted in Figure 11. During control, saline and d-AMP sessions up through 1.0 mg/kg, there were generally between 3 and 20 responses per visit before a reinforcer was collected. There were more right responses per visit (thick wavy line) than left responses per visit (thin wavy line) indicating a bias to the right lever. This bias was not as evident during the 3.0 mg/kg d-AMP session; however, it reappears at 6.0 mg/kg d-AMP. Overall, there were generally between 125 and 150

Responses Per Visit as a Function of Cumulative Reinforcers During No-Transition Sessions for Subject 111

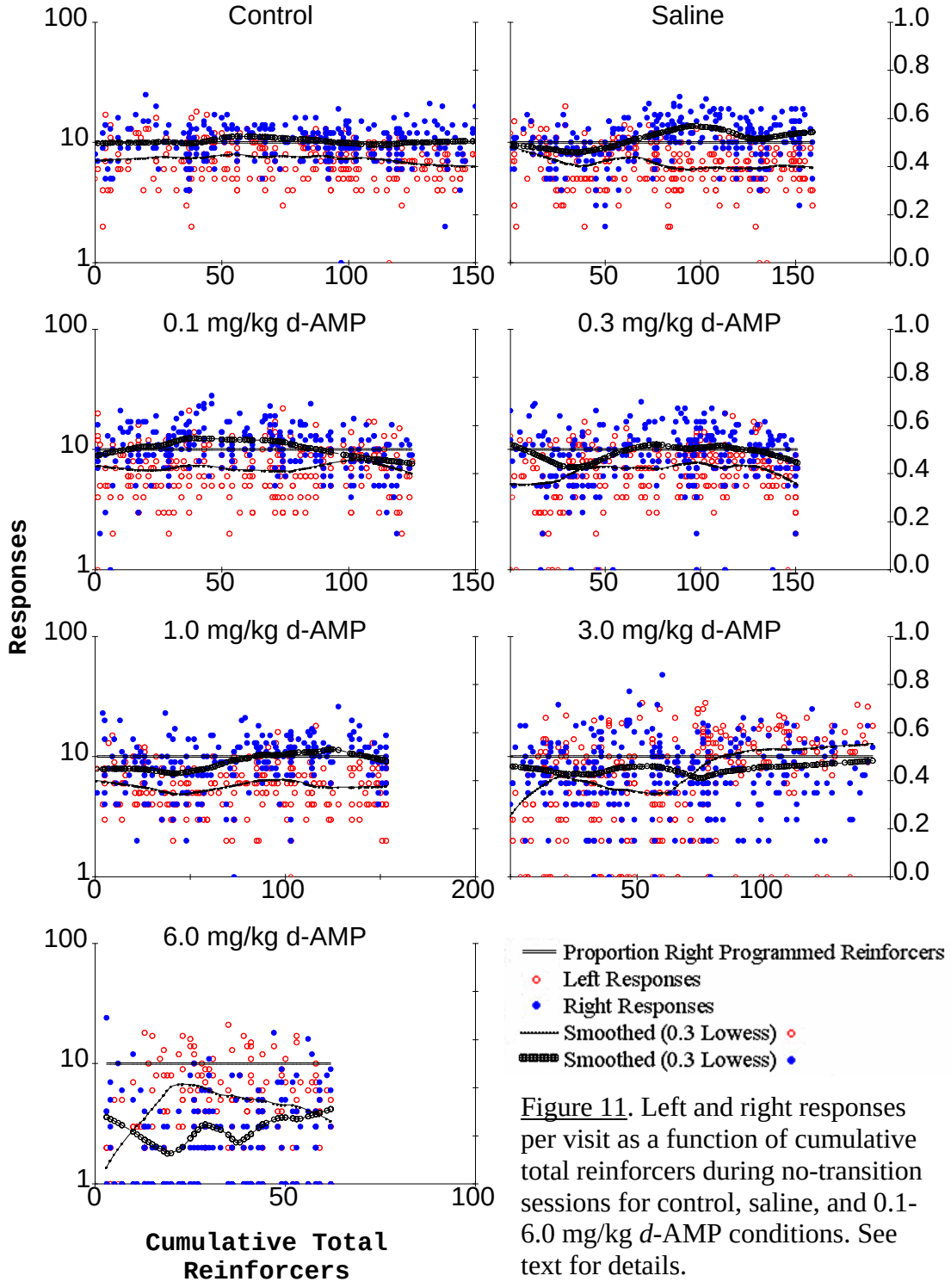

Figure 11. Left and right responses per visit as a function of cumulative total reinforcers during no-transition sessions for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions. See text for details.

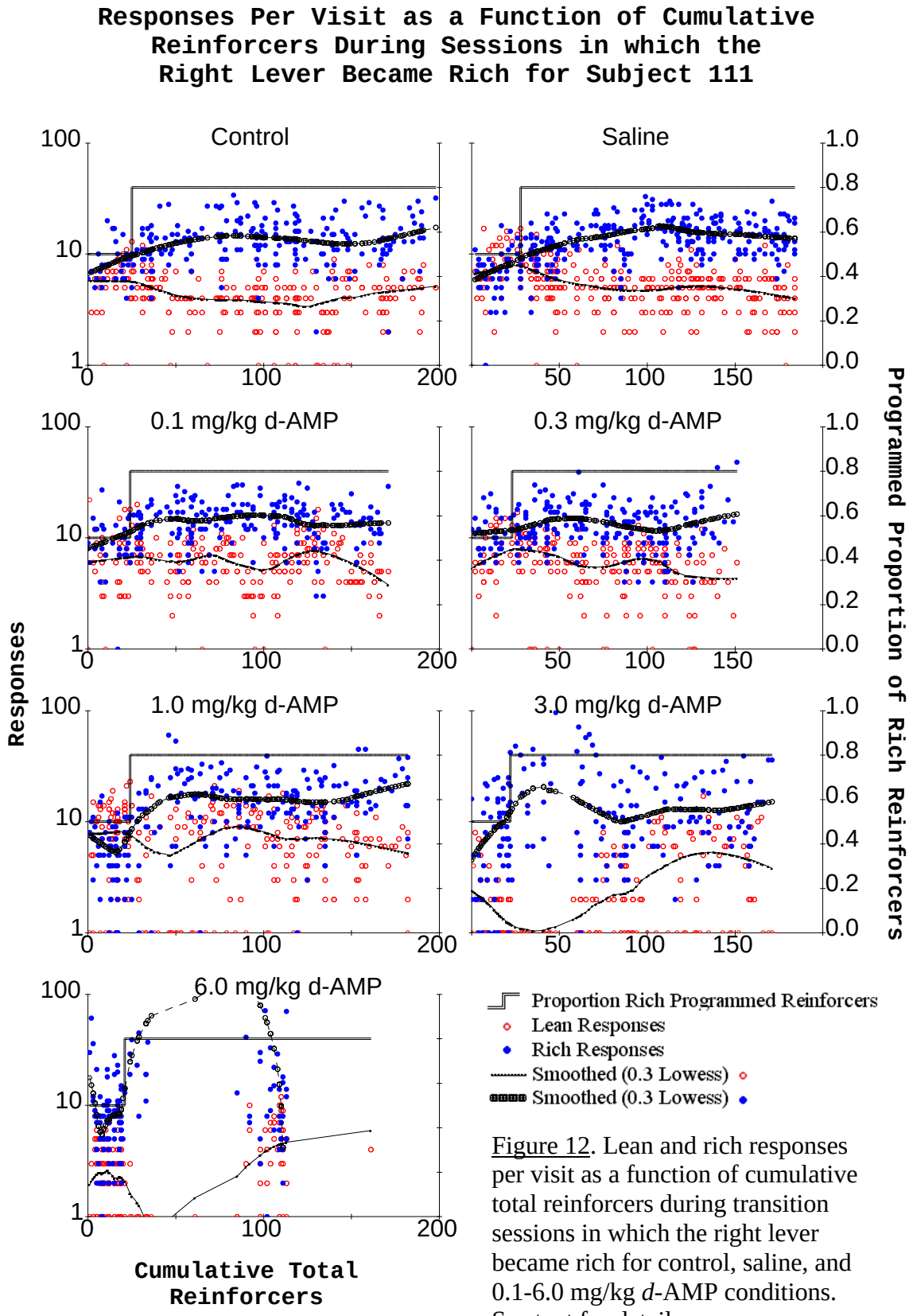

Figure 12. Lean and rich responses per visit as a function of cumulative total reinforcers during transition sessions in which the right lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions. See text for details.

reinforcers collected per session except during the 6.0 mg/kg d-AMP session during which approximately 85 reinforcers were collected. Responses per visit are plotted as a function of cumulative reinforcers during transition sessions for Subject 111 in Figure 12. These graphs reveal that although this subject emits slightly more responses per visit on the right lever before the transition, once the transition occurs, the difference in responses per visit becomes more apparent. For the control and saline sessions, it took approximately 75-100 reinforcers for the ratio of lean to rich responses per visit to stabilize at approximately 4:12 reinforcers. For the 0.1 mg/kg, 0.3 mg/kg, and 1.0 mg/kg d-AMP sessions, there was more variability in the lean measure through the session. However, the ratio of responses per visit on the lean and rich levers, overall, fluctuated between approximately 4:12 to 6:12. During the 3.0 mg/kg and 6.0 mg/kg d-AMP sessions, there was a strong preference for responding on the rich lever especially early in the session.

Figure 13 shows cumulative response, time, and reinforcer ratios (right/left) during no-transition sessions for Subject 111. For control, saline, 0.1 mg/kg, 0.3 mg/kg and 1.0 mg/kg d-AMP sessions, time and reinforcer ratios approximate 1.0 and the response ratio was approximately 1.3 to 1.5. For the 3.0 mg/kg d-AMP session, the reinforcer ratio approximates 1.0, the response ratio was slightly higher at 1.2, and the time ratio was approximately 1.8 throughout the session. Finally, during the 6.0 mg/kg d-AMP session, both the ratios were very large during the early part of the session; hence, the scale for the y-axis is different from the other graphs in the figure. At this dose, the time ratio initially starts near 200:1 and declines to approximately 25:1 at 50 visits. The response and reinforcer ratios were also high in the initial part of the session,

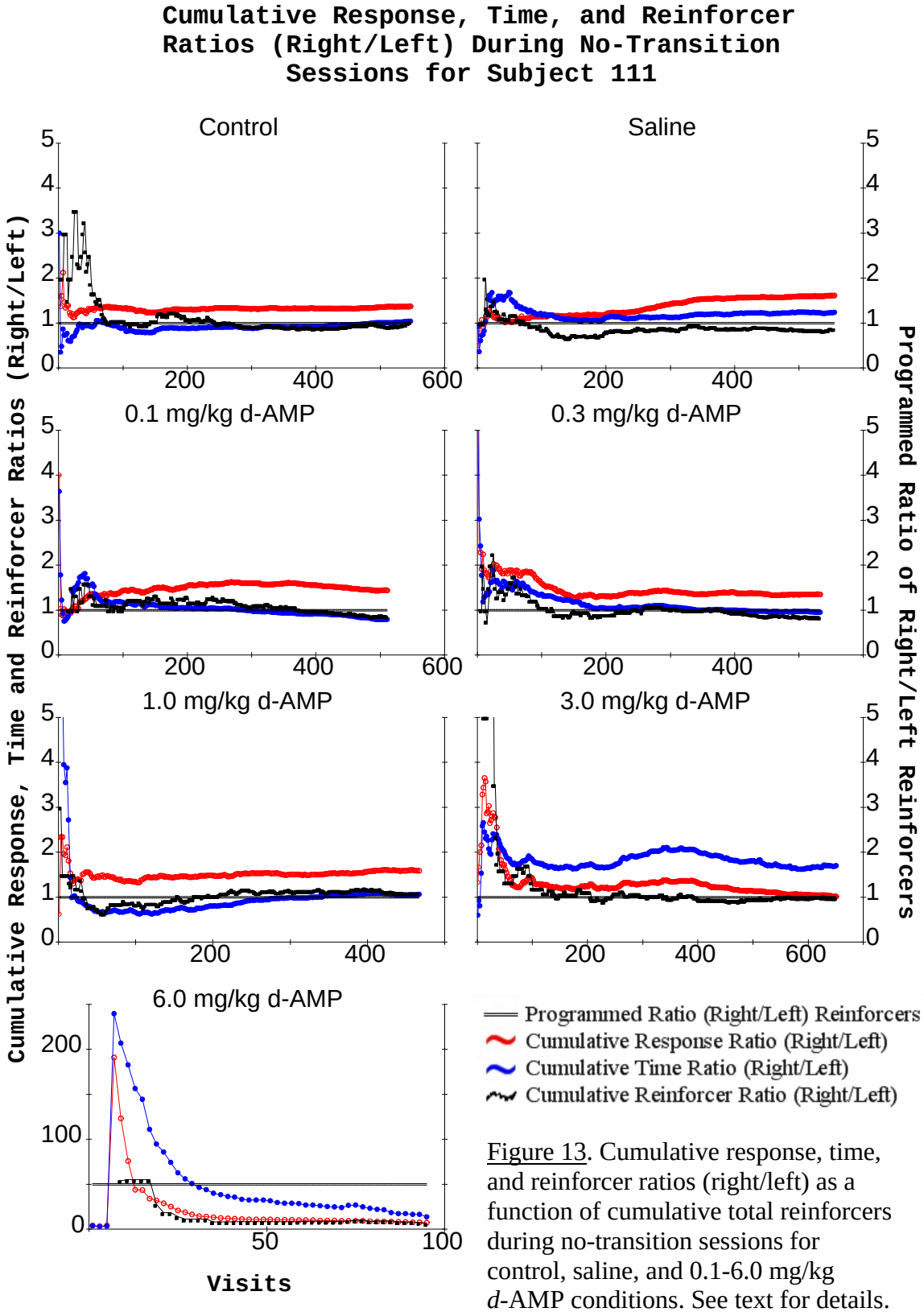

Figure 13. Cumulative response, time, and reinforcer ratios (right/left) as a function of cumulative total reinforcers during no-transition sessions for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions. See text for details.

however, at the 25 visit mark, they were closer to 4:1 and remained at that level for the rest of the session.

Figure 14 shows cumulative response, time, and reinforcer ratios (right/left) during transition sessions for Subject 111. The general pattern of the ratio changes during the control and saline sessions were similar in that the cumulative time and response ratios follow the same course and appear distinct from the lower time ratio. The control session ratios, however, better approximated the programmed ratio of rich/lean reinforcers (double line step-wise function on the right axis). The general pattern of the ratio changes during the 0.1 mg/kg and 0.3 mg/kg d-AMP sessions were similar in that the ratios follow the same course and, during these sessions, they were all distinct from one another. The reinforcer ratios in both of these sessions were approximately 2.5:1 and were higher than the response ratios of approximately 2.0:1 and the time ratios of approximately 1.5:1. The change in reinforcer ratios after the transition also appears more quickly during these sessions than during the control and saline sessions.

During the 1.0 mg/kg d-AMP session, reinforcer ratios come very close to the programmed 4:1 ratio, however, the response and time ratios follow a similar course to that in lower-dose sessions. During the 3.0 mg/kg d-AMP session, all ratios exceed the programmed ratio (note the change in the y-axis). The ratios began at 4:1 before the transition indicating a strong bias to the right lever.

After the transition, the ratios climbed to approximately 10:1 at the 200-visit mark and slowly returned to the programmed ratio of 4:1 by the 400-visit mark at the end of the session. Finally, during the 6.0 mg/kg d-AMP session, the reinforcer ratio

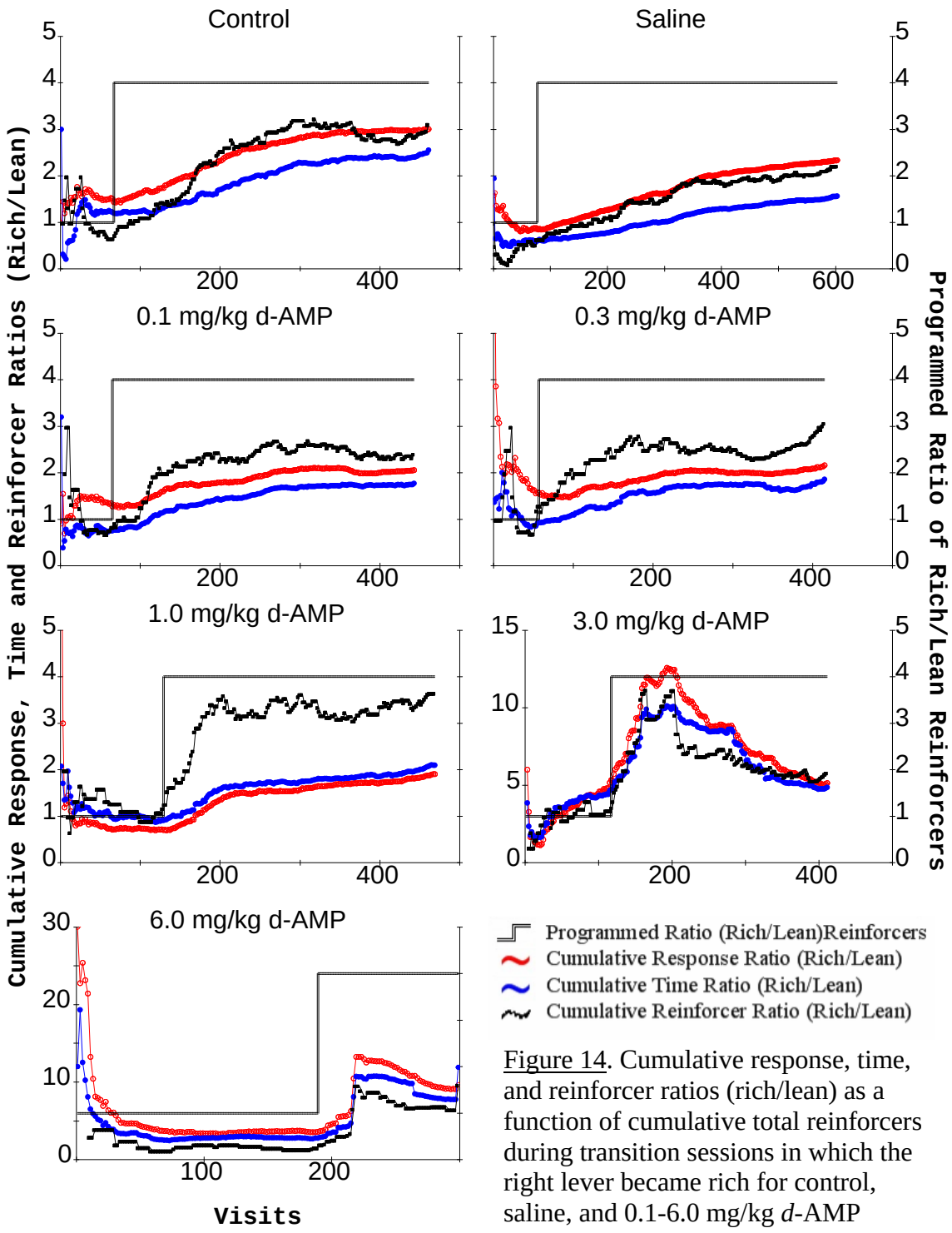

Figure 14. Cumulative response, time, and reinforcer ratios (rich/lean) as a function of cumulative total reinforcers during transition sessions in which the right lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions. See text for details.

before the transition was approximately 2:1 while the time and response ratios were approximately 3:1 and 4:1, respectively. After the transition, the ratios climbed to 10:1, 9:1, and 8:1, respectively, and remained there through the rest of the session.

Cumulative left, right, and total reinforcers during no-transition sessions for Subject 111 are plotted in Figure 15. This figure shows a steady climb in all measures to approximately the same number of reinforcers (approximately 150 in total) throughout all sessions except for the 6.0 mg/kg d-AMP session during which approximately 75 total reinforcers were obtained. The figure also shows that left and right reinforcers were obtained at the same rate throughout all sessions except for the 6.0 mg/kg d-AMP session. During the 6.0 mg/kg session, there was a large difference between reinforcers obtained on the right and left levers and there were few reinforcers obtained before and after approximately the 10^{th} visit indicating a long response run on the right lever during that visit.

Cumulative lean, rich, and total reinforcers during transition sessions for Subject 111 are plotted in Figure 16. This figure shows a steady climb in all measures to approximately the same number of reinforcers (approximately 150 total) throughout all sessions including the 6.0 mg/kg d-AMP session. In addition, reinforcers from responding on both the left and right levers are accumulated at the same rate until after the programmed transition in which the right lever became rich. At that point, rich reinforcers were accumulated more rapidly. The number of visits that elapsed before a difference in rates of accumulating reinforcers on each lever varied across doses. For control and saline sessions, it took approximately 50 and 100 visits, respectively. For 0.1 mg/kg, 0.3 mg/kg d-AMP it took approximately 25 and 10 visits, respectively

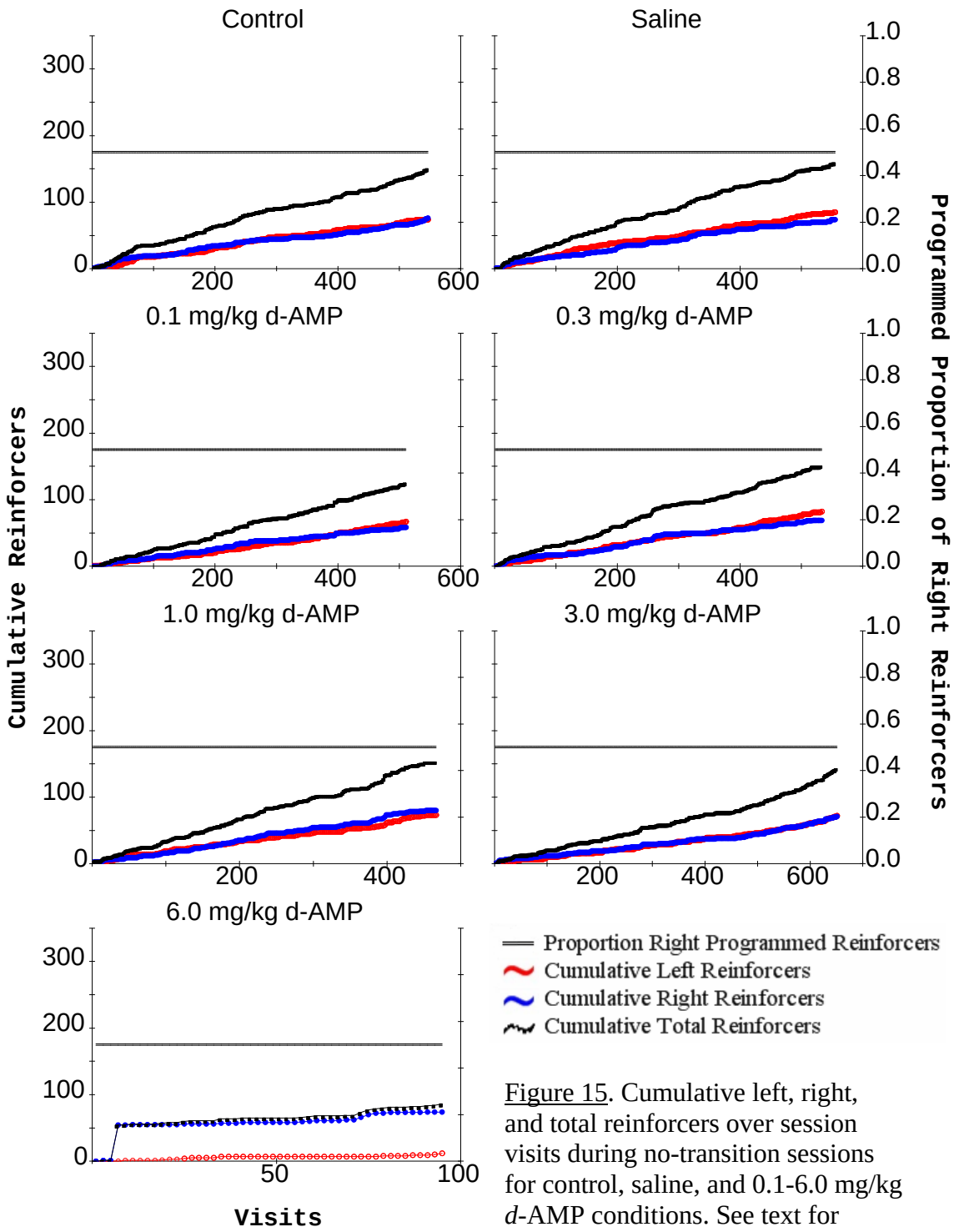

Figure 15. Cumulative left, right, and total reinforcers over session visits during no-transition sessions for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions. See text for details.

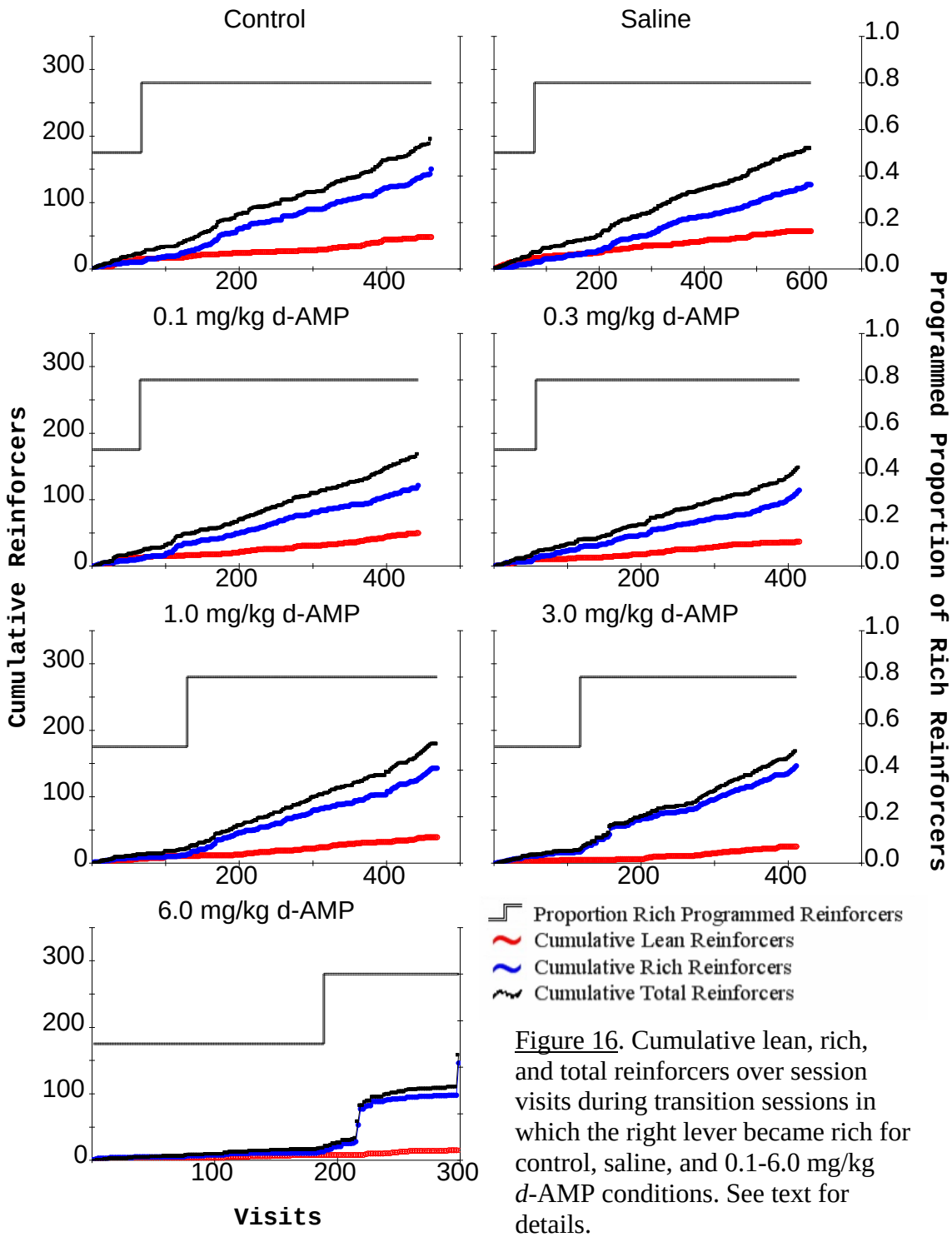

Figure 16. Cumulative lean, rich, and total reinforcers over session visits during transition sessions in which the right lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions. See text for details.

before a change in rate of cumulative left and right reinforcers was observed. Finally, for all doses of d-AMP, the change in rate of cumulative left and right reinforcers was immediate, although, not as steep in the 6.0 mg/kg d-AMP session. During the 6.0 mg/kg session, a majority of the reinforcers were obtained during two visits: visit 225 and visit 300.

Visit response rates as a function of time between the preceding pair of lean reinforcers and rich reinforcers during transition sessions are shown in Figures 17 and 18, respectively. The scatter of data points looks similar for control, saline, and doses of d-AMP up to 1.0 mg/kg. During the 3.0 mg/kg session, the scatter seems to shift to the left, but it remained within the range of visit response rate of the lower doses and control session. This result suggests that the visit response rate remained the same, although the majority of visits occurred after a shorter time between the preceding pair of lean reinforcers. The visit response rates on the lean and rich levers varied very little as a function of time between the preceding pair of lean (Figure 17) or rich reinforcers (Figure 18). In addition, the visit response rates on the lean and rich levers were comparable, indicating that preference for the rich lever must have been evident in increased time on the rich lever, and increased total responses (see Figure 8). This pattern differs from the visit response rates as a function of time between preceding pair of right reinforcers observed during no-transition sessions (see Figure 19). There was little difference in visit response rates as a function of time between preceding pair of right reinforcers.

Lastly, all figures showing data from transition sessions (2, 4, 6, 8, 10, 12, 14, and 16) are from the same sessions. Therefore, the programmed proportion of rich

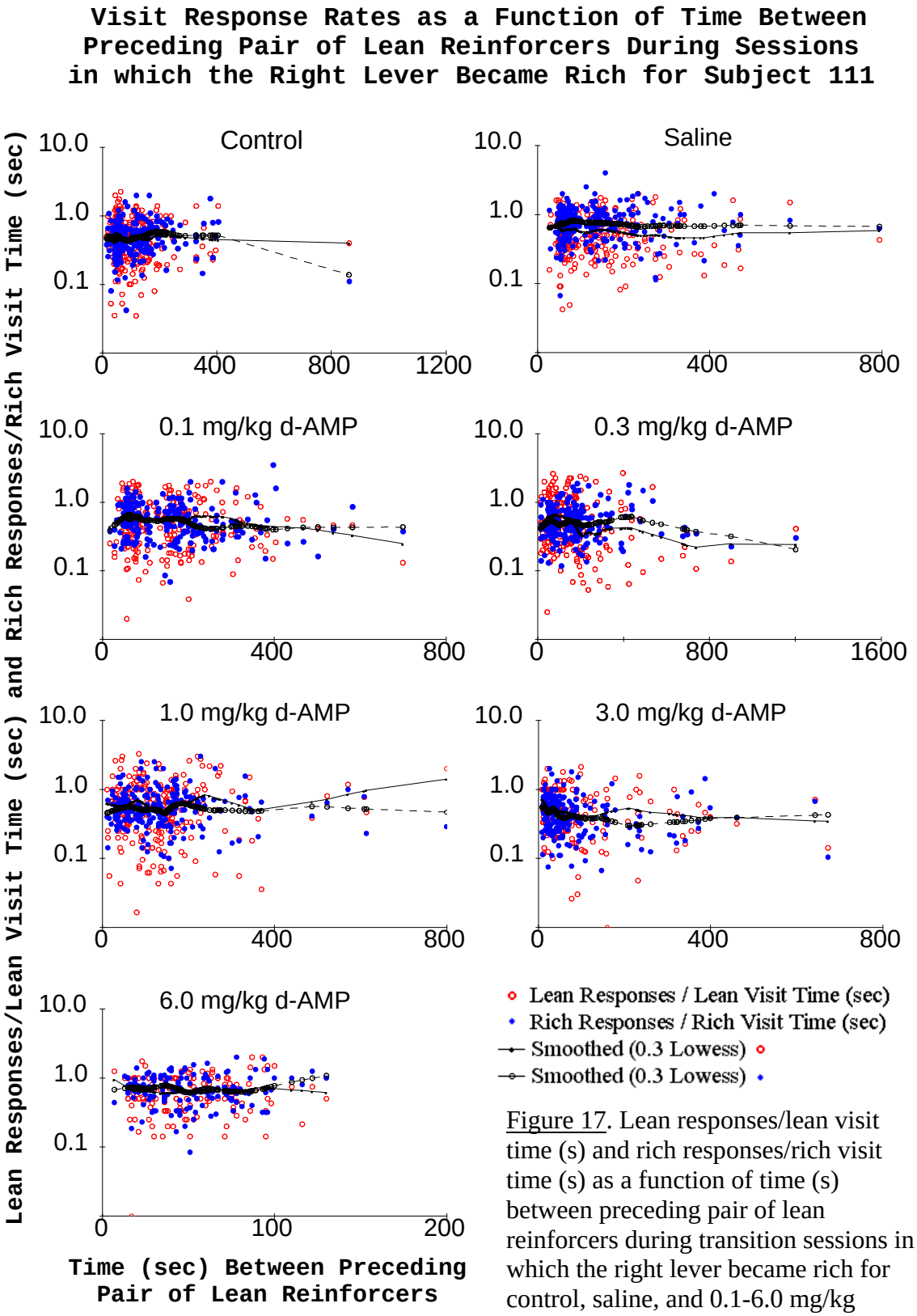

Figure 17. Lean responses/lean visit time (s) and rich responses/rich visit time (s) as a function of time (s) between preceding pair of lean reinforcers during transition sessions in which the right lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions. See text for details.

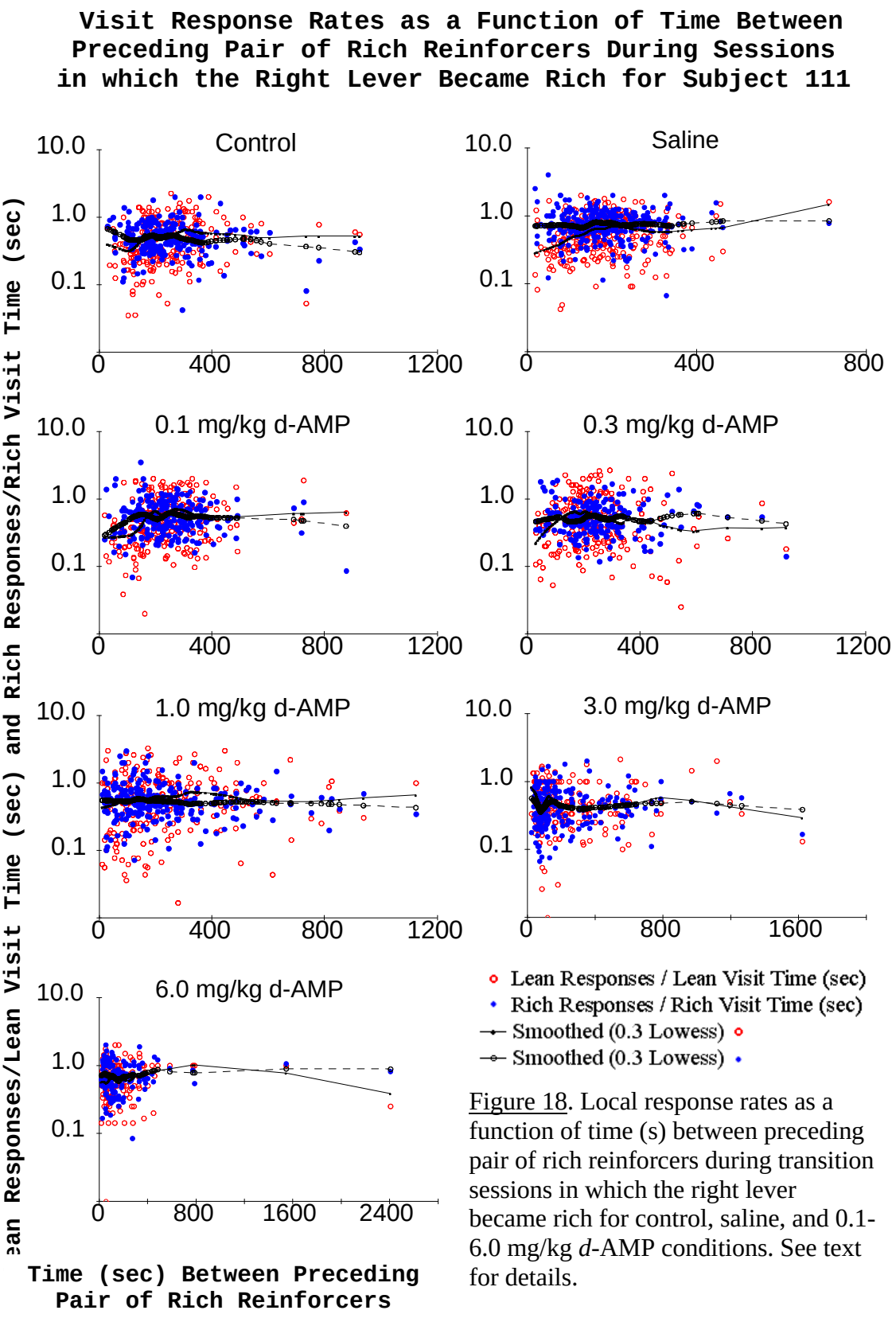

Figure 18. Local response rates as a function of time (s) between preceding pair of rich reinforcers during transition sessions in which the right lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions. See text for details.

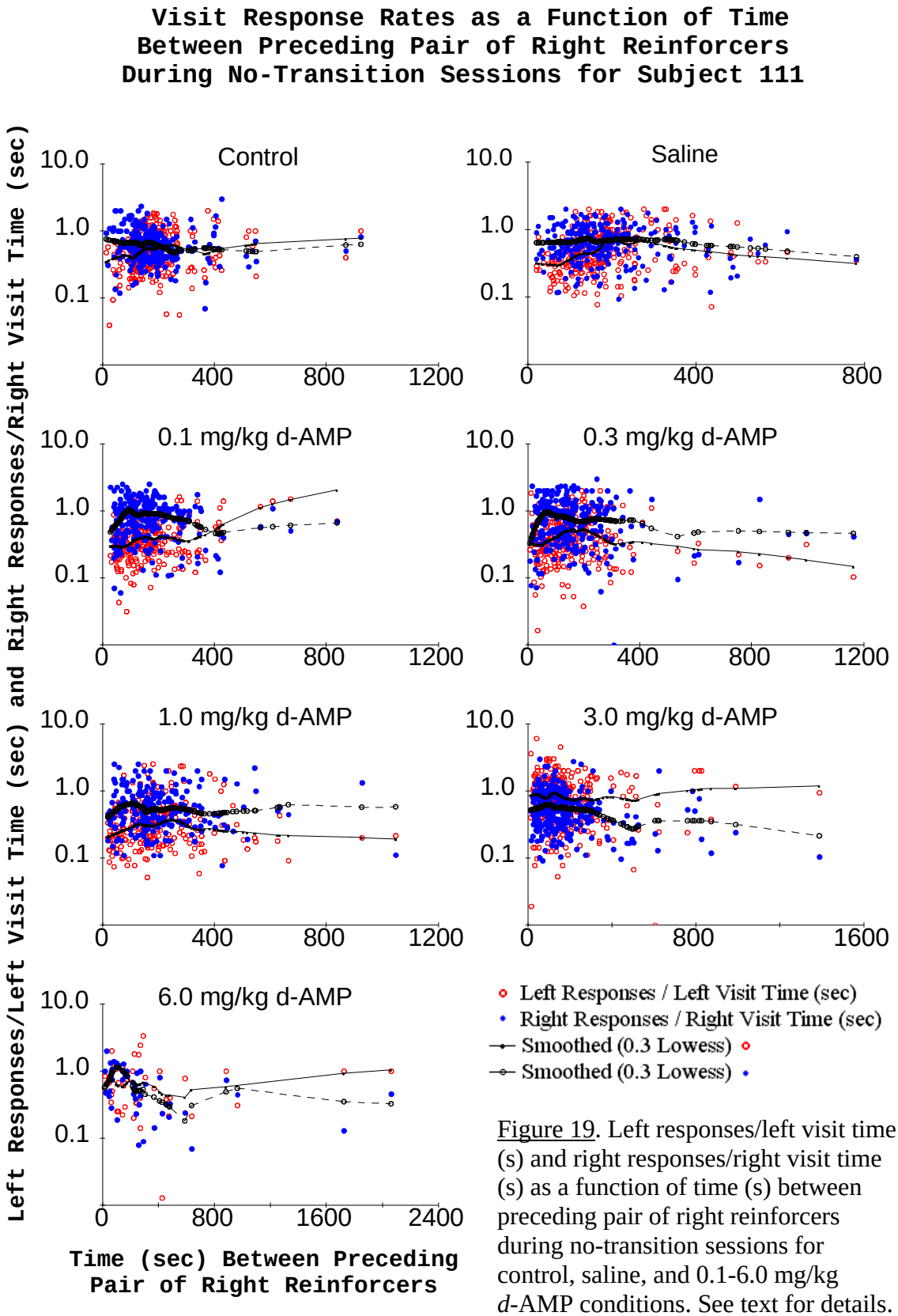

Figure 19. Left responses/left visit time (s) and right responses/right visit time (s) as a function of time (s) between preceding pair of right reinforcers during no-transition sessions for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions. See text for details.

reinforcers are plotted across visits for all figures except figure 12, which plots the programmed proportion of rich reinforcers against cumulative total reinforcers. The former figures reveal that approximately 75 visits occur before the programmed transition from 1:1 to 1:4 during control, saline, 0.1 mg/kg, and 0.3 mg/kg d-AMP sessions. During the 1.0 mg/kg and 3.0 mg/kg d-AMP sessions, there were approximately 125 visits before the transition occurred and finally, during the 6.0 mg/kg session, there were almost 200 visits before the transition occurred. Figure 12, however, reveals that there were approximately 25 reinforcers collected before the transition except during the 6 mg/kg d-AMP session in which there was a slight decline. Reinforcers collected before the transition are also shown in Figure 2 (blue filled circles).

IV. DISCUSSION

The summary data presented in Tables 2 and 3 and Figures 2 through 6 are the type of data often presented in studies in behavioral pharmacology and are presented here as comparisons to the microanalytic data presented in Figures 7 through 19. The purpose was to see if the microanalytic data could reveal any behavioral mechanisms underlying changes in behavior that are not readily apparent with a molar analysis (e.g. Baron & Leinenweber, 1994; Ziriax et al., 1993) or vice versa. The summary data as presented in Table 2 and 3 and Figures 2 through 6 are fairly typical of results obtained in other studies of d-AMP (e.g., Fletcher & Korth, 1999; Paule & McMillan, 1984; Ziriax et al., 1993), with a few exceptions noted below. Typically, as found in this study, amphetamine both has no effect or increases response rates at low to moderate doses and attenuates lever-press responding at higher doses.

The group averages (Table 2) did not reveal the peak in reinforcers occurring at doses that increased responding that was observed with the individual averages (Table 3). Both group and individual averages revealed the drop in response rates at the highest dose along with the corresponding decrease in total reinforcers. The peak in reinforcers, albeit a small peak, at low to moderate doses suggests that the subjects were perhaps better able to learn the contingencies than under control conditions. The individual averages, however, are unable to reveal if performance was improved during transition or no-transition sessions. If there was improvement during transition sessions, the

averages also do not reveal if it applied to responding before or immediately after the transition, or at some later point in the session. Figure 3 shows that there were more lean reinforcers collected during no-transition sessions than transition sessions. More lean reinforcers would be expected because there really was no “lean” schedule in that condition. Similarly, in Figure 3, there were fewer rich reinforcers collected during the no-transition session for the same reason, that is, there really was no “rich” schedule.

The transition data presented in Figures 7 through 16 show a more rapid transition in response proportions after the programmed changes under some doses. For example, in Figure 8 and 14, the graphs for the 1.0 mg/kg d-AMP session show a steeper transition in behavior than in any other session. In addition, the proportion of rich obtained reinforcers (thick black line) more closely matches the proportion of rich programmed reinforcers (thin double lines). These findings are also true for Subject 121 under 3.0 mg/kg d-AMP and for Subject 131 under 0.3 mg/kg d-AMP. Reinforcers peaked slightly at 1.0 mg/kg for Subject 141 under 1.0 mg/kg; however, total responses peaked at 0.1 mg/kg for that subject (see figures in the Appendix). The graphs for Subject 141 in the 1.0 mg/kg d-AMP session do appear to show a steeper transition in proportion of rich responses and reinforcers (not time) than in any other session. There is also a more rapid transition in cumulative reinforcer ratios after the transition than during the control and saline sessions (Figure 14). The steeper or more rapid transitions could only have been observed by the microanalytic data presented in this study.

The above findings, however, are a bit puzzling and lead to a question about which mechanism would offer an explanation. Did moderate doses of *d*-AMP increase sensitivity to reinforcement? …improve attention? …decrease perseverative

responding? …or is there an alternative explanation? Figure 16 suggests that it might be increased sensitivity to the change in reinforcement contingencies. Compared to control and saline sessions, the curves for cumulative lean and rich reinforcers begin to diverge more rapidly once the programmed transition begins for all doses of d-AMP, but especially during the 3.0 mg/kg session.

Another enigma is that the present study contradicts evidence found by others. Schulze and Paule (1990) found that *d*-amphetamine (0.01-1.0 mg/kg IV) produced dose-dependent decreases in the number of reinforcers obtained on an IRA task. In fact, when examining the dose effect curves plotted in Figures 2 through 6 of the present study, which are similar to their study, the peaks in reinforcers observed with averages are not readily apparent. Looking closely at Figure 4, however, there are slight peaks in rich reinforcers obtained for Subject 111 at 1.0 mg/kg, for Subject 121 at 3.0 mg/kg and for Subject 131, at 0.3 mg/kg. In addition, for Subject 121 only, there was an obvious increase in visits in the 3.0 mg/kg and 6.0 mg/kg d-AMP sessions (see Figure 5). Whether the peaks in reinforcers simultaneous with the peaks in total session responses are significant is debatable. In addition, there were only four subjects in this experiment and for each subject, there were only three sessions per dose, one under each of the terminal reinforcer ratios (4:1, 1:1, and 1:4). Future research will have to explore this finding more thoroughly with multiple replications at each of the doses under each of the terminal reinforcer ratios before concluding that there is an effect.

The difference in results between this experiment and the Schulze and Paule (1990) study could, in fact, be due a number of things: (a) the longer sessions used in this experiment (3 hr vs. 30 min), (b) the different routes of administration (IP vs. IV),

(c) the type of data collected and the manner of data presentation, or (d) the type of task (trials vs. free-operant). The latter explanation seems more plausible because the IRA task emphasizes the stimulus-response portion of the 3-term contingency, whereas the mixed concurrent procedure as used in this study emphasizes the response-reinforcer portion of the 3-term contingency (see also Newland & Reile, 1999).

Schulze and Paule (1990) concluded that the decrease in performance on the IRA task was due to the decreases in responding. They did not present moment-by-moment records of responding through the session, therefore, it is not possible to see the actual patterns of responding across the four levers used in their study. Schrot and Thomas (1983), however, did such an analysis of d-AMP (0.5-4.0 mg/kg) using the same IRA procedure with rats. They found that higher doses of d-AMP produced increases in the number of error and timeout responses emitted. Furthermore, the majority of those responses occurred as runs (a series of responses on one lever such as a visit in the present study) rather than traverse responding (switching from one lever to another). Paule and McMillan (1984) also found increased errors because of perseverative responding.

In the present study, visit response rates were not affected by d-AMP until reduced at the highest dose (except for in one session for Subject 141 at 3.0 mg/kg) and the number of visits increased (i.e., traversing increased) at low to moderate doses and decreased at the highest dose especially during no-transition sessions (see Figure 7). An increase in visits suggests an increase in variability of responding rather than perseveration. Greater variability would be expected in no-transition sessions because the equal ratios in programmed reinforcers would result in more sampling between the

two levers whereas during transition sessions the unequal ratios necessarily bias responding toward the rich lever and reduce sampling but not eliminate it. The microanalytic data smoothed with the Lowess smoothing algorithm, enabled the detection of the moment-by-moment changes in responding through the session as shown in Figure 7 where the curves for proportion of responses and time closely follow the proportion of reinforcers obtained throughout the session. In addition, the detailed plots also show that although the effect of 6.0 mg/kg d-AMP was greater during the no-transition than the transition session (see Figures 7 and 8), both sessions show variability in proportion of responses and proportion of time to the right and rich lever in the no-transition and transition sessions, respectively.

Using an IRA procedure, Schrot, Boren, Moerschbaecher, and Simoes Fontes (1978) found an increase in response rates with a repeated acquisition baseline with timeout from avoidance procedure. *d*-Amphetamine increased the sequence completion rate as well as the rate of shock delivery for both subjects in their study. Schrot and Thomas (1983) concluded that the increase in responding during runs and not in changeover responses is consistent with the idea that *d*-amphetamine disrupts stimulus control and produces perseverative responding.

Although the present study's findings were contrary to the Schrot and Thomas study in terms of visit length and changeovers at low to moderate doses, there was some evidence of perseverative responding in the current study as well. In Figure 11, for example, the plots for the 3.0 mg/kg and 6.0 mg/kg d-AMP sessions show increasing longer runs across cumulative reinforcers. Increasing longer runs are also evident in the data of the other three subjects presented in the Appendix. In this study, the increase in

visits due to more changeovers (increased variability) and the increase in perseverative responding due to a greater number of longer runs at higher doses, occur simultaneously at the dose with the peak number of total reinforcers. In other words, an overall increase in responding and switching together account for the slight increase in reinforcers. During higher-dose sessions, there was an increase in perseverative responding and a decrease in overall response rate that disrupted performance and resulted in fewer reinforcers (e.g., see 6.0 mg/kg in Figure 7).

Mayorga et al. (2000) compared the effects of *d*-amphetamine and methylphenidate on acquisition on an IRA task with rats. Both drugs increased response rate at lower doses and decreased response rate at higher doses; however, the increases in response rate were not significant for either drug. Furthermore, they found that either drug did not significantly affect accuracy until doses that did not affect response rate or decreased response rate were administered. These results are more comparable to the results in the present study and differ from the study by Schulze and Paule (1990) which found performance on the IRA task to be compromised even at low-moderate doses.

One difference between the present study and the study by Mayorga et al. is that d-AMP (0.1, 0.3, 1, 3, 6 mg/kg) was administered to rats IP 30 min and 15 min prior to the session, respectively, whereas in the Schulze and Paule study, d-AMP (0.01, 0.03, 0.1, 0.3, and 1 mg/kg) was administered to monkeys IV 15 min before the session. Another difference between the two IRA tasks that confuses the issue more, is that like the present study, Schulze and Paule (1990) did not use any salient stimuli to signal or indicate performance, whereas, in the study by Mayorga et al. (2000), indicator lights

signaled position in the response sequence and the number of correct responses required for reinforcer delivery.

It is unclear, in the current study, whether the decrease in obtained reinforcers at high doses was simply due to the disrupted response rates as discussed above and also observed in other studies (Mobini, Chiang, Ho, Bradshaw, & Szabadi, 2000; Paule & McMillan, 1984) or whether it was due to decreased effectiveness of food pellets as a reinforcer as suggested by Reilly (2003). The latter claim is accentuated by a study that found (+)-amphetamine depressed food intake of free feeding food-deprived and satiated mice in a dose-dependent manner (Dobrzanski & Doggett, 1976). Furthermore, Foltin (2001) found that amphetamine increased food seeking, but decreased food consumption. Foltin suggested that the decreased effectiveness of food pellets as a reinforcer may be due to decreased sensitivity to the sensory stimuli associated with hunger or it may be due to increased sensitivity to other extraneous competing stimuli.

Others (Mingote, Weber, Ishiwari, Correa, & Salamone, 2005; Salamone, Correa, Farrar, & Mingote, 2007) noted that rats with depleted dopamine in the accumbens as would occur after administration of a high dose of d-AMP (Anderson, Chen, Gutman, & Ewing, 1998), modify their behavior away from food-reinforced tasks when the response requirements are greater. The researchers also argued that dopamine activity in the accumbens has a potent influence over effort-related choice behavior. According to Salamone (2007), this area of investigation is currently undergoing a paradigm shift. The traditional approach was to view the major function of accumbens DA as regulating hedonia and reward. Salamone described the new conceptual

framework as emphasizing the role of accumbens DA in operant and respondent learning, reward prediction, incentive salience, and behavioral activation.

The above-mentioned findings have major implications for individuals diagnosed with ADHD, especially children, learning in the classroom. Individuals with ADHD are described as exhibiting poor attention, an excess of behavior, and impulsivity, usually interfering with performance at school. Because of these characteristics, methylphenidate is widely prescribed for the treatment of children with ADHD and it appears to have a major positive impact on the behavior of children with ADHD (Vitiello, 2001). Children with ADHD appear to do better in school as a result taking stimulants (Vitiello, 2001). There remains a need, however, to examine the effects of these drugs on the process of learning not only while they are used in the child, but also after they are withdrawn in the adult.

Long-term use of a stimulant even at low doses may be cause for concern. Because methylphenidate is similar to *d*-amphetamine, one might expect that it change the brain in a similar manner with continued use. In fact, with adolescent rats, repeated use of methylphenidate was shown to alter gene regulation in the striatum mirroring the neuronal effects produced by other stimulants (Brandon & Steiner, 2003). Taylor and Jentsch (2001) found that stimulant-induced sensitization produced lasting alterations in Pavlovian learning suggested lasting changes in the limbic system from stimulant use. Shen, Choong, and Thompson (2007) recently found that there was long-term reduction in the activity of dopamine neurons in the ventral tegmental area following repeated amphetamine administration. Both of the latter groups of researchers suggested that

these changes in neuronal responses might contribute to the pattern of drug taking commonly seen in addiction.

In fact, Faraone and Wilens (2003) and Wilens, Faraone, Biederman, and Gunawardene (2003) conducted meta-analyses of several studies following children to adolescence and concluded that treatment of ADHD in youth with stimulants appears to reduce the risk for substance use disorders to levels found within the normal population. The meta-analyses do not report, however, risk to the adult who was prescribed methylphenidate during childhood or adolescence. It would be disheartening to find out that, low-dose methylphenidate leads to increased difficulties in learning when it is later withdrawn or that it brings about Parkinson's disease or some other disorder in the adult. Future research should continue to investigate the effects stimulant drugs have not only on behavior and on gross measures of acquisition, but on the more subtle processes involved in learning and on the long-term effects in the adult.

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APPENDIX

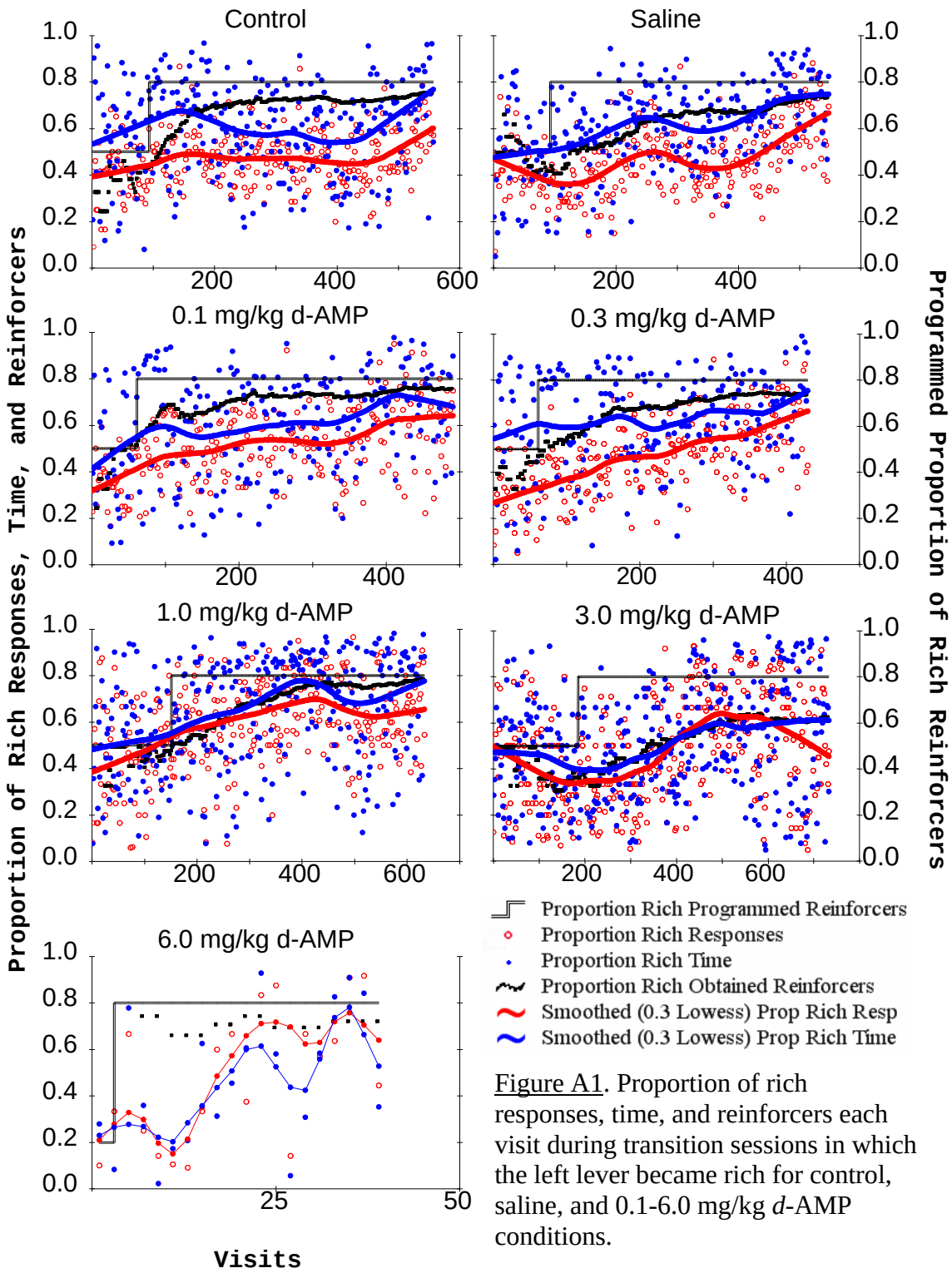


Figure A1. Proportion of rich responses, time, and reinforcers each visit during transition sessions in which the left lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

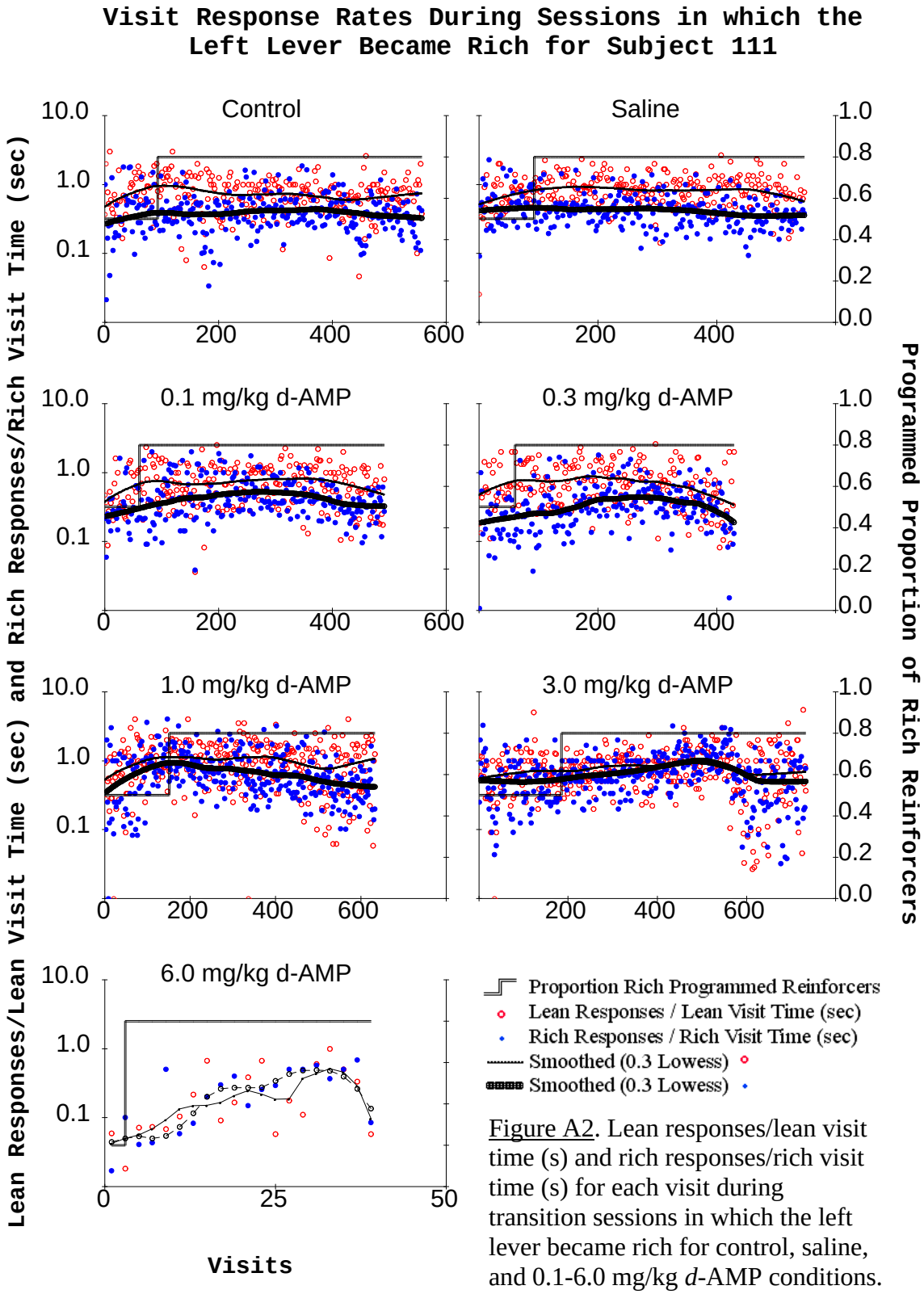


Figure A2. Lean responses/lean visit time (s) and rich responses/rich visit time (s) for each visit during transition sessions in which the left lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

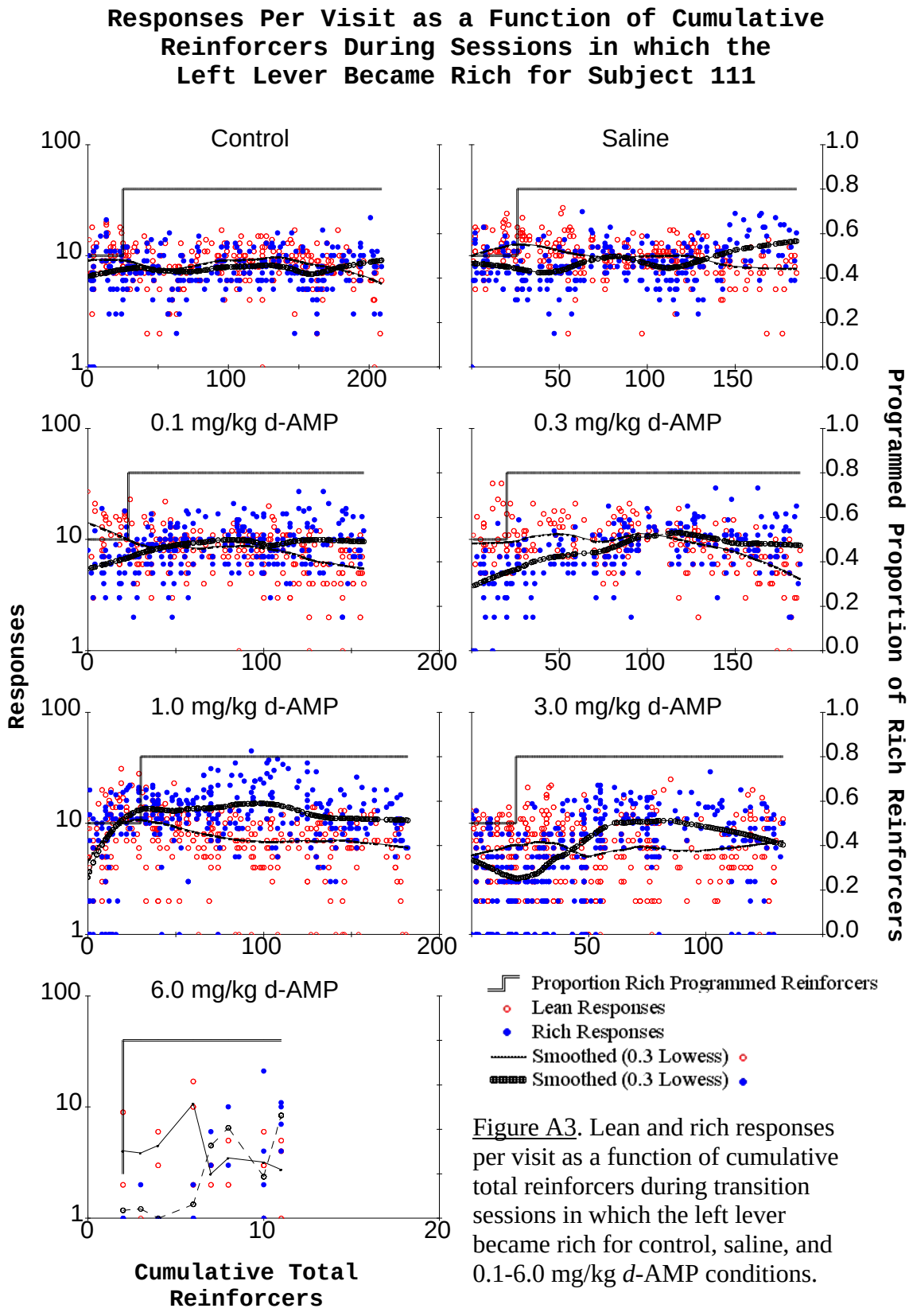


Figure A3. Lean and rich responses per visit as a function of cumulative total reinforcers during transition sessions in which the left lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

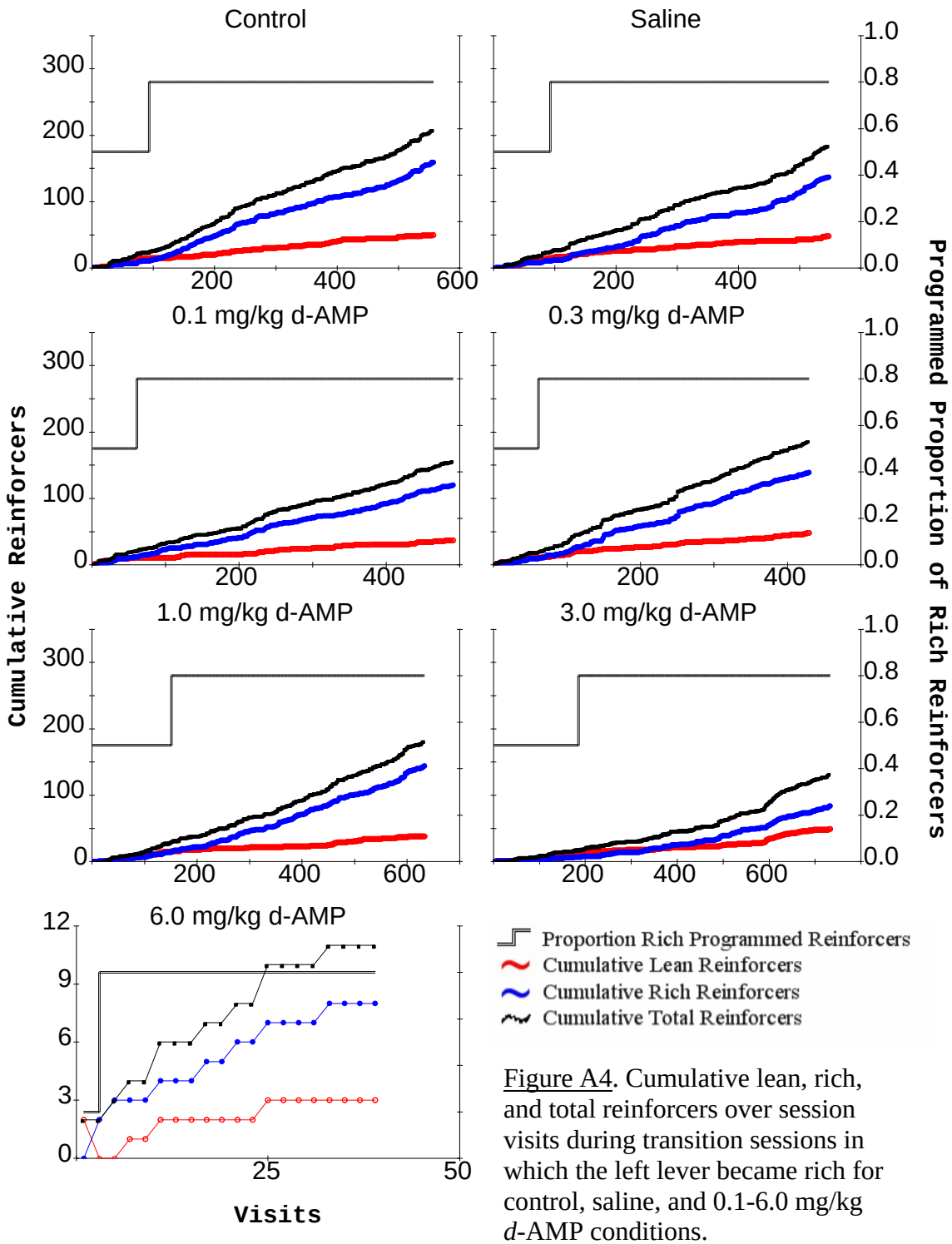


Figure A4. Cumulative lean, rich, and total reinforcers over session visits during transition sessions in which the left lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

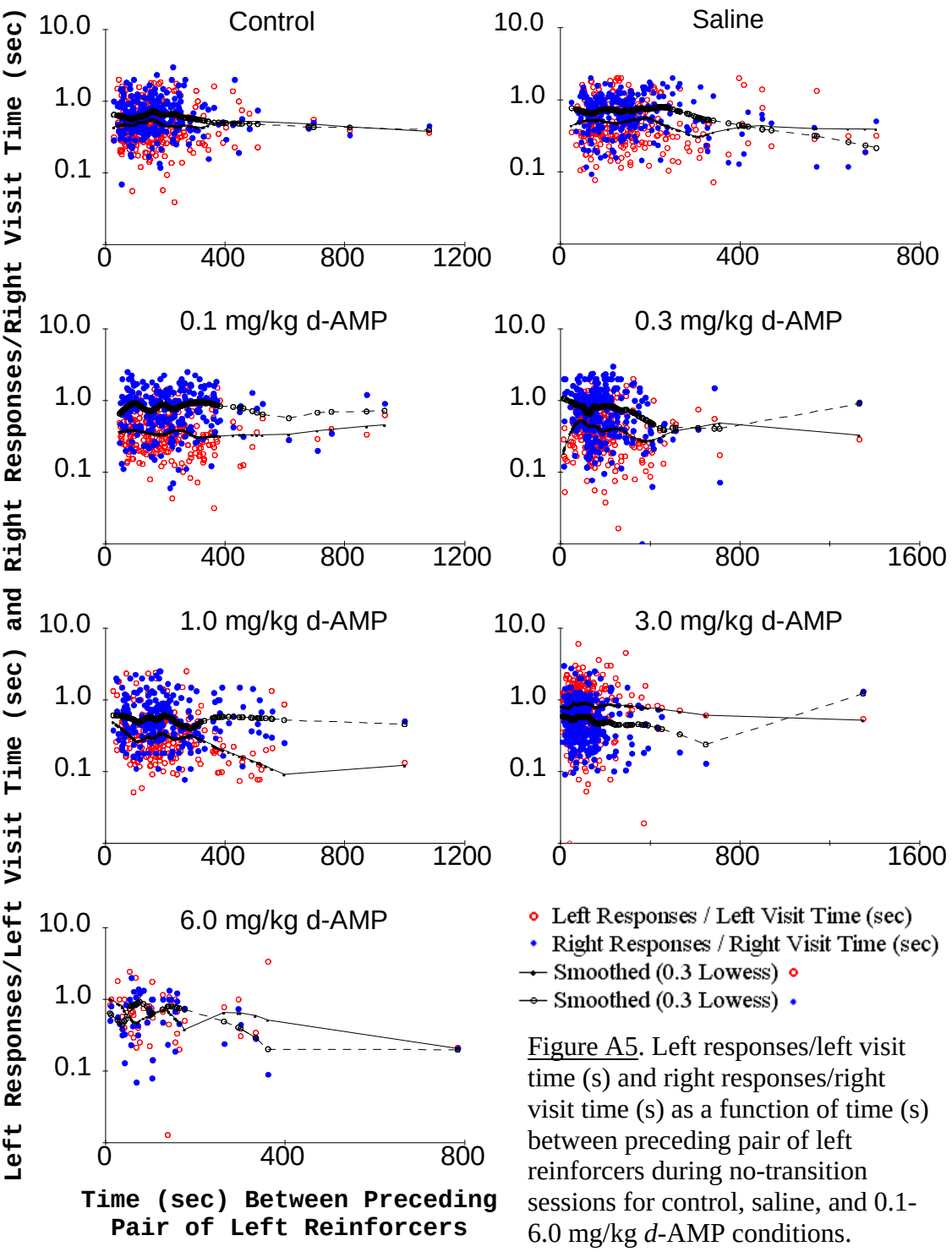


Figure A5. Left responses/left visit time (s) and right responses/right visit time (s) as a function of time (s) between preceding pair of left reinforcers during no-transition sessions for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

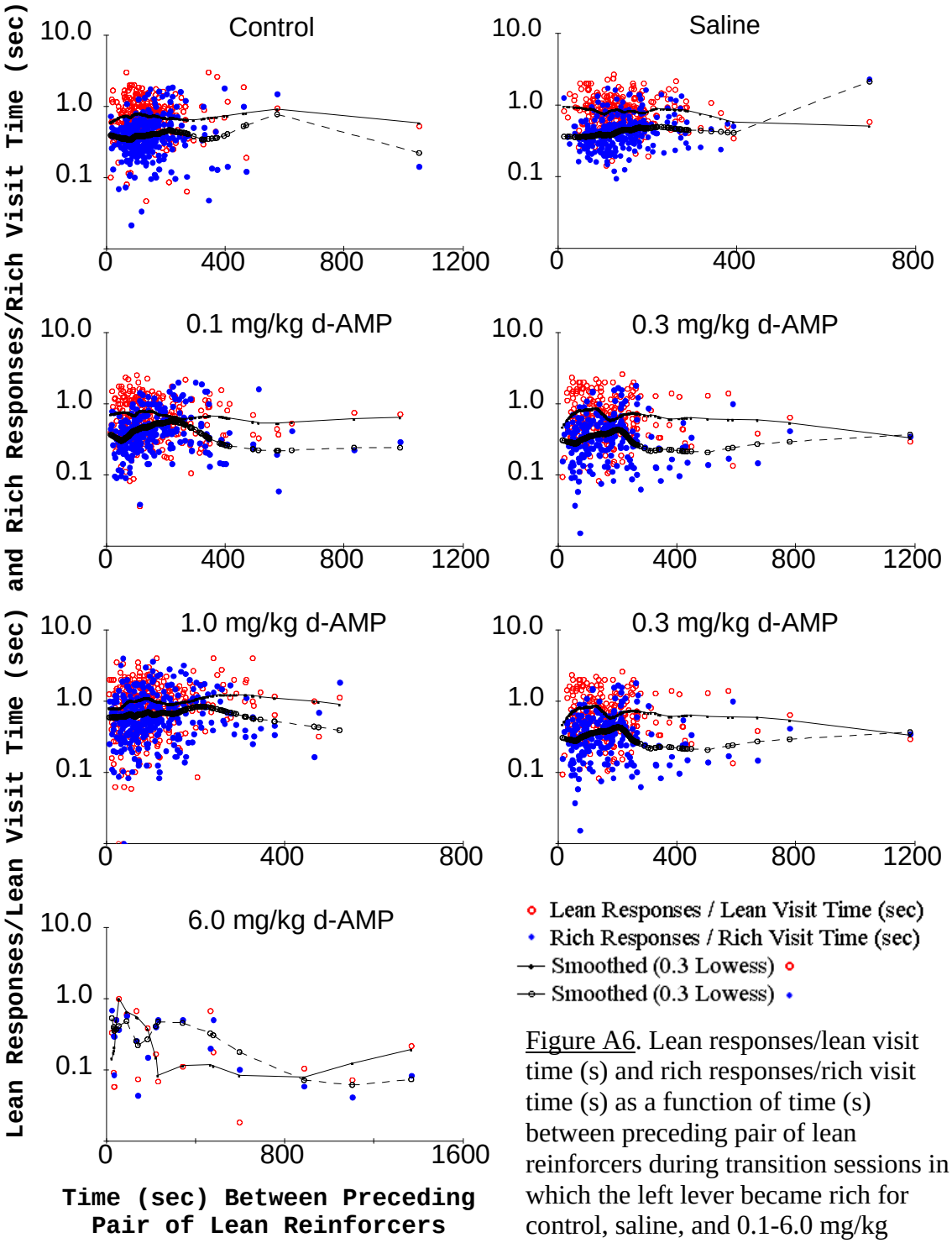


Figure A6. Lean responses/lean visit time (s) and rich responses/rich visit time (s) as a function of time (s) between preceding pair of lean reinforcers during transition sessions in which the left lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

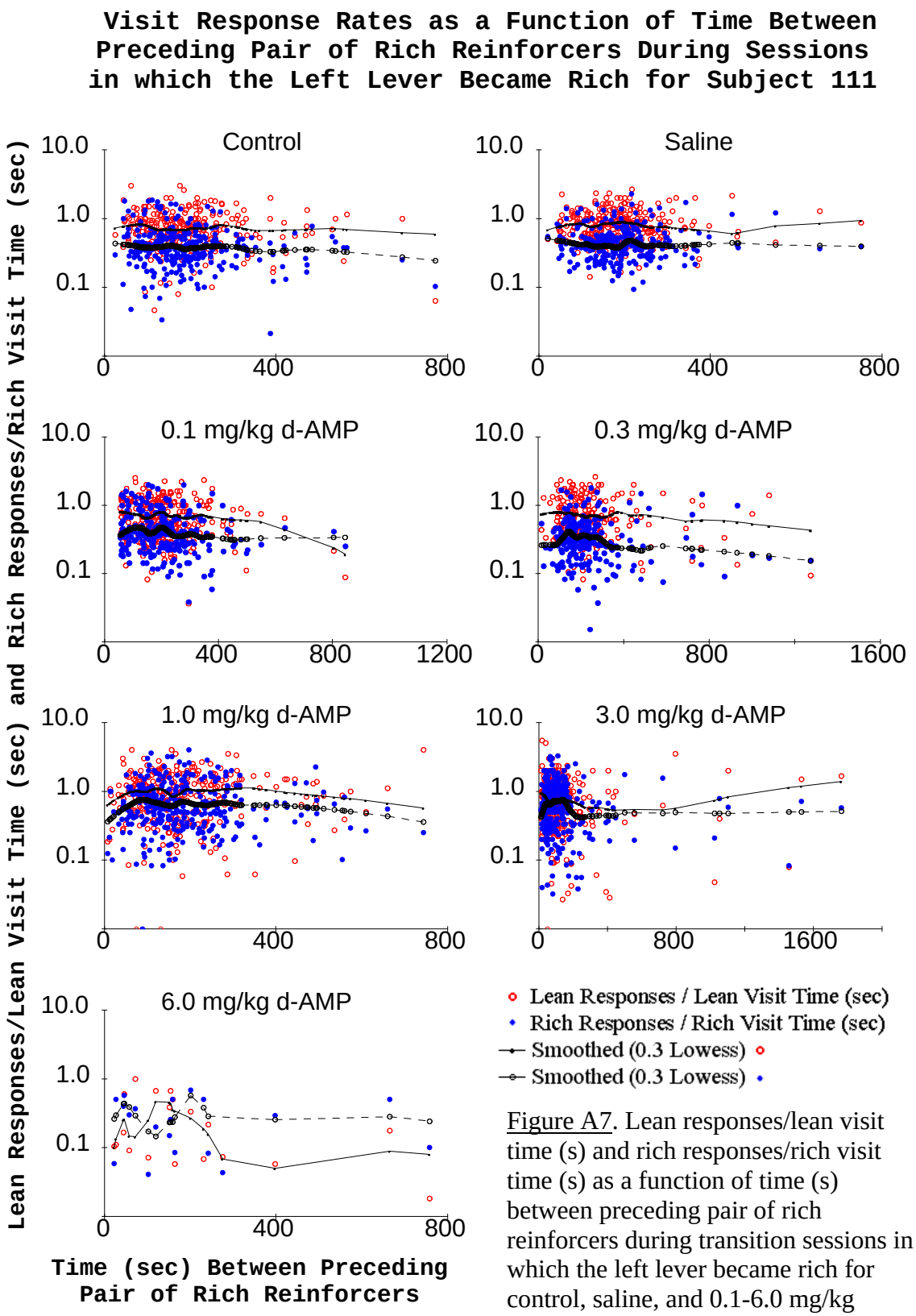


Figure A7. Lean responses/lean visit time (s) and rich responses/rich visit time (s) as a function of time (s) between preceding pair of rich reinforcers during transition sessions in which the left lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

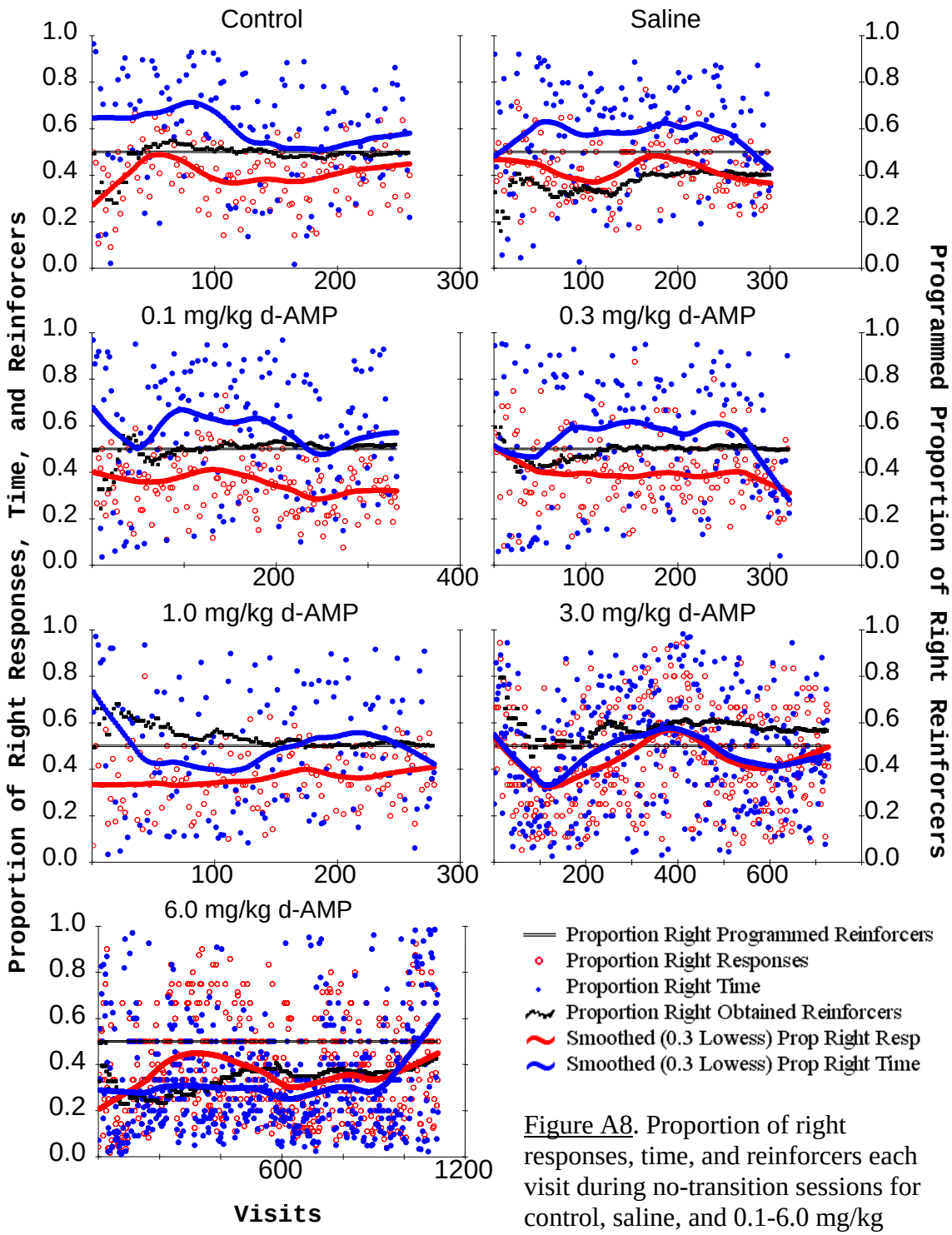


Figure A8. Proportion of right responses, time, and reinforcers each visit during no-transition sessions for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

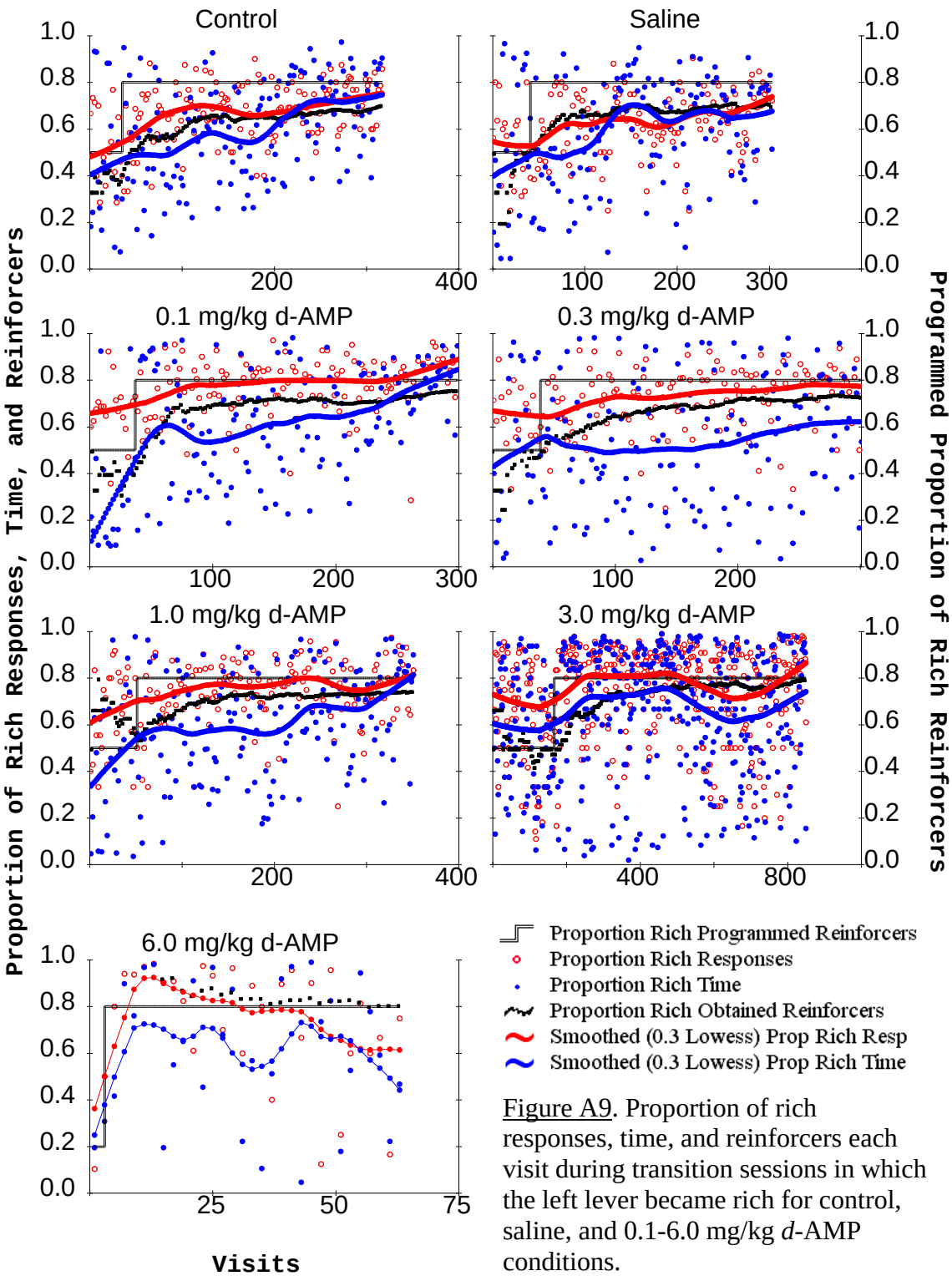


Figure A9. Proportion of rich responses, time, and reinforcers each visit during transition sessions in which the left lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

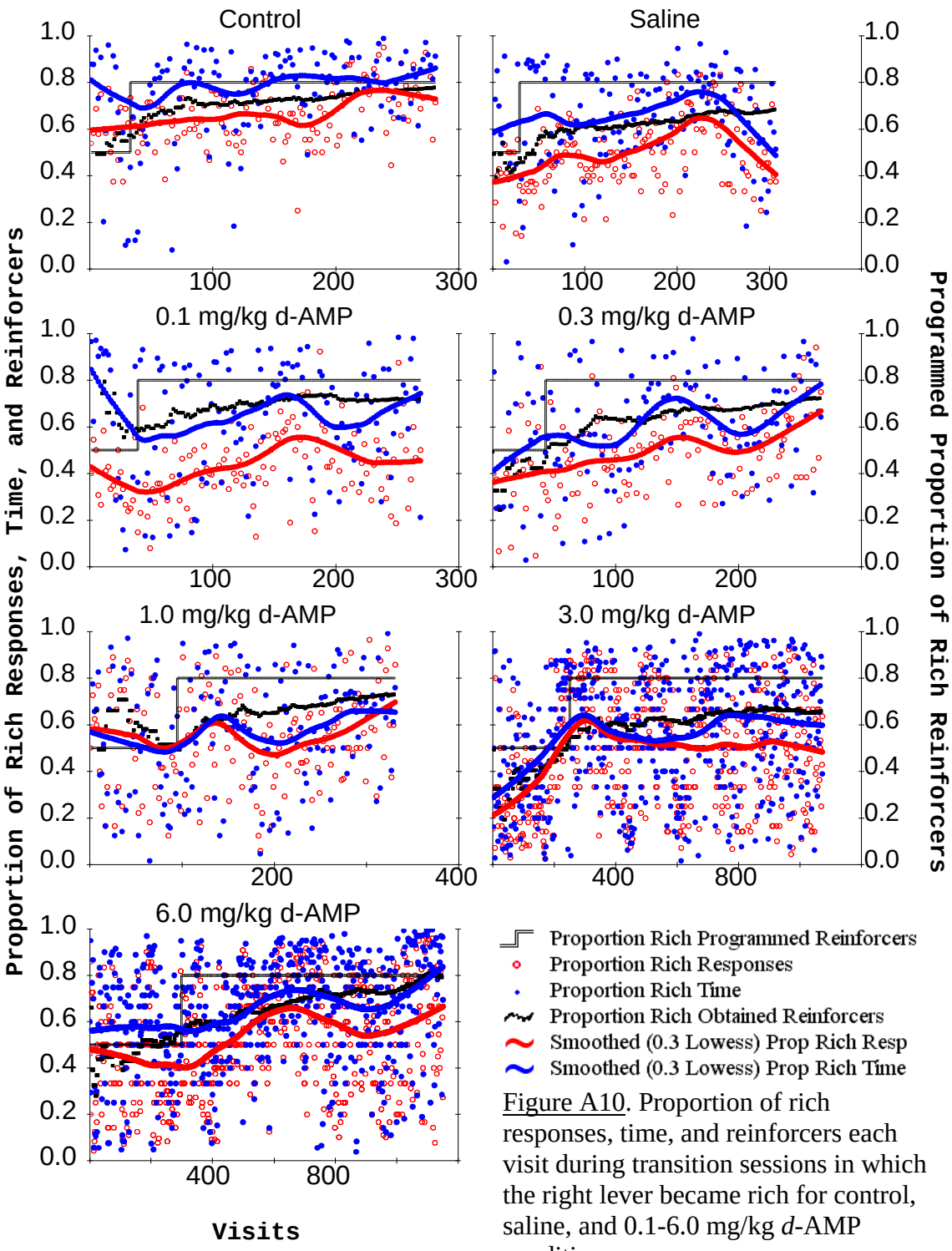


Figure A10. Proportion of rich responses, time, and reinforcers each visit during transition sessions in which the right lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

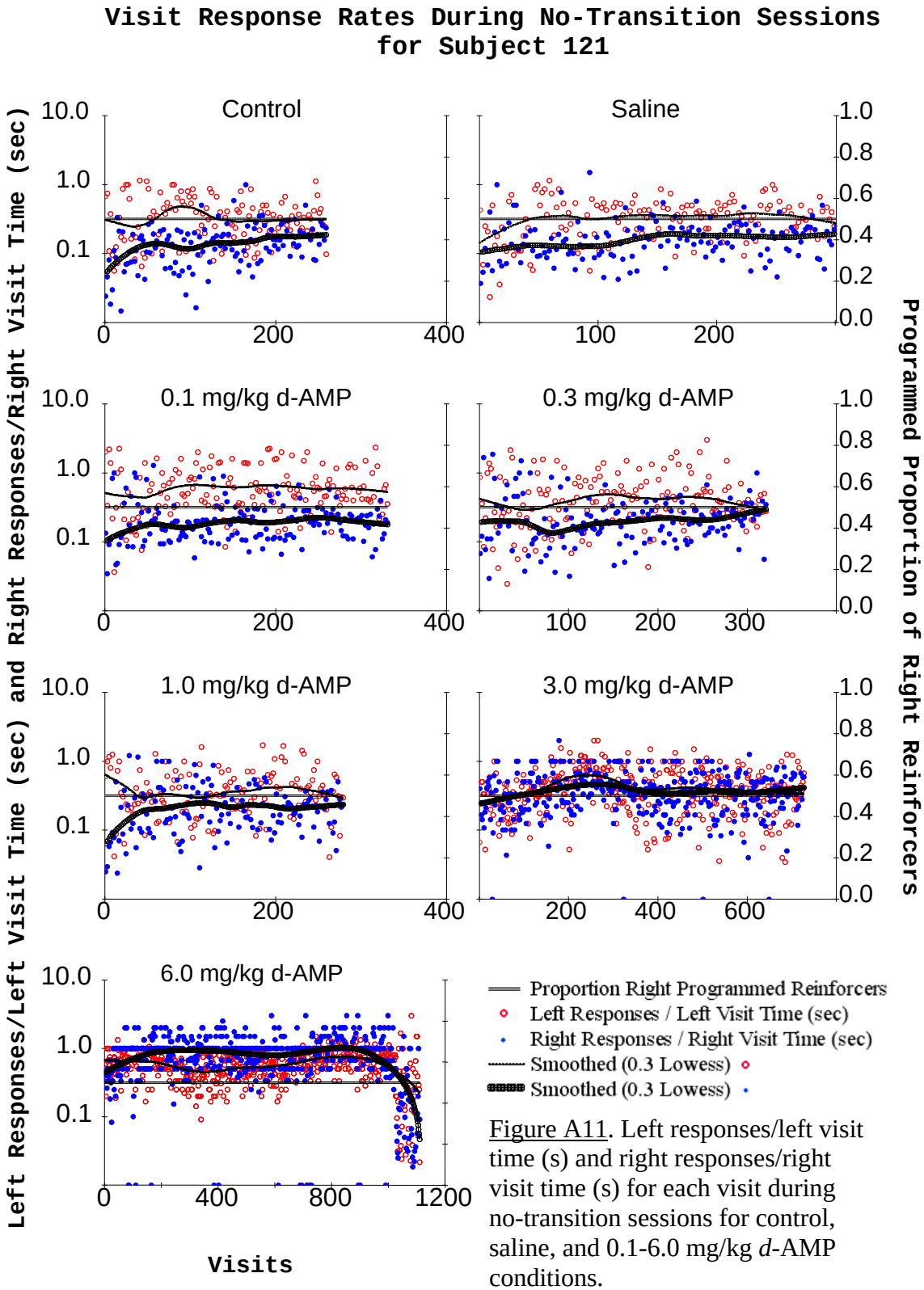


Figure A11. Left responses/left visit time (s) and right responses/right visit time (s) for each visit during no-transition sessions for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

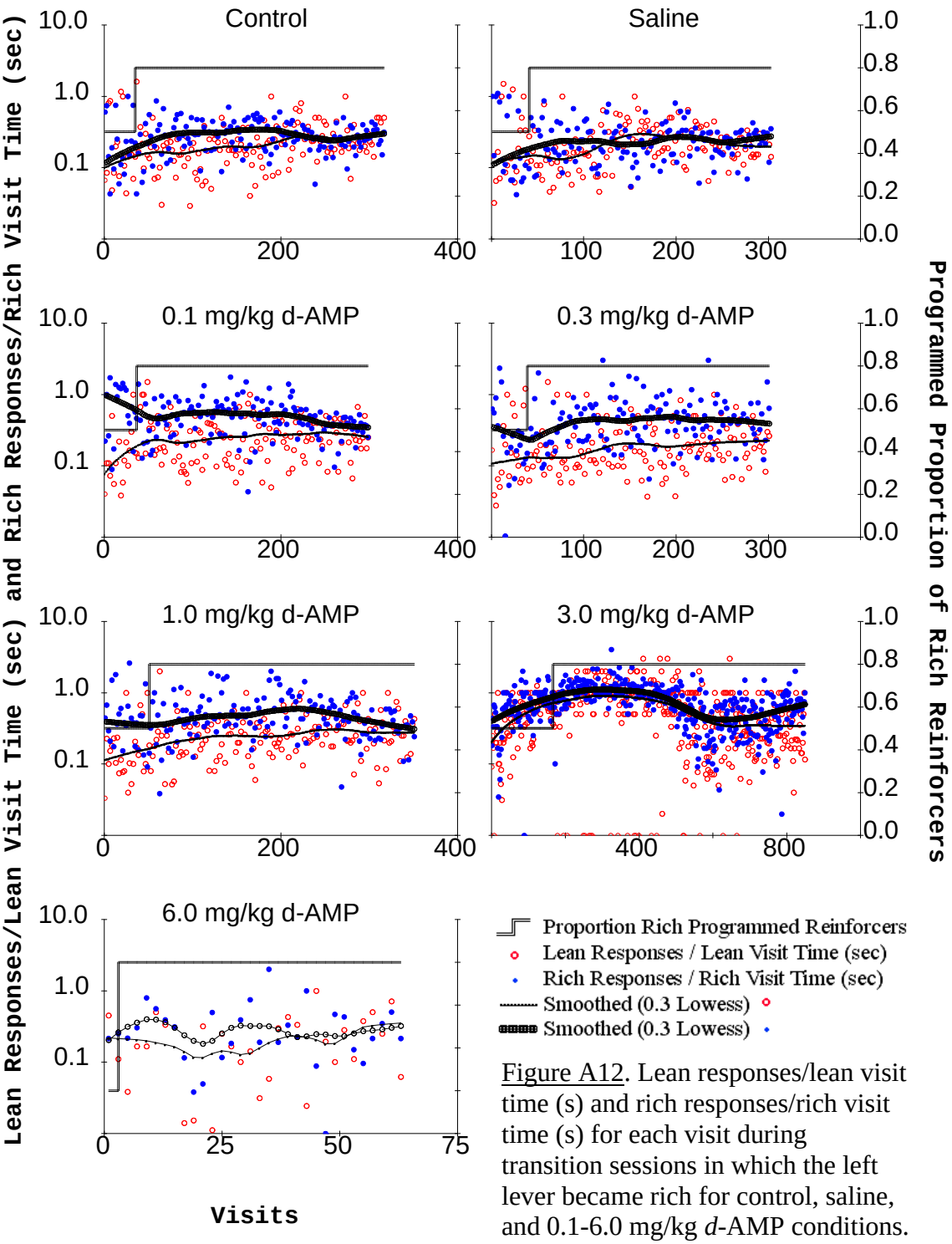


Figure A12. Lean responses/lean visit time (s) and rich responses/rich visit time (s) for each visit during transition sessions in which the left lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

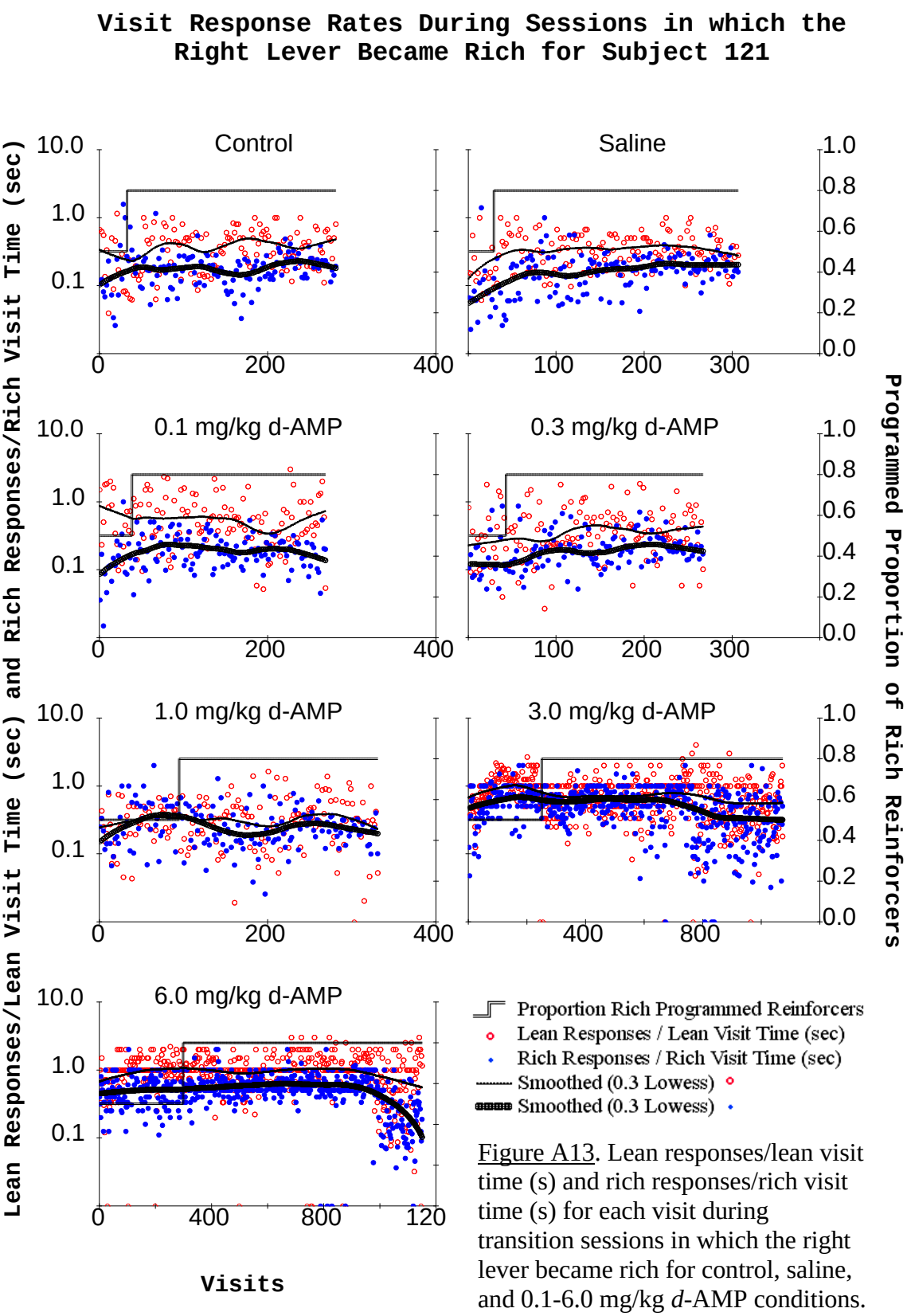


Figure A13. Lean responses/lean visit time (s) and rich responses/rich visit time (s) for each visit during transition sessions in which the right lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

Responses Per Visit as a Function of Cumulative Reinforcers During No-Transition Sessions for Subject 121

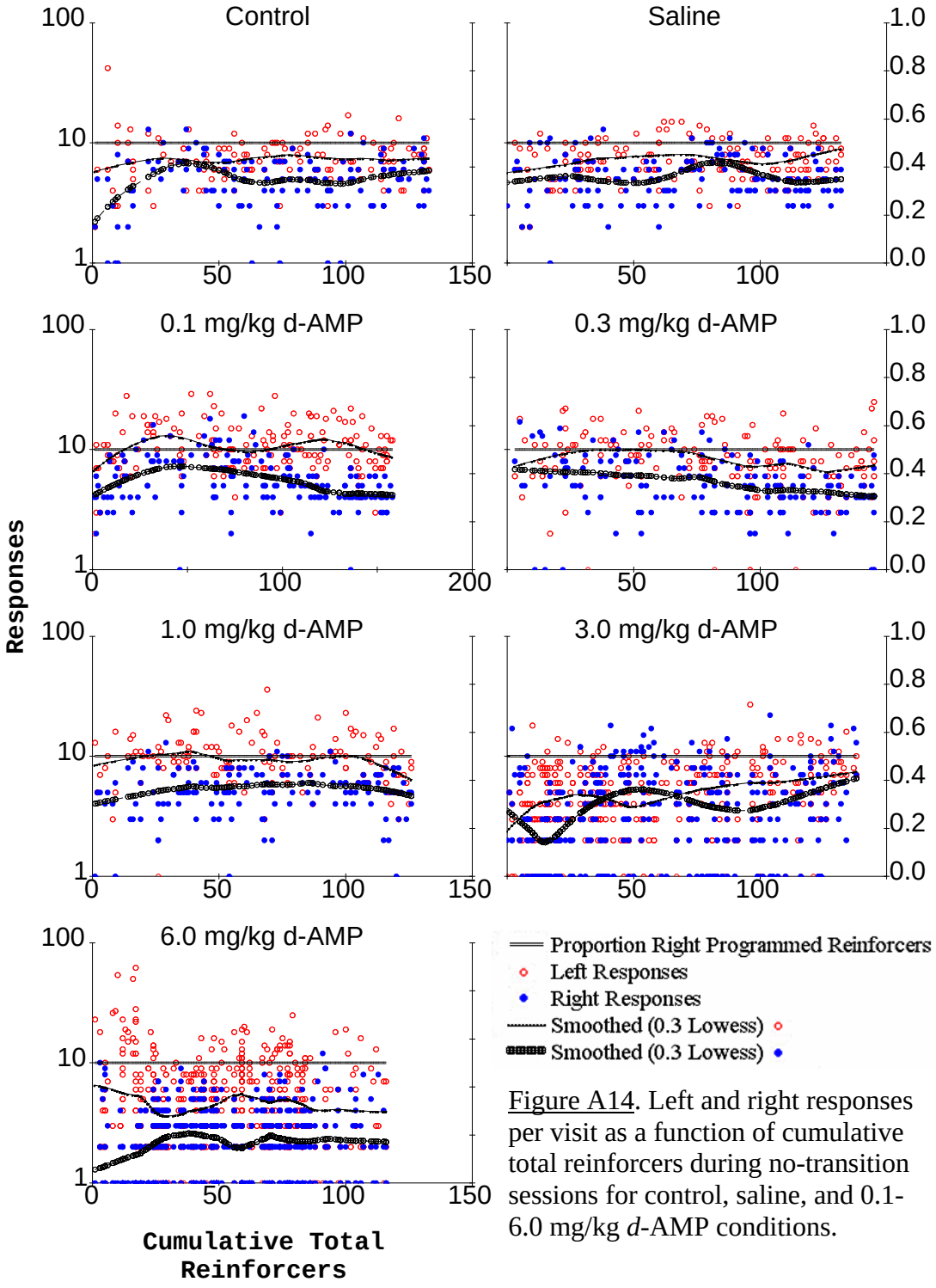


Figure A14. Left and right responses per visit as a function of cumulative total reinforcers during no-transition sessions for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

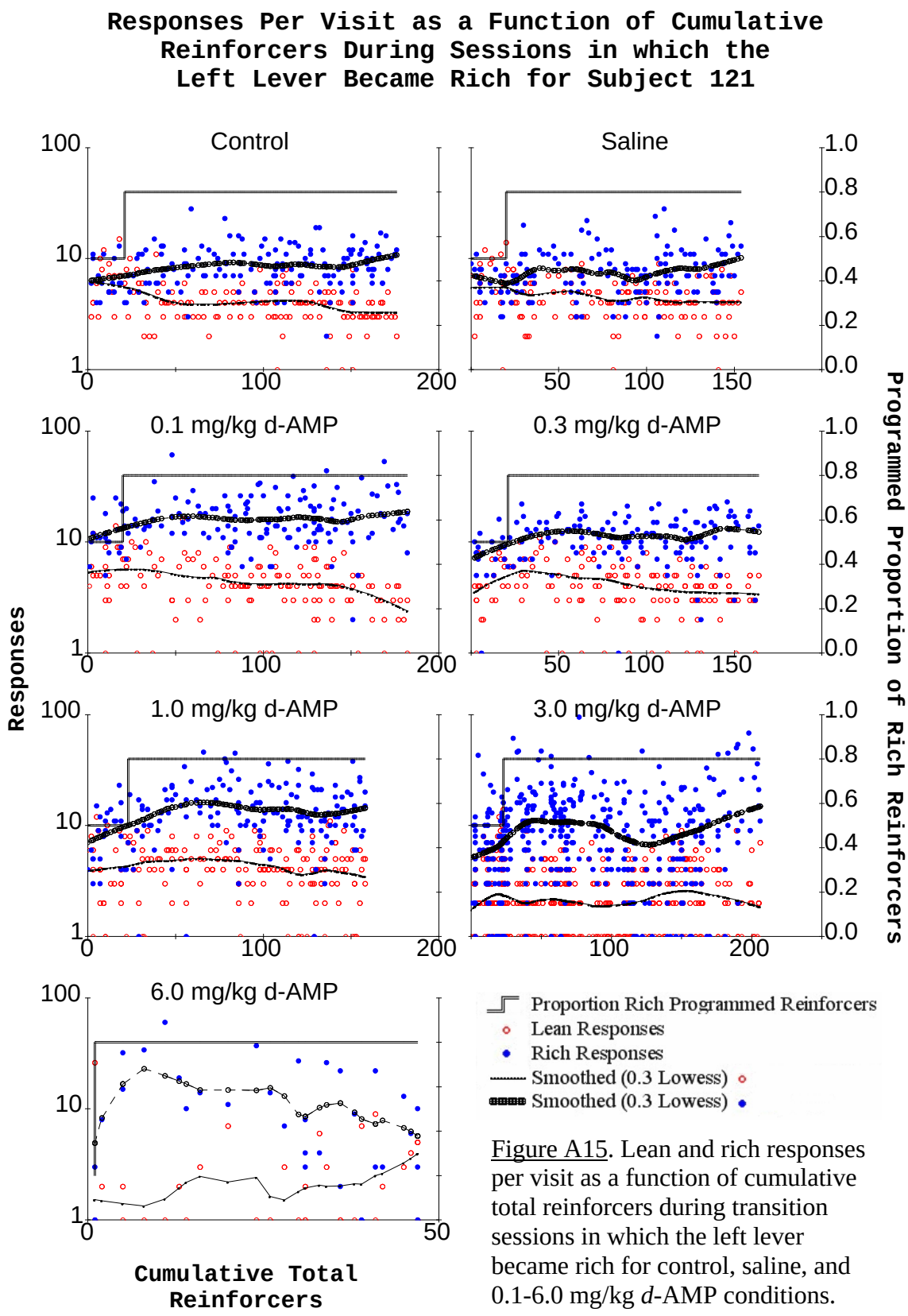


Figure A15. Lean and rich responses per visit as a function of cumulative total reinforcers during transition sessions in which the left lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

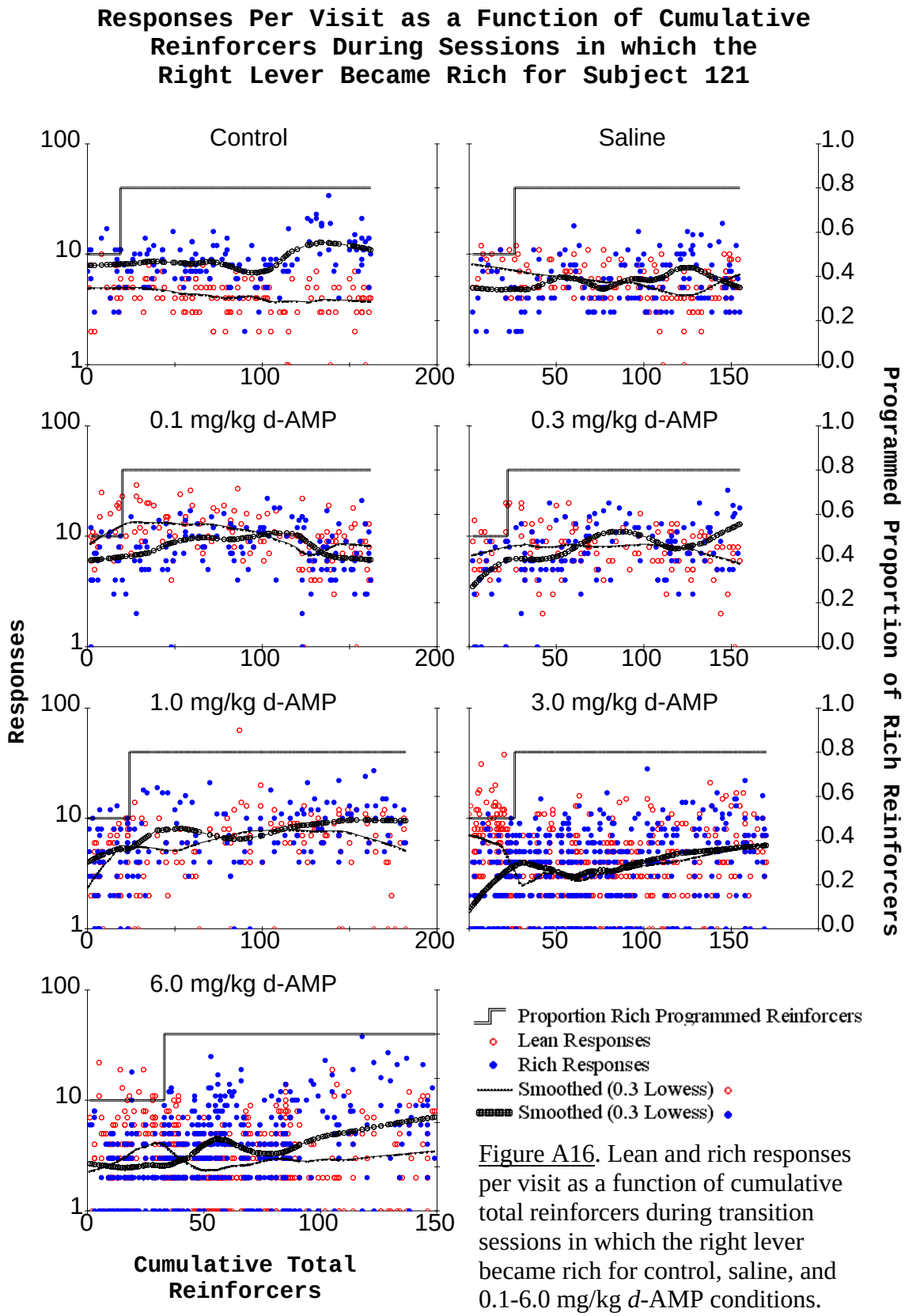


Figure A16. Lean and rich responses per visit as a function of cumulative total reinforcers during transition sessions in which the right lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

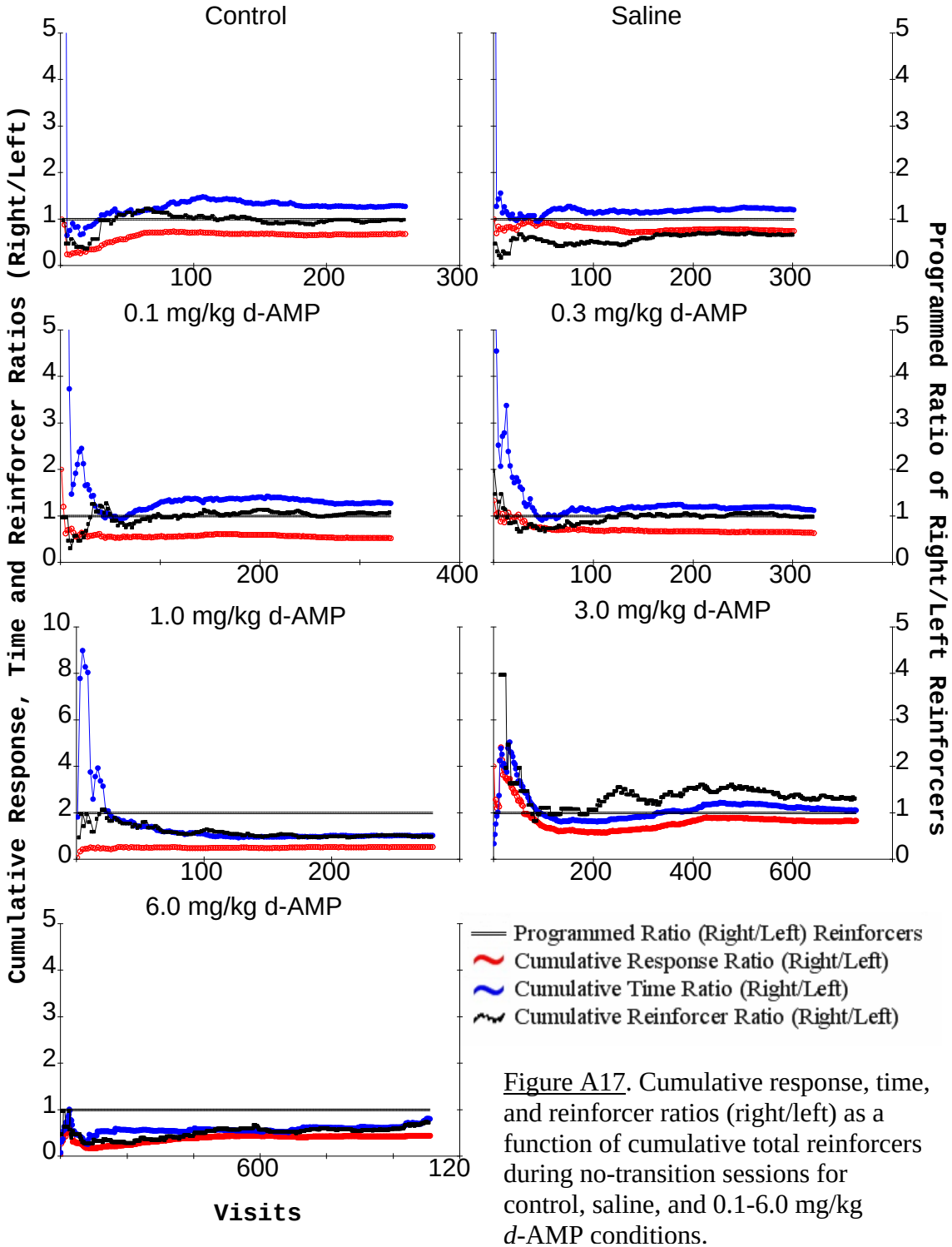


Figure A17. Cumulative response, time, and reinforcer ratios (right/left) as a function of cumulative total reinforcers during no-transition sessions for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

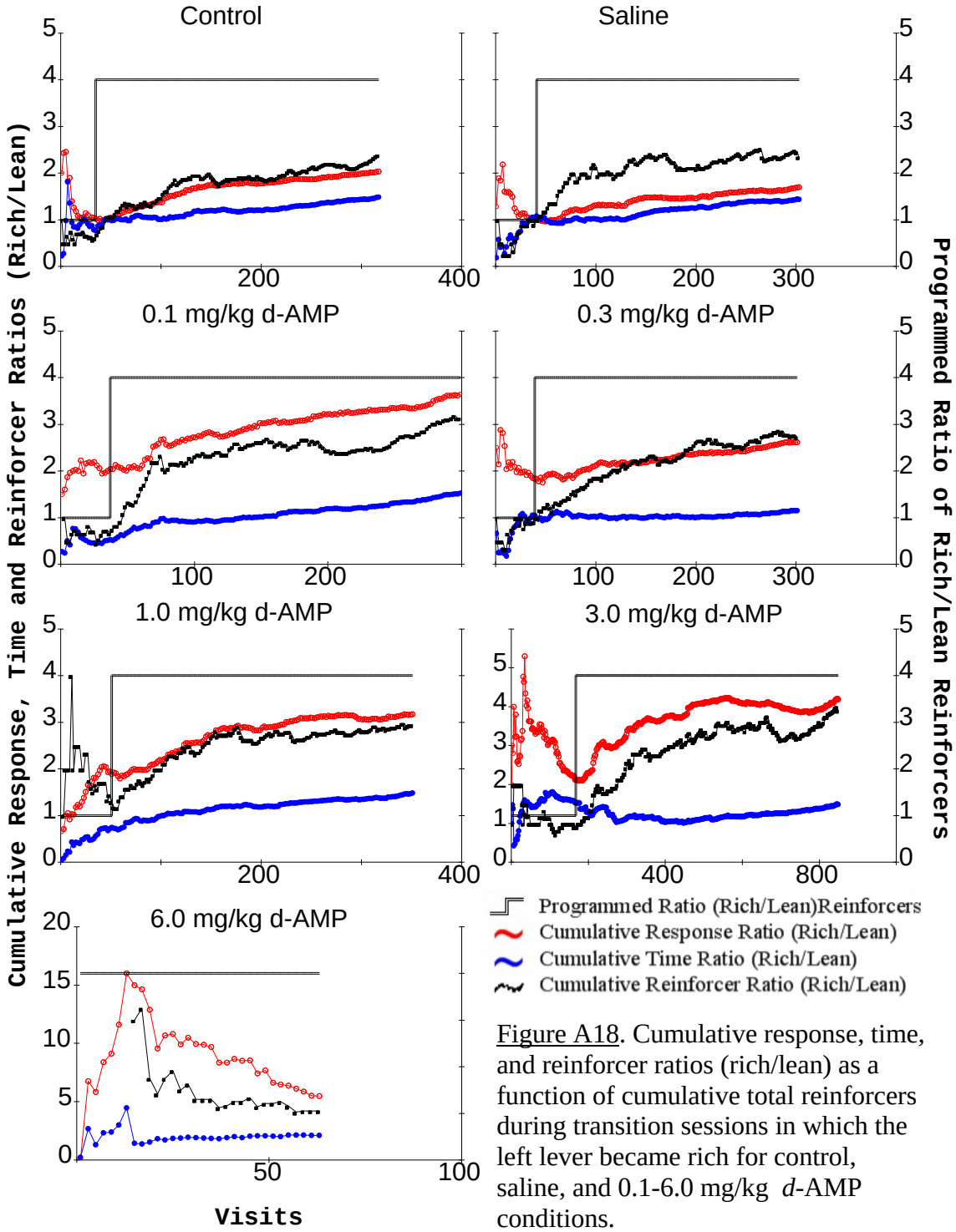


Figure A18. Cumulative response, time, and reinforcer ratios (rich/lean) as a function of cumulative total reinforcers during transition sessions in which the left lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

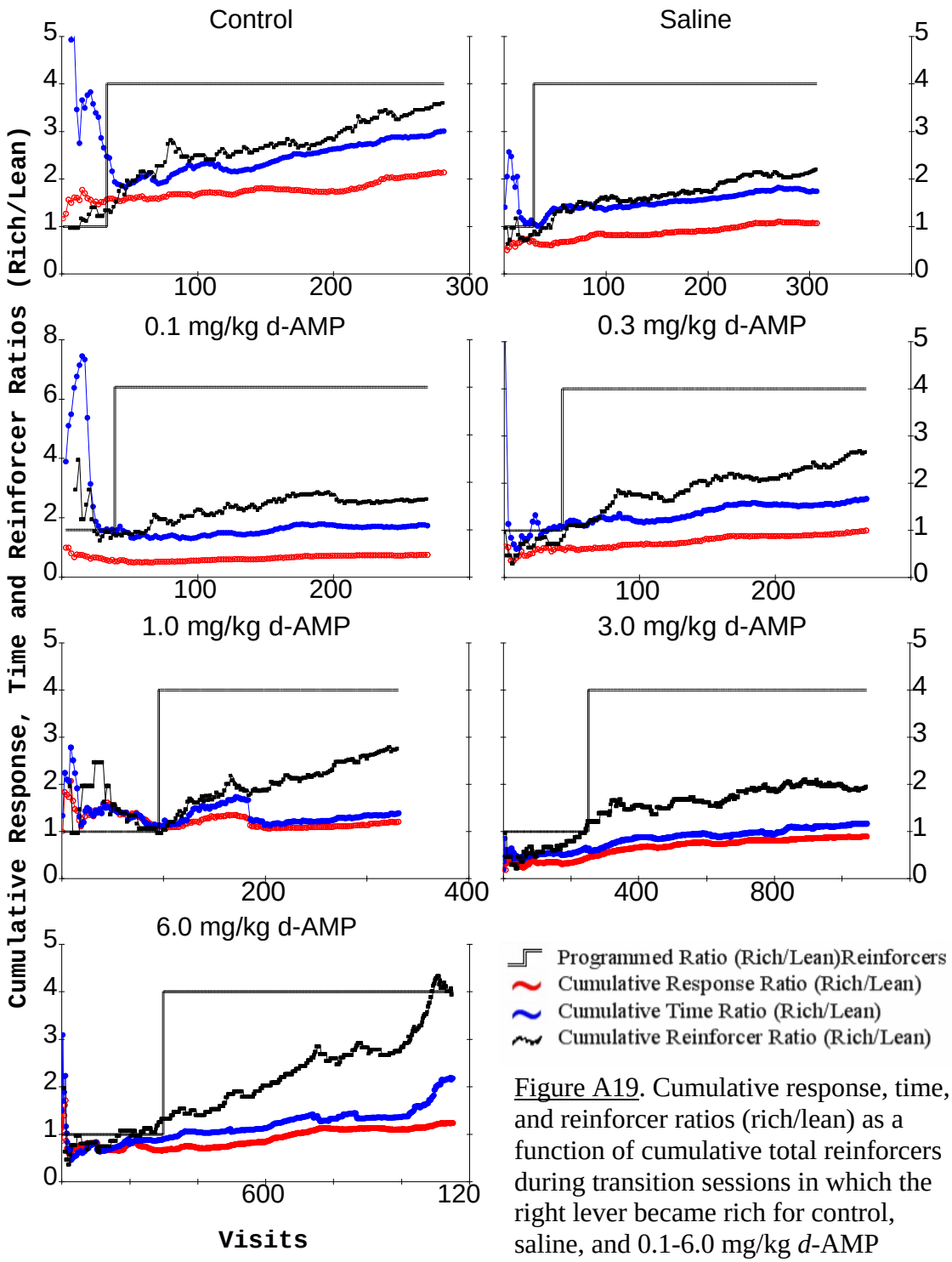


Figure A19. Cumulative response, time, and reinforcer ratios (rich/lean) as a function of cumulative total reinforcers during transition sessions in which the right lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

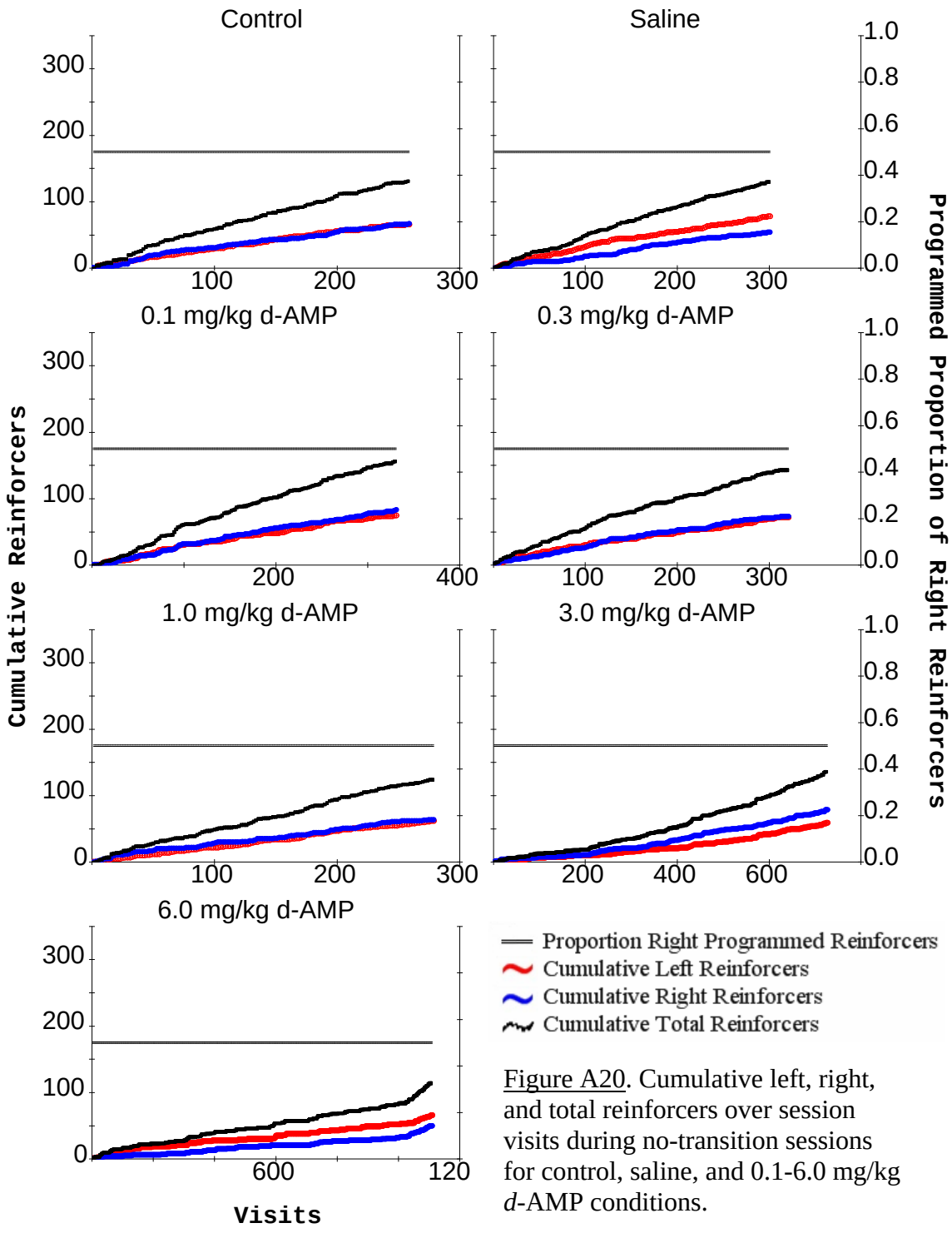


Figure A20. Cumulative left, right, and total reinforcers over session visits during no-transition sessions for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

Cumulative Lean, Rich, and Total Reinforcers through Sessions in which the Left Lever Became Rich for Subject 121

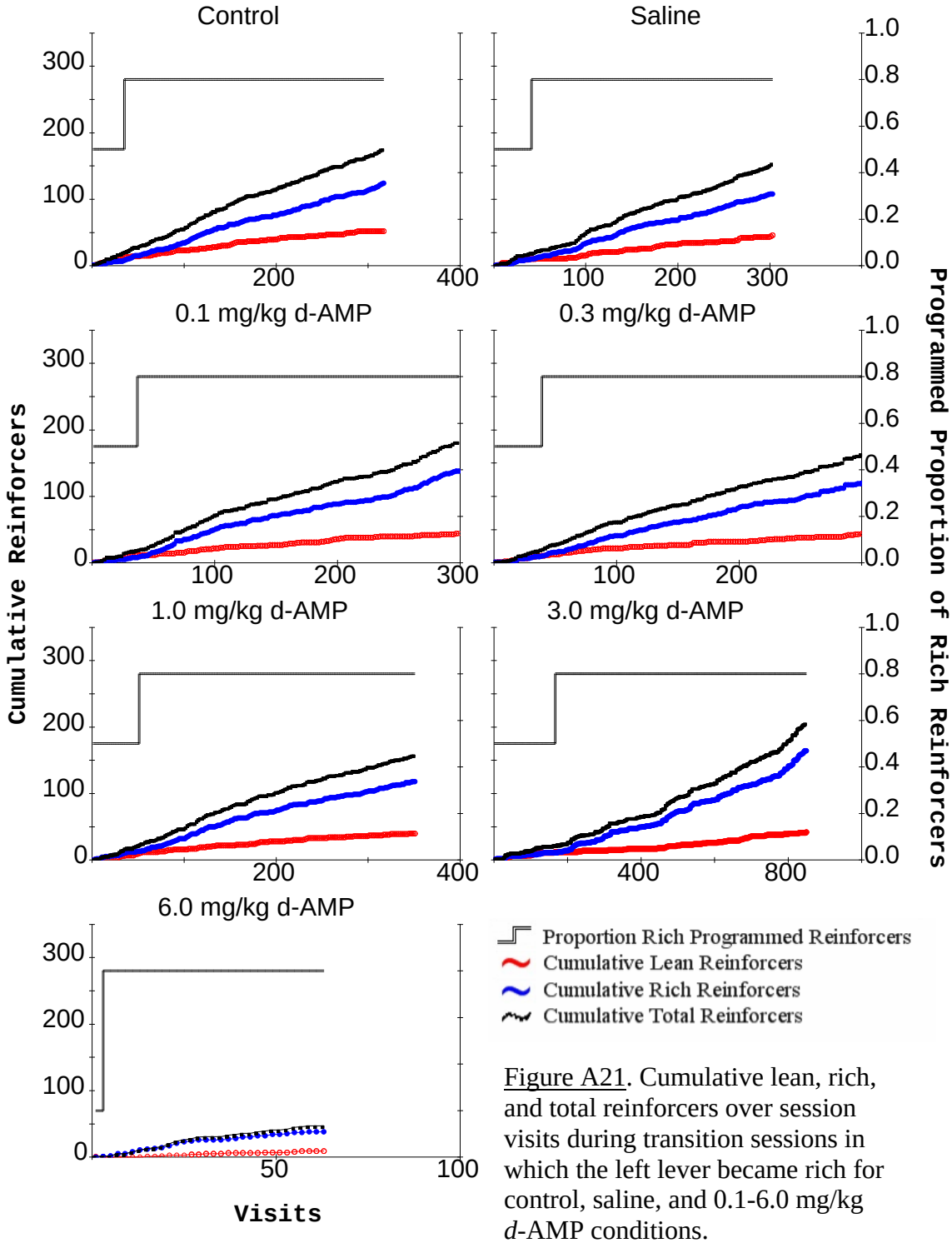


Figure A21. Cumulative lean, rich, and total reinforcers over session visits during transition sessions in which the left lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

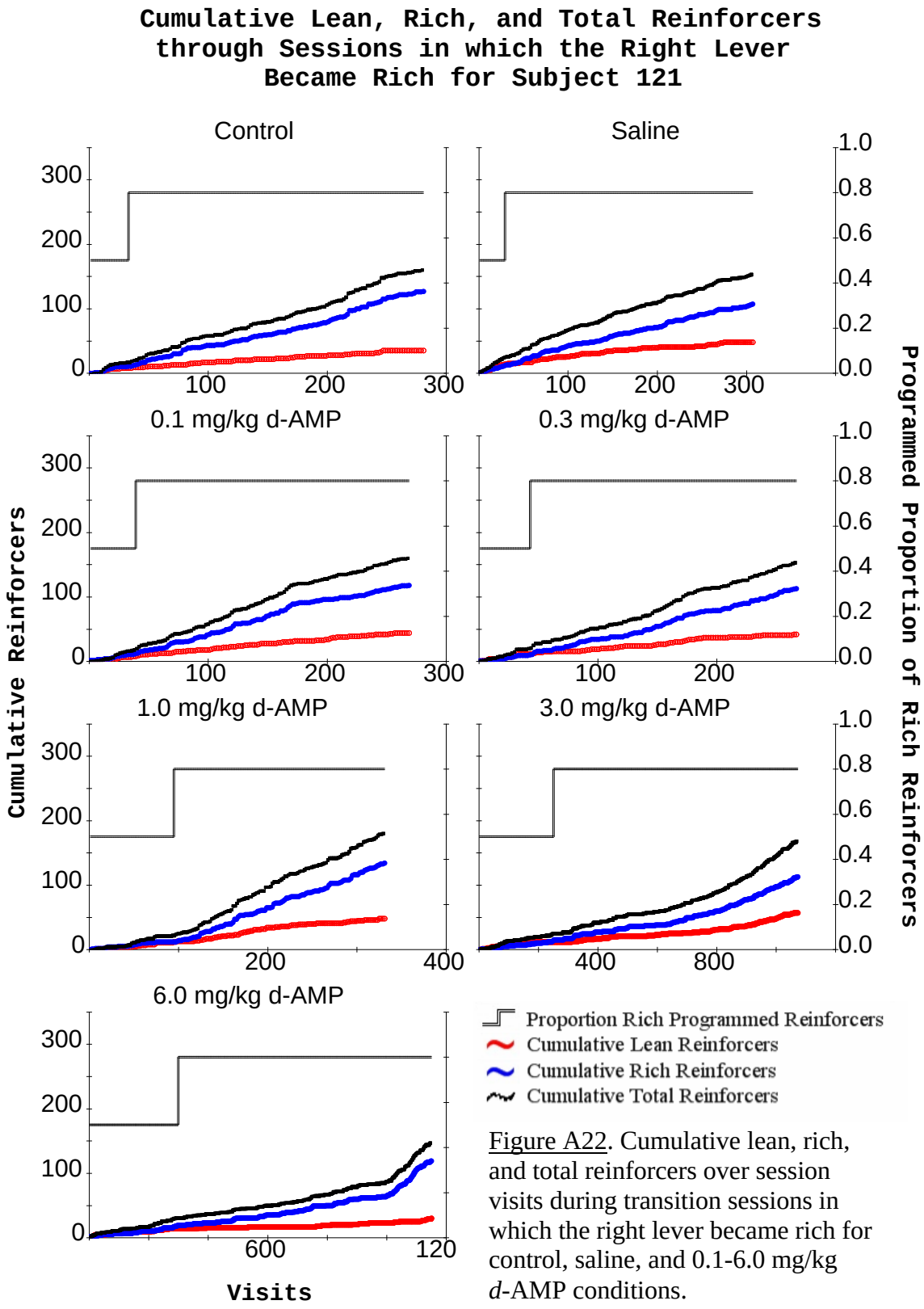


Figure A22. Cumulative lean, rich, and total reinforcers over session visits during transition sessions in which the right lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

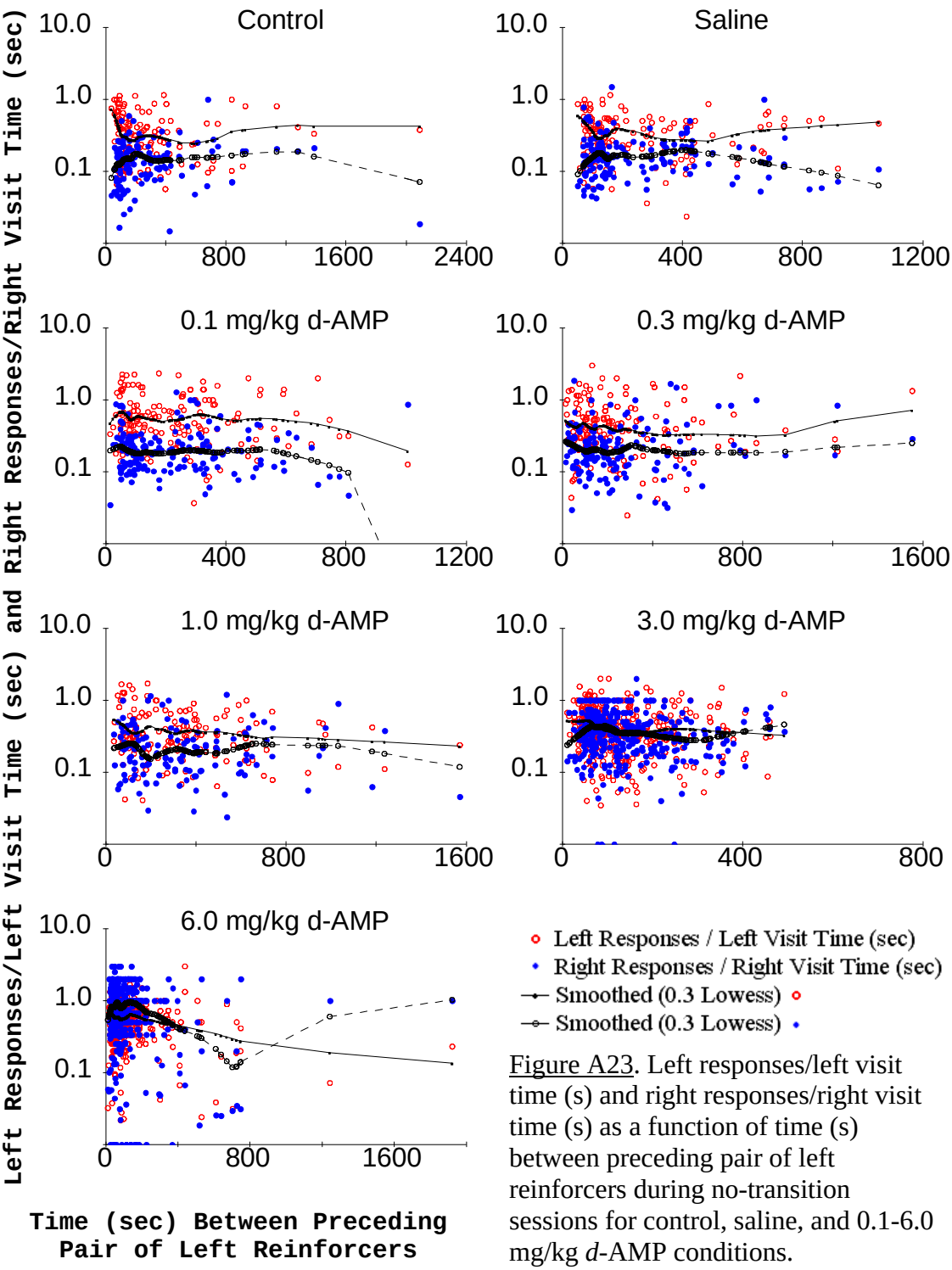


Figure A23. Left responses/left visit time (s) and right responses/right visit time (s) as a function of time (s) between preceding pair of left reinforcers during no-transition sessions for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

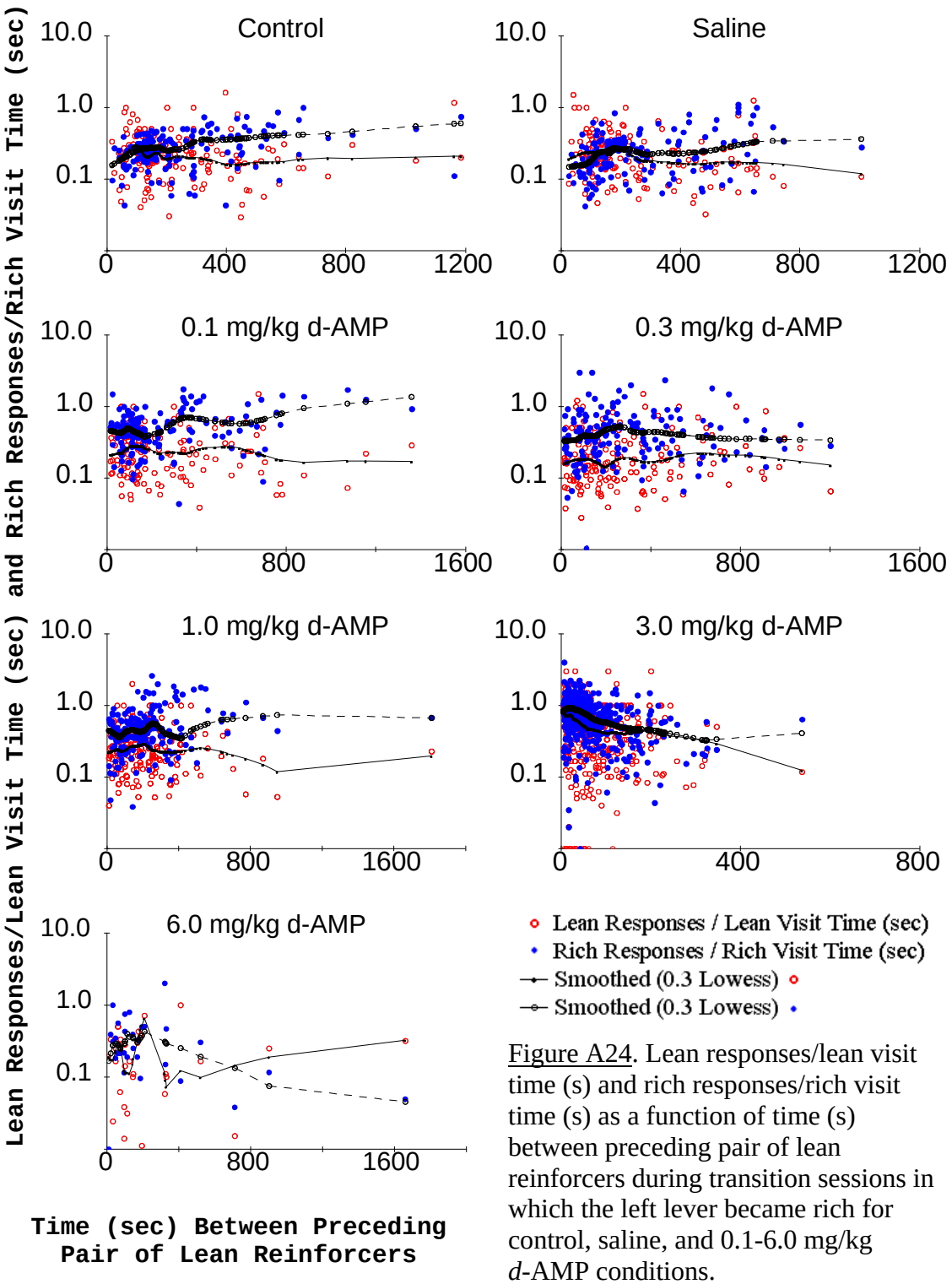


Figure A24. Lean responses/lean visit time (s) and rich responses/rich visit time (s) as a function of time (s) between preceding pair of lean reinforcers during transition sessions in which the left lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

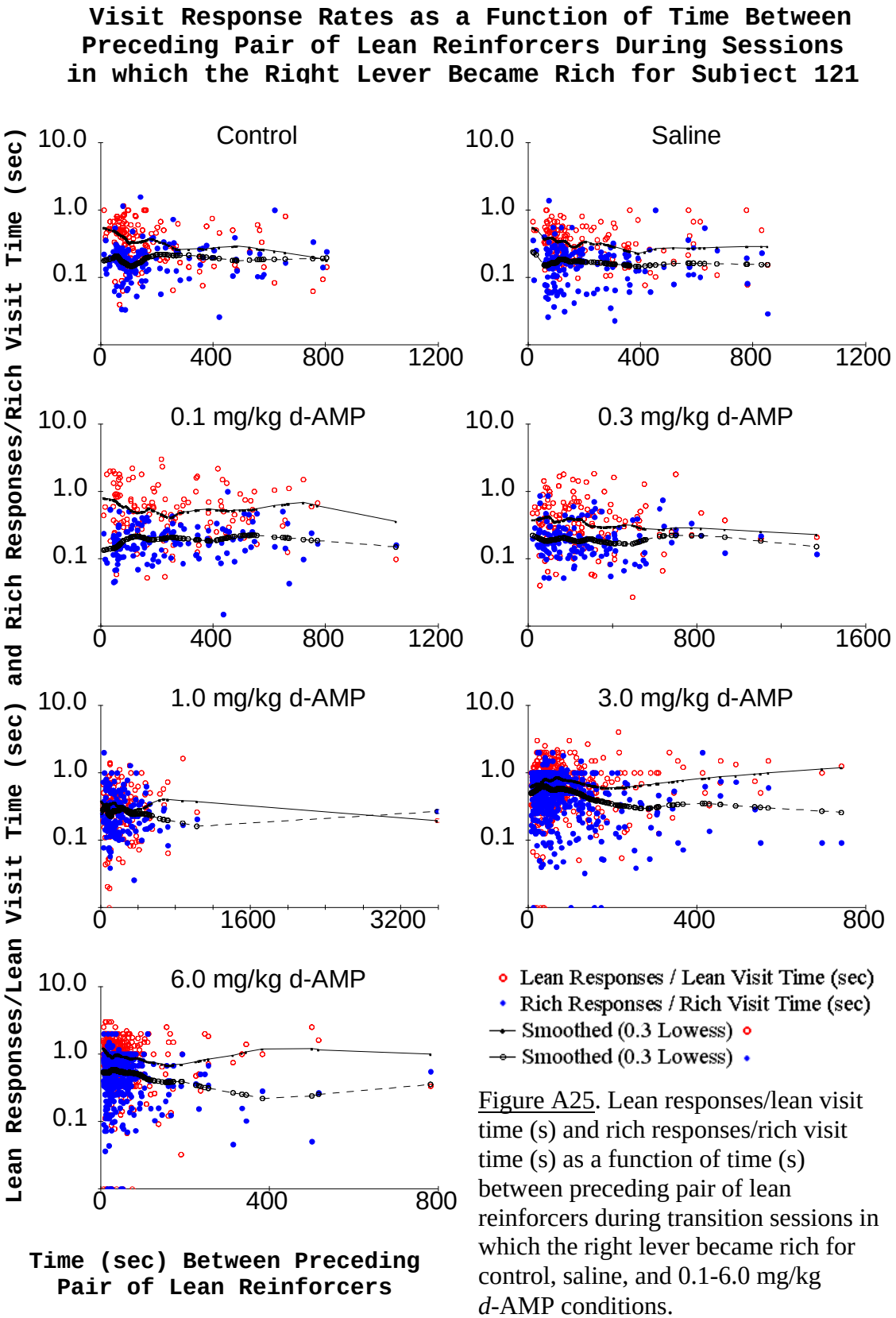


Figure A25. Lean responses/lean visit time (s) and rich responses/rich visit time (s) as a function of time (s) between preceding pair of lean reinforcers during transition sessions in which the right lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

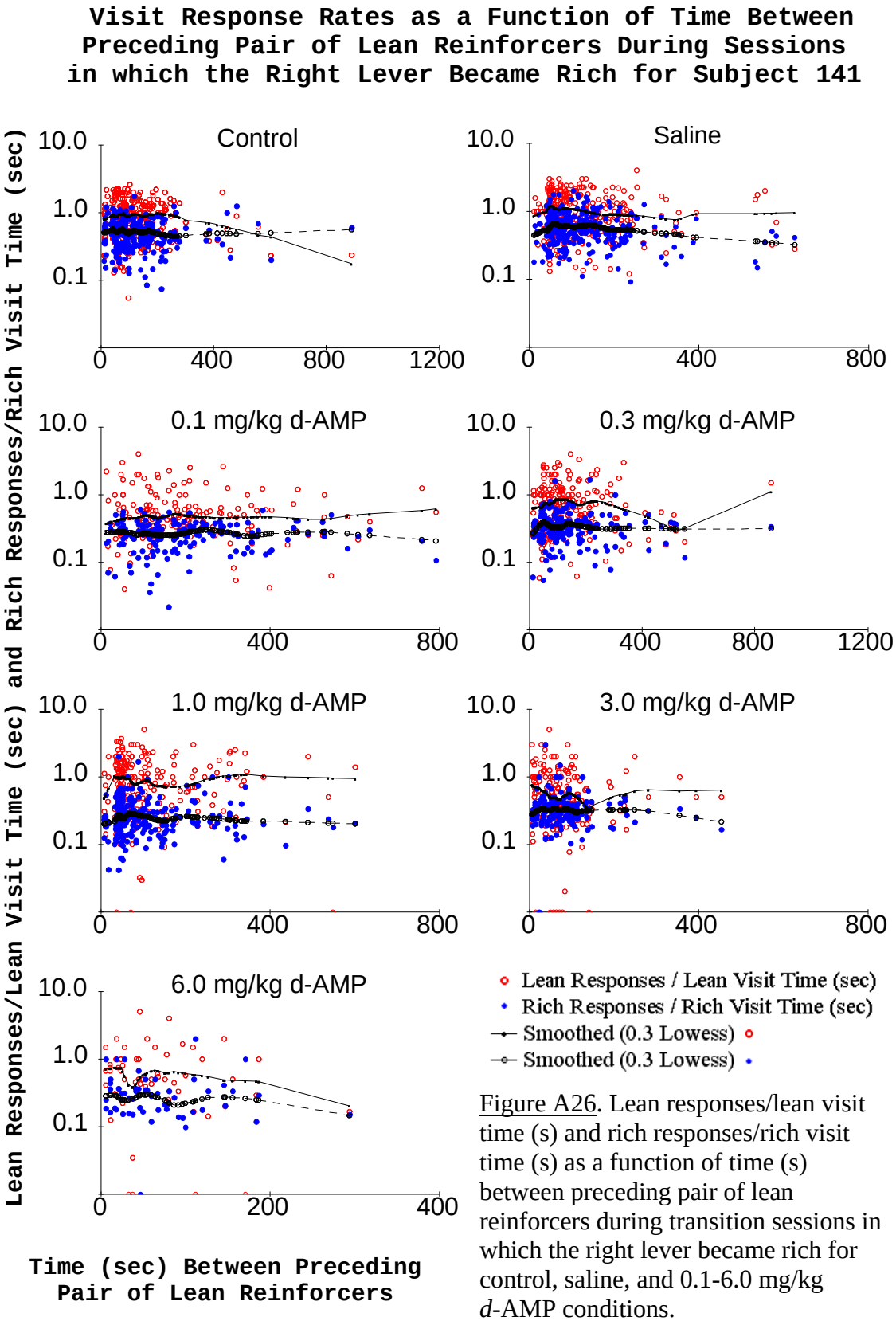


Figure A26. Lean responses/lean visit time (s) and rich responses/rich visit time (s) as a function of time (s) between preceding pair of lean reinforcers during transition sessions in which the right lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

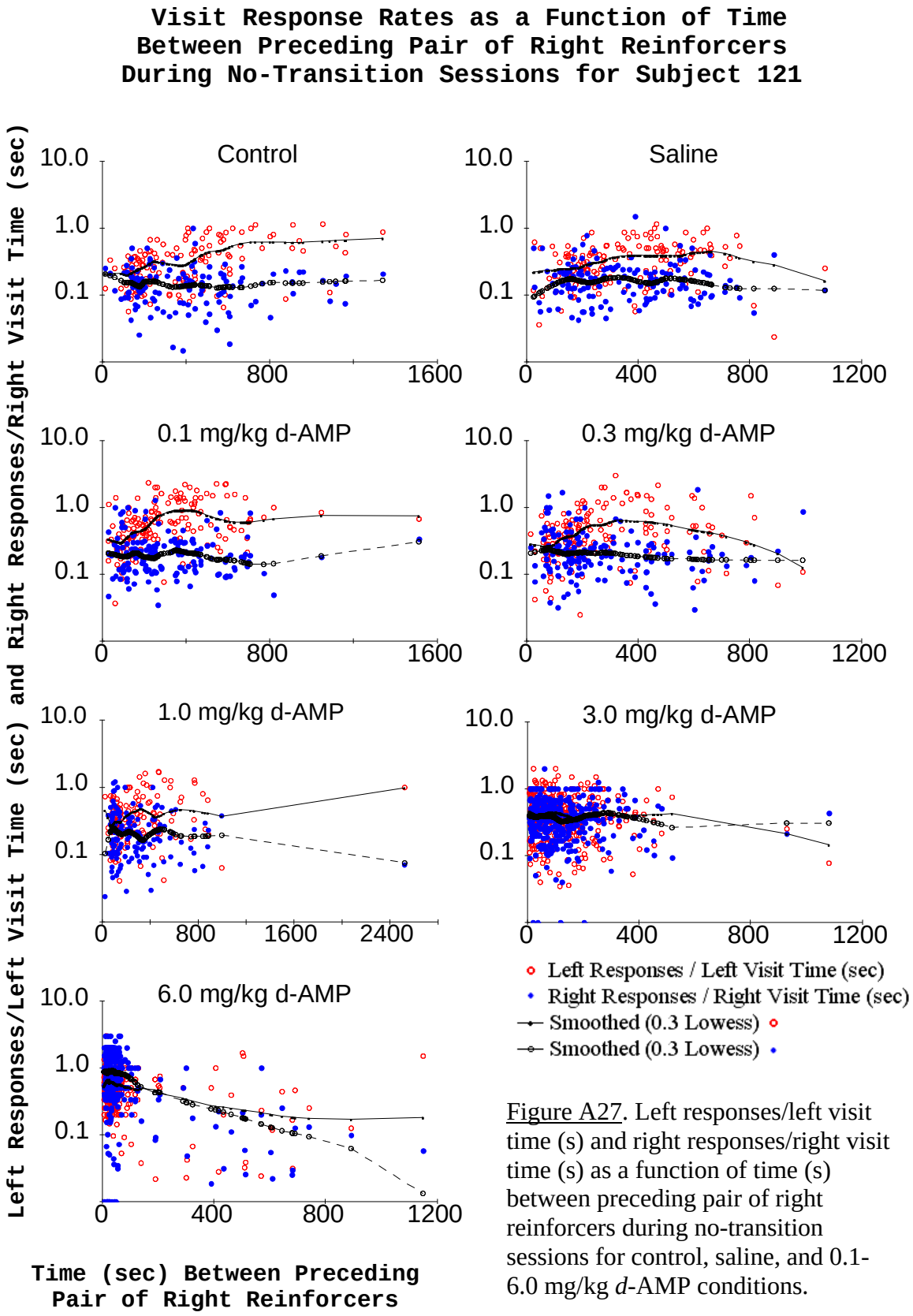


Figure A27. Left responses/left visit time (s) and right responses/right visit time (s) as a function of time (s) between preceding pair of right reinforcers during no-transition sessions for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

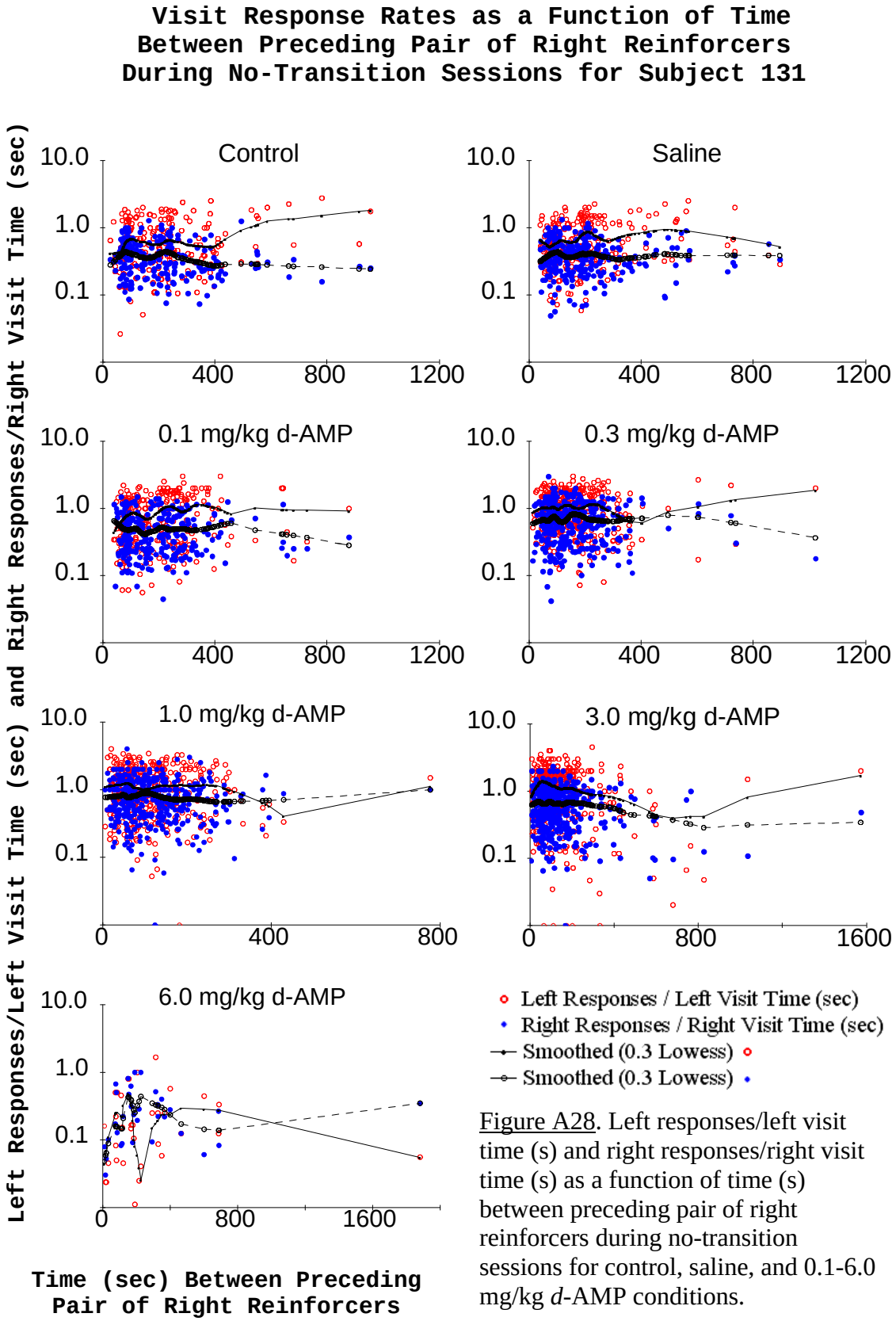


Figure A28. Left responses/left visit time (s) and right responses/right visit time (s) as a function of time (s) between preceding pair of right reinforcers during no-transition sessions for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

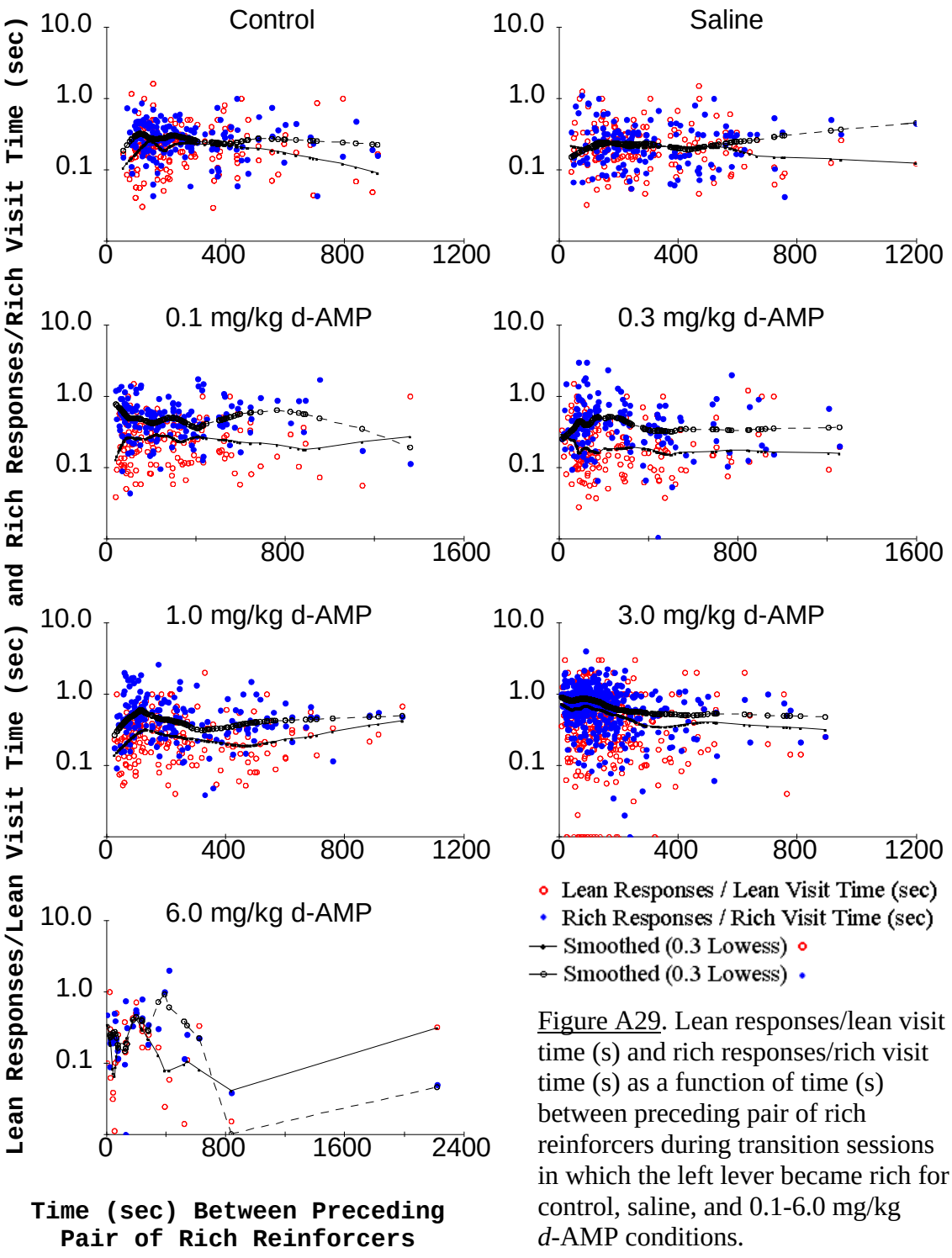


Figure A29. Lean responses/lean visit time (s) and rich responses/rich visit time (s) as a function of time (s) between preceding pair of rich reinforcers during transition sessions in which the left lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

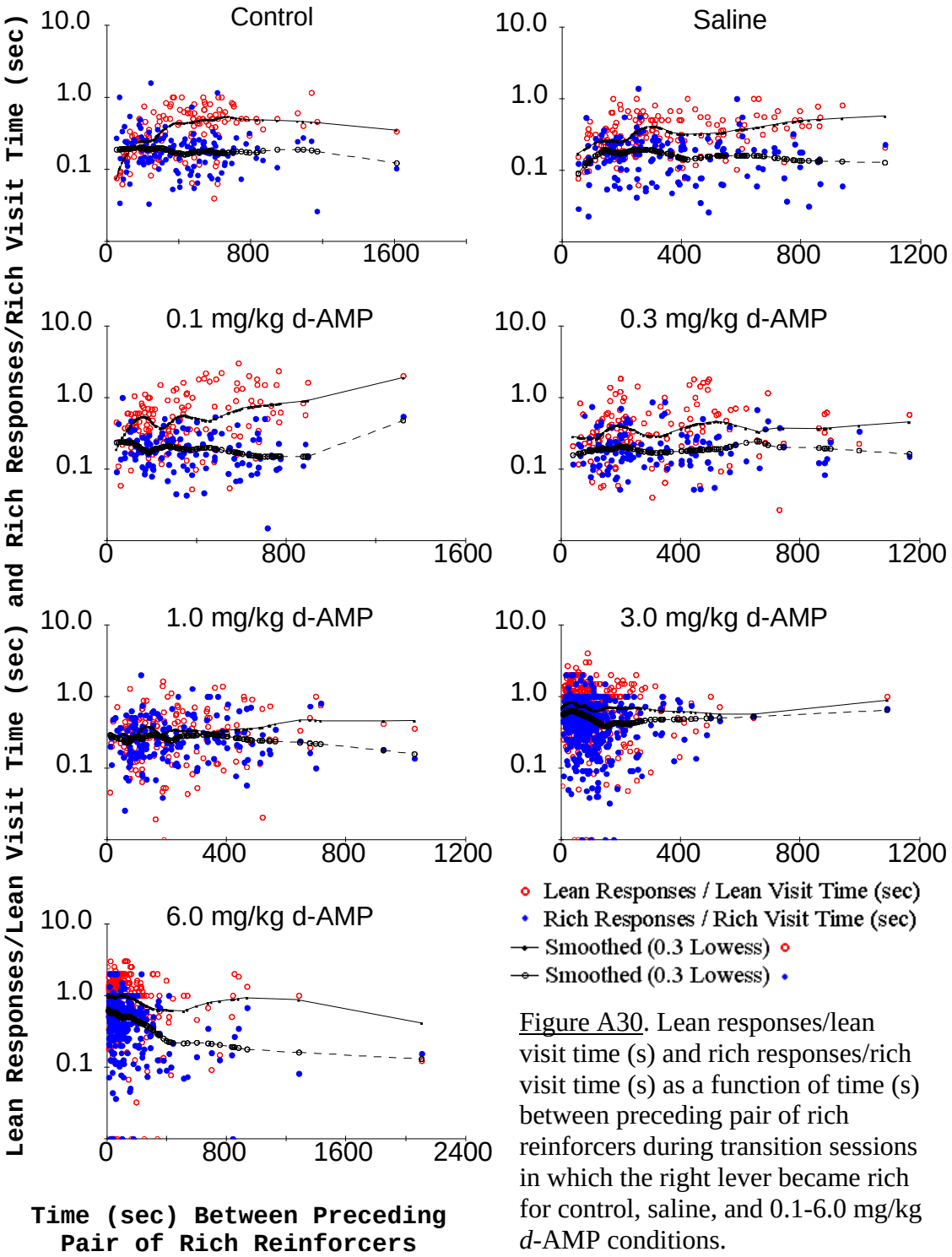


Figure A30. Lean responses/lean visit time (s) and rich responses/rich visit time (s) as a function of time (s) between preceding pair of rich reinforcers during transition sessions in which the right lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

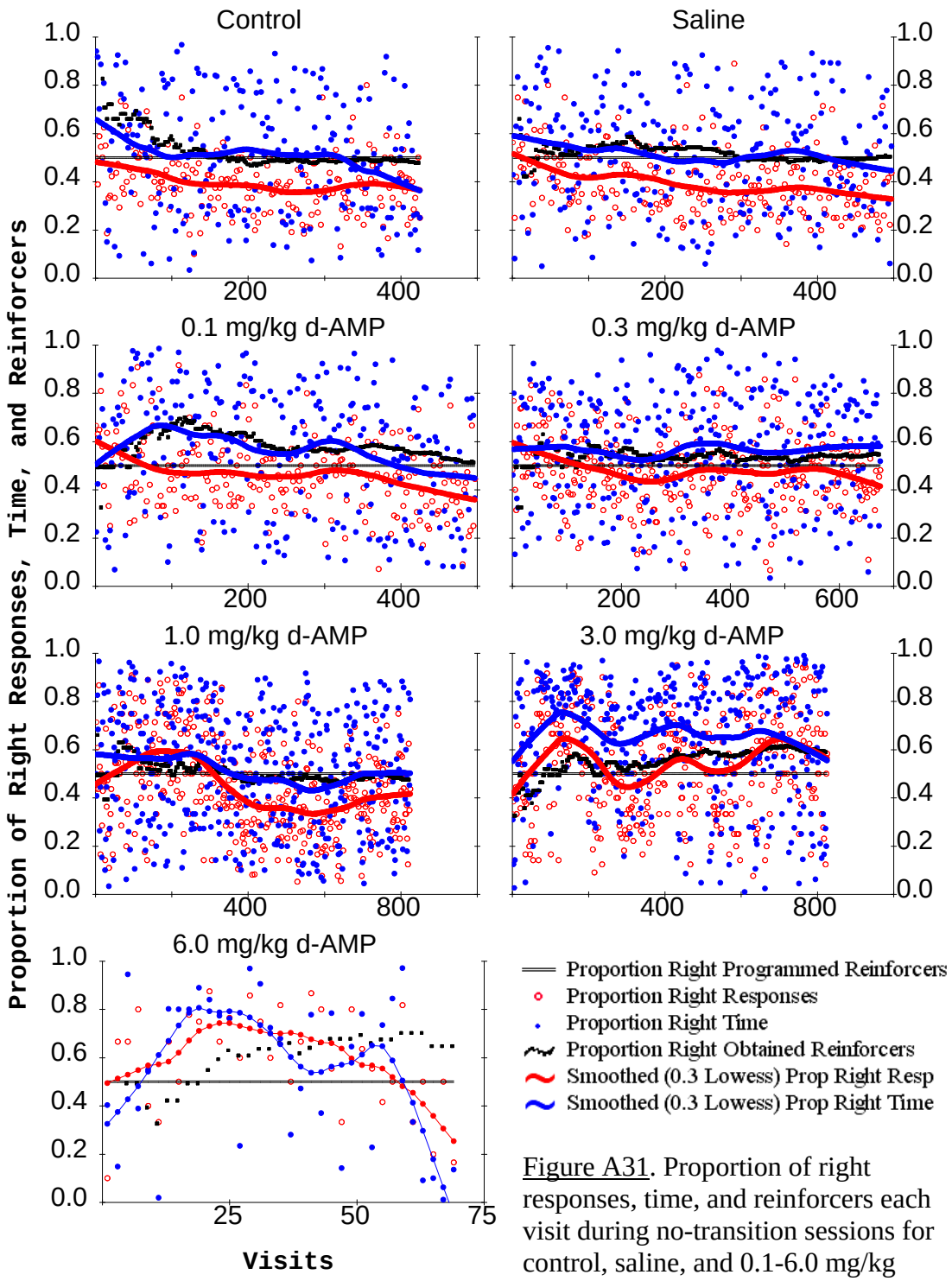


Figure A31. Proportion of right responses, time, and reinforcers each visit during no-transition sessions for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

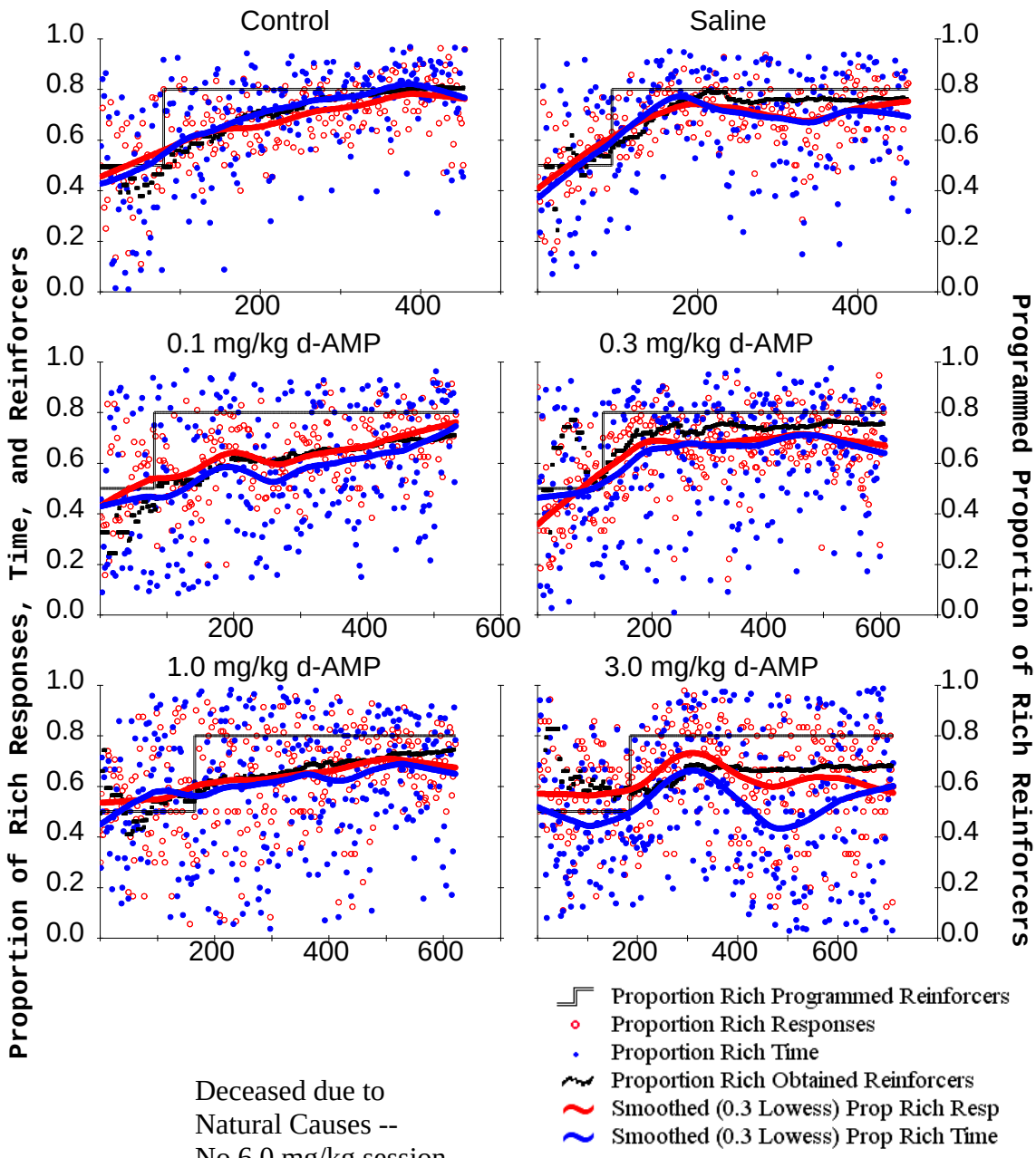


Figure A32. Proportion of rich responses, time, and reinforcers each visit during transition sessions in which the left lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

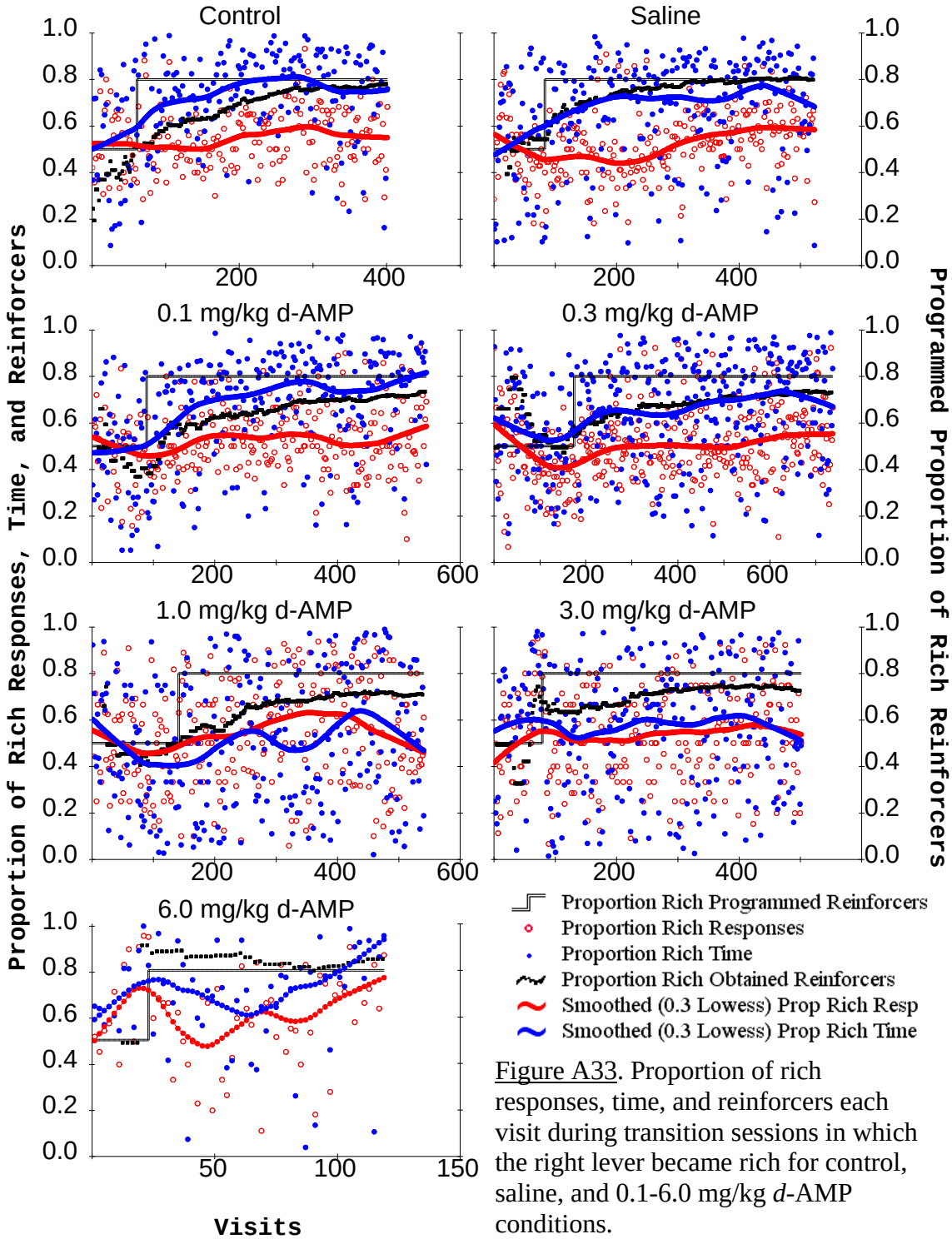


Figure A33. Proportion of rich responses, time, and reinforcers each visit during transition sessions in which the right lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

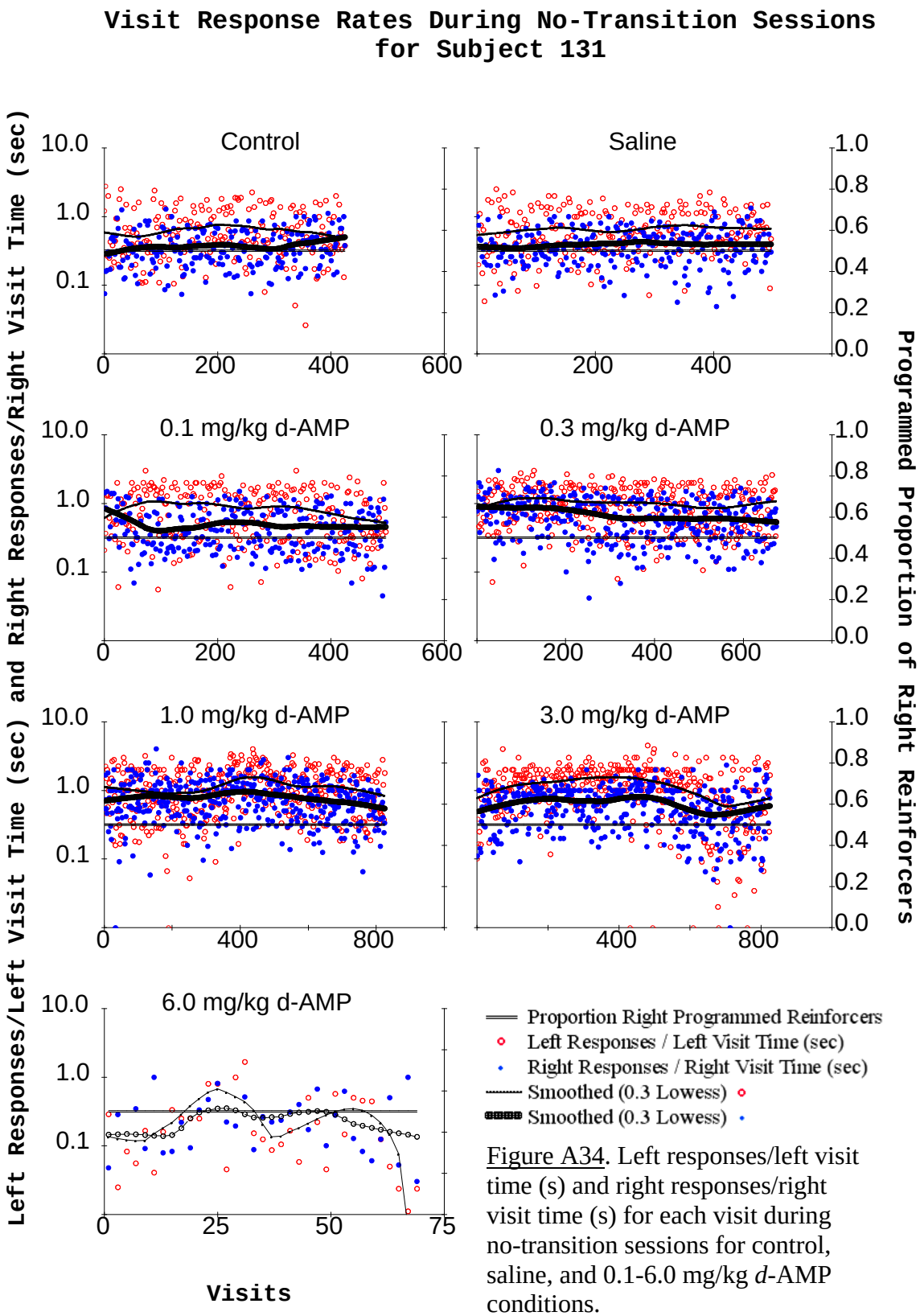
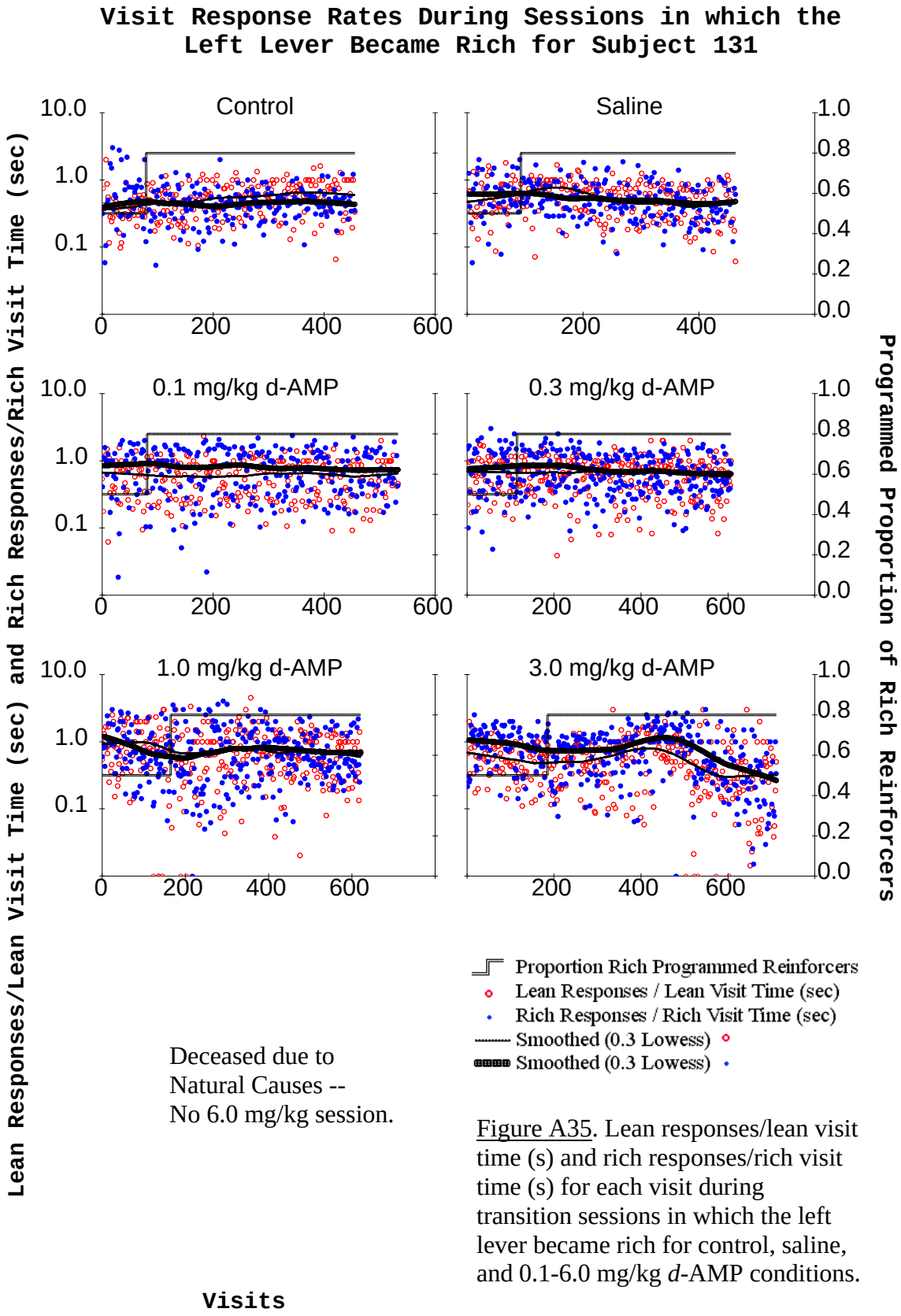


Figure A34. Left responses/left visit time (s) and right responses/right visit time (s) for each visit during no-transition sessions for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.



Deceased due to
Natural Causes --
No 6.0 mg/kg session.

Figure A35. Lean responses/lean visit time (s) and rich responses/rich visit time (s) for each visit during transition sessions in which the left lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

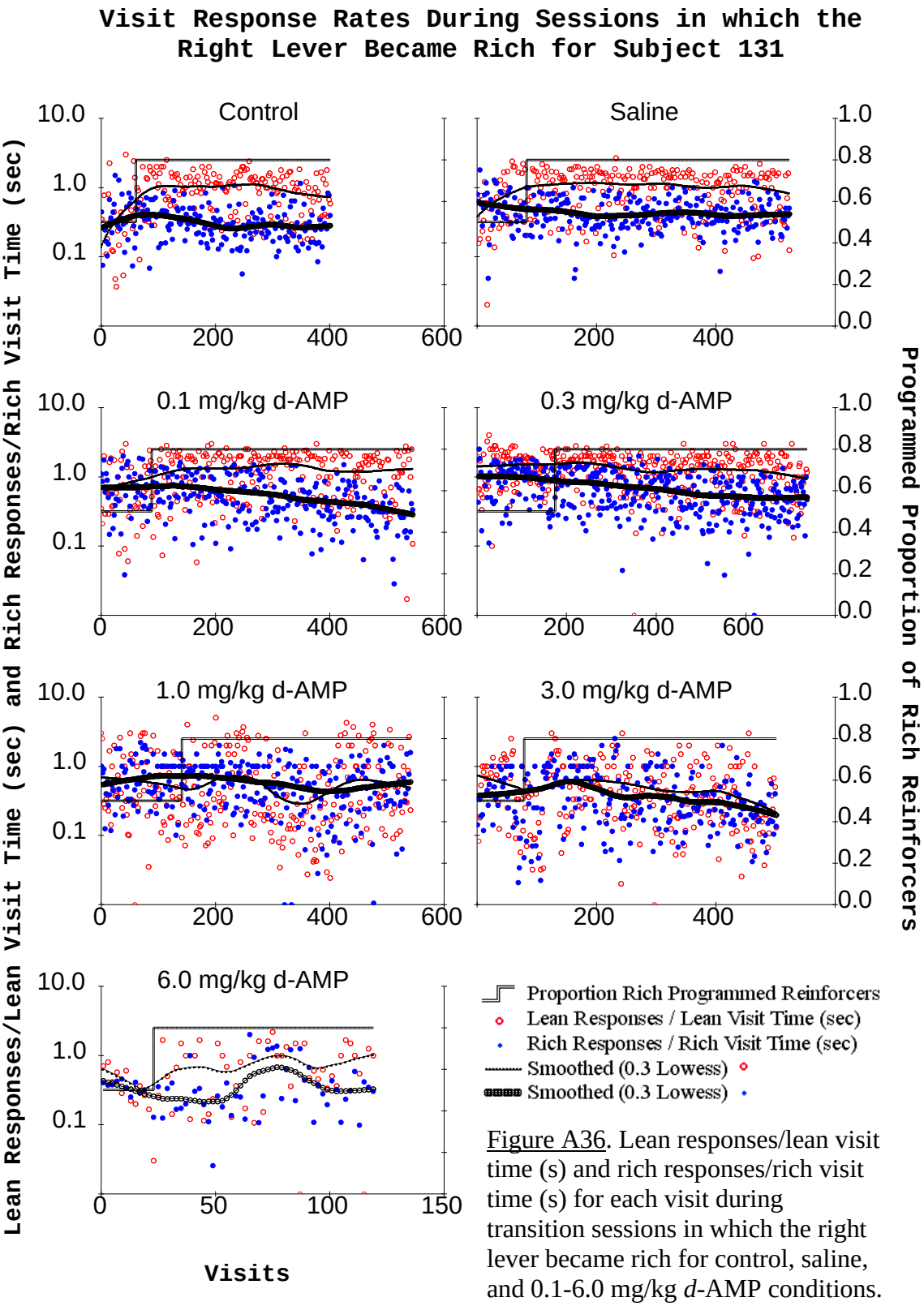


Figure A36. Lean responses/lean visit time (s) and rich responses/rich visit time (s) for each visit during transition sessions in which the right lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

Responses Per Visit as a Function of Cumulative Reinforcers During No-Transition Sessions for Subject 131

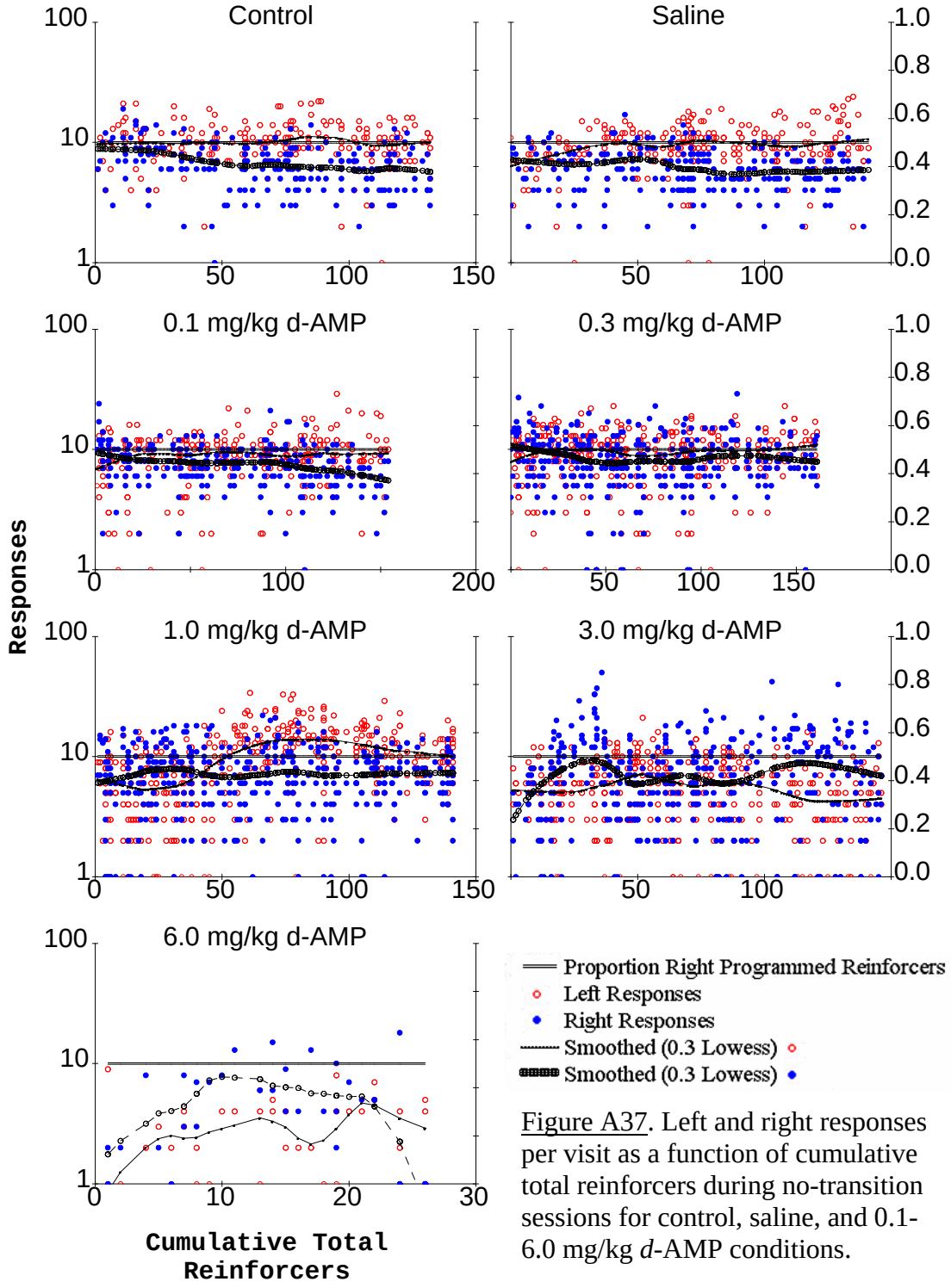
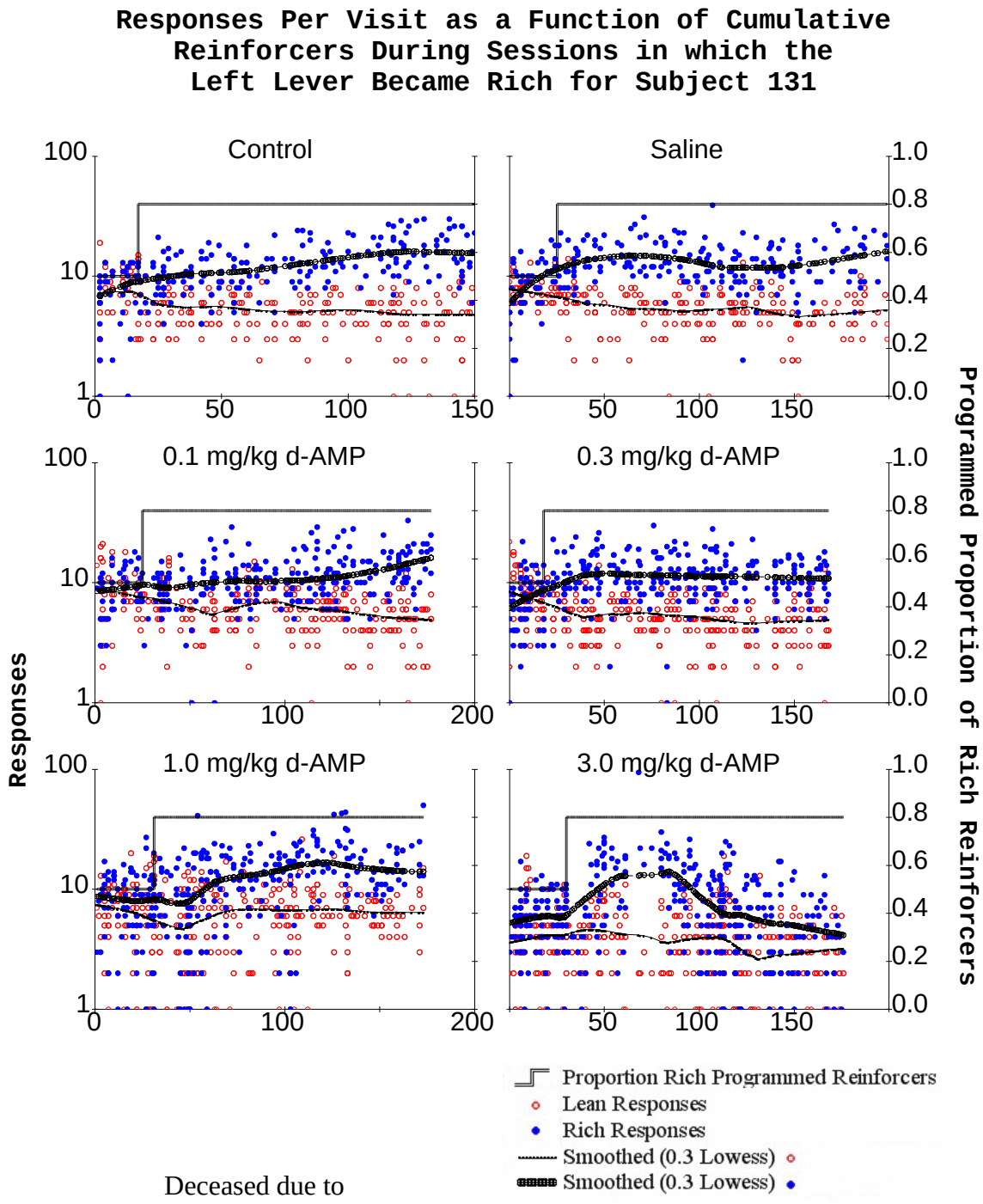


Figure A37. Left and right responses per visit as a function of cumulative total reinforcers during no-transition sessions for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.



Deceased due to
Natural Causes --
No 6.0 mg/kg session.

Figure A38. Lean and rich responses per visit as a function of cumulative total reinforcers during transition sessions in which the left lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

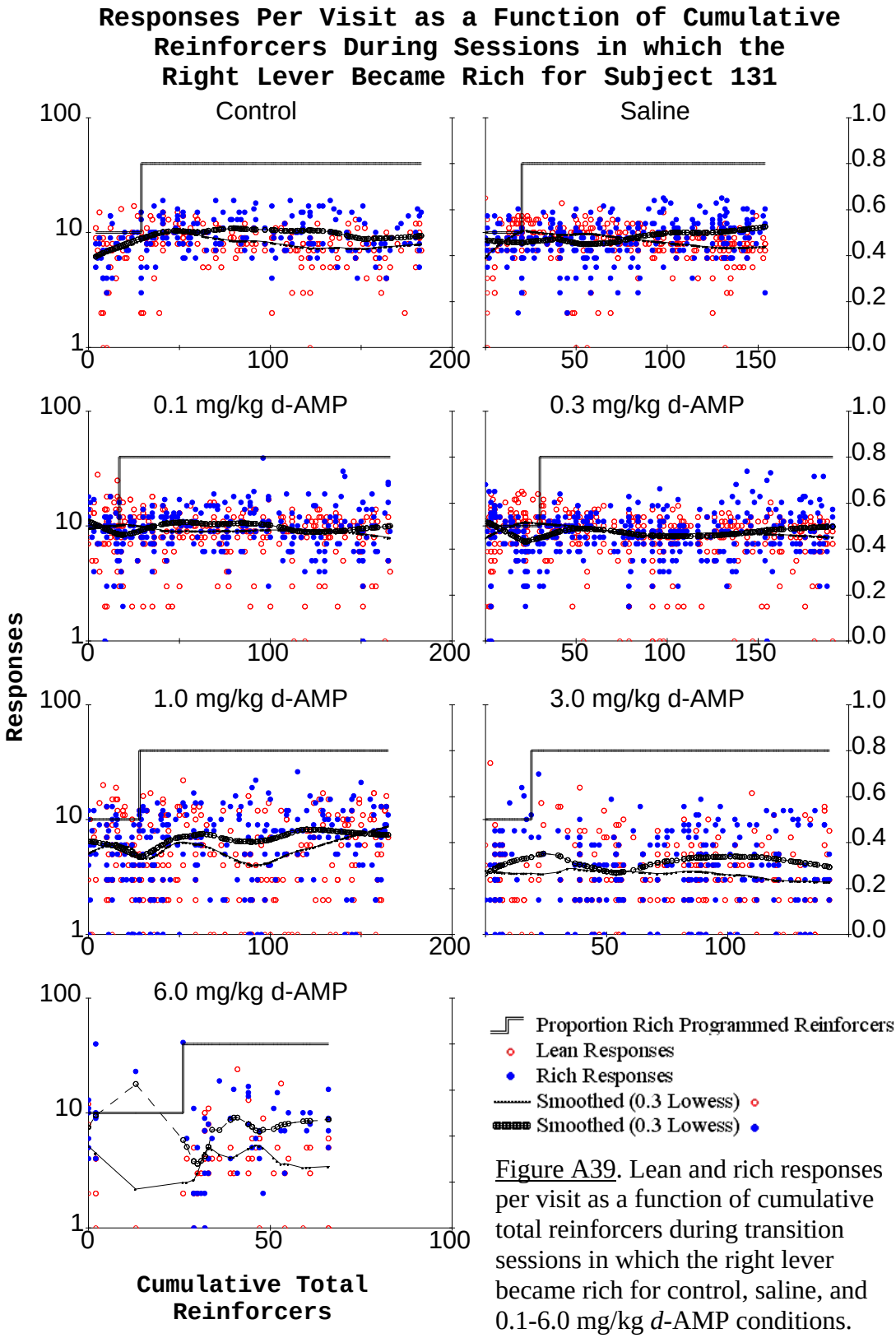


Figure A39. Lean and rich responses per visit as a function of cumulative total reinforcers during transition sessions in which the right lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

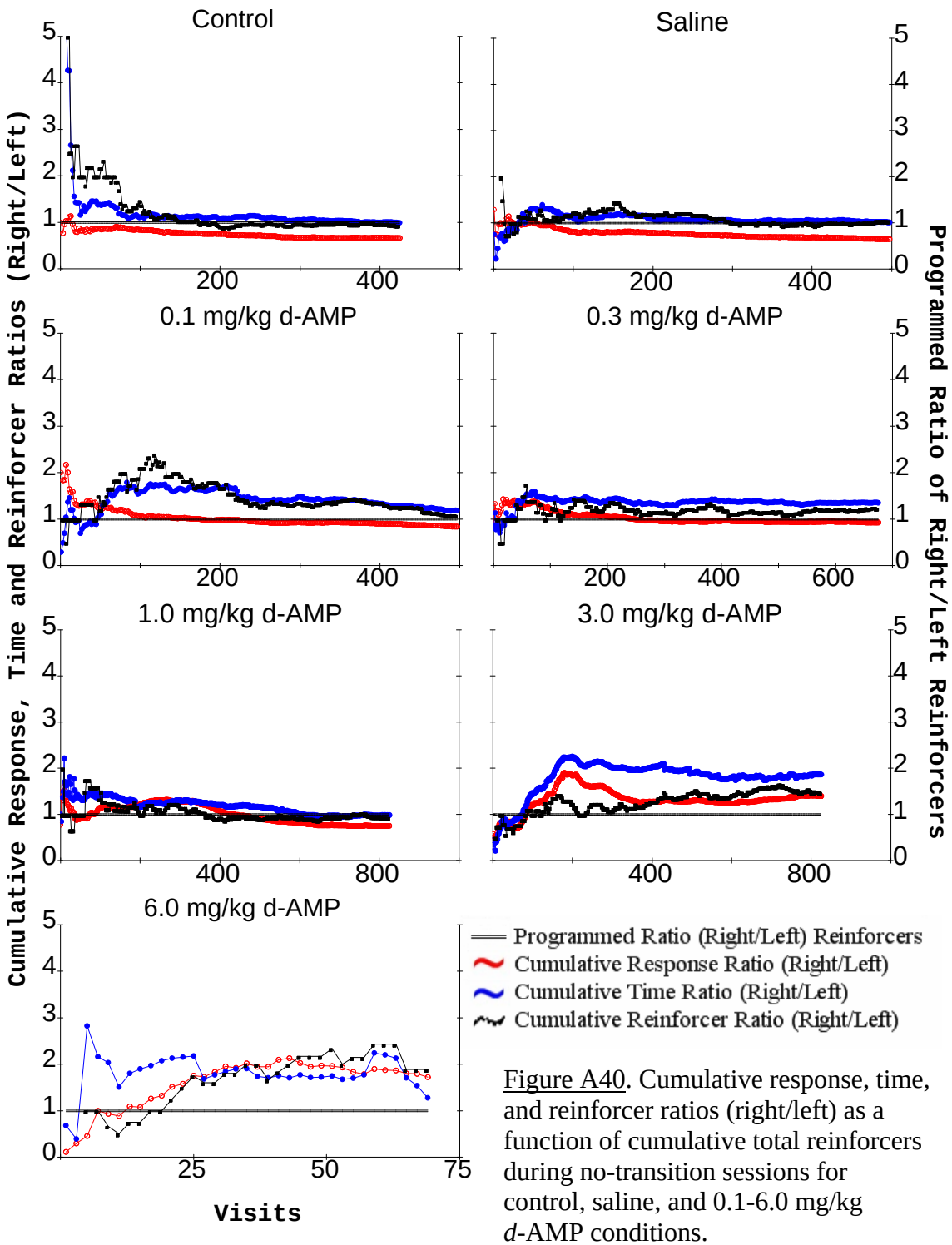
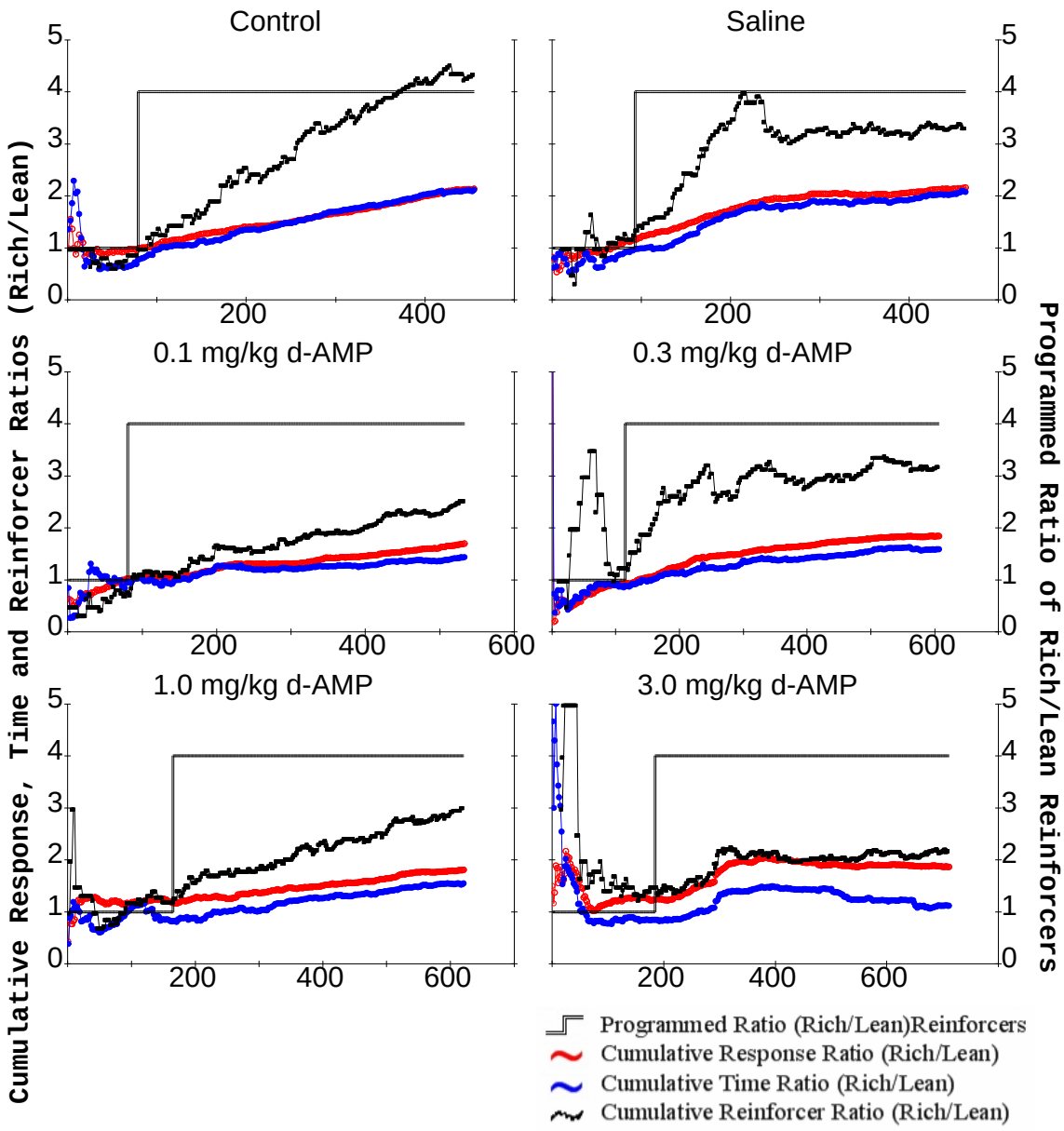


Figure A40. Cumulative response, time, and reinforcer ratios (right/left) as a function of cumulative total reinforcers during no-transition sessions for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.



Deceased due to
Natural Causes --
No 6.0 mg/kg session.

Figure A41. Cumulative response, time, and reinforcer ratios (rich/lean) as a function of cumulative total reinforcers during transition sessions in which the left lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

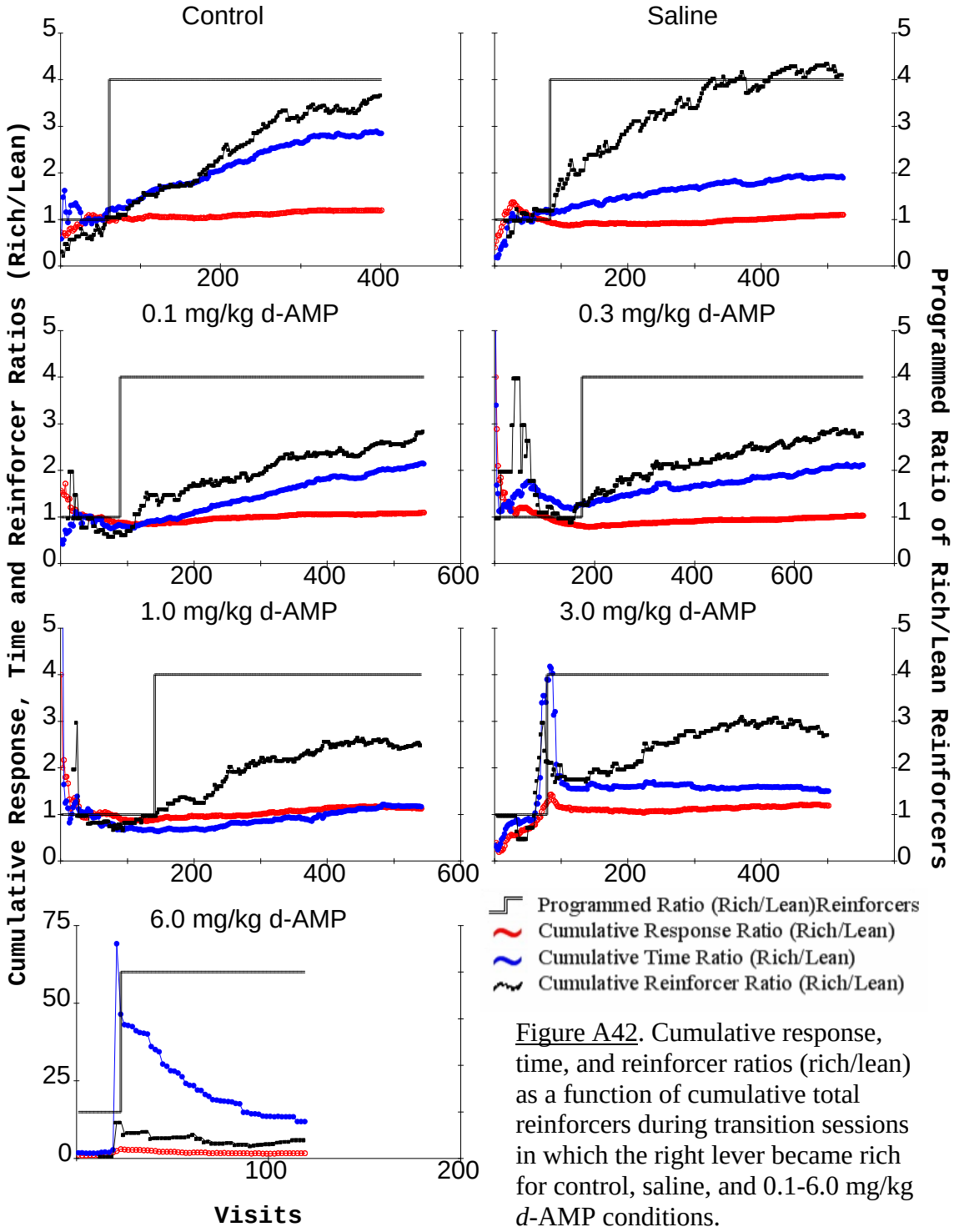


Figure A42. Cumulative response, time, and reinforcer ratios (rich/lean) as a function of cumulative total reinforcers during transition sessions in which the right lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

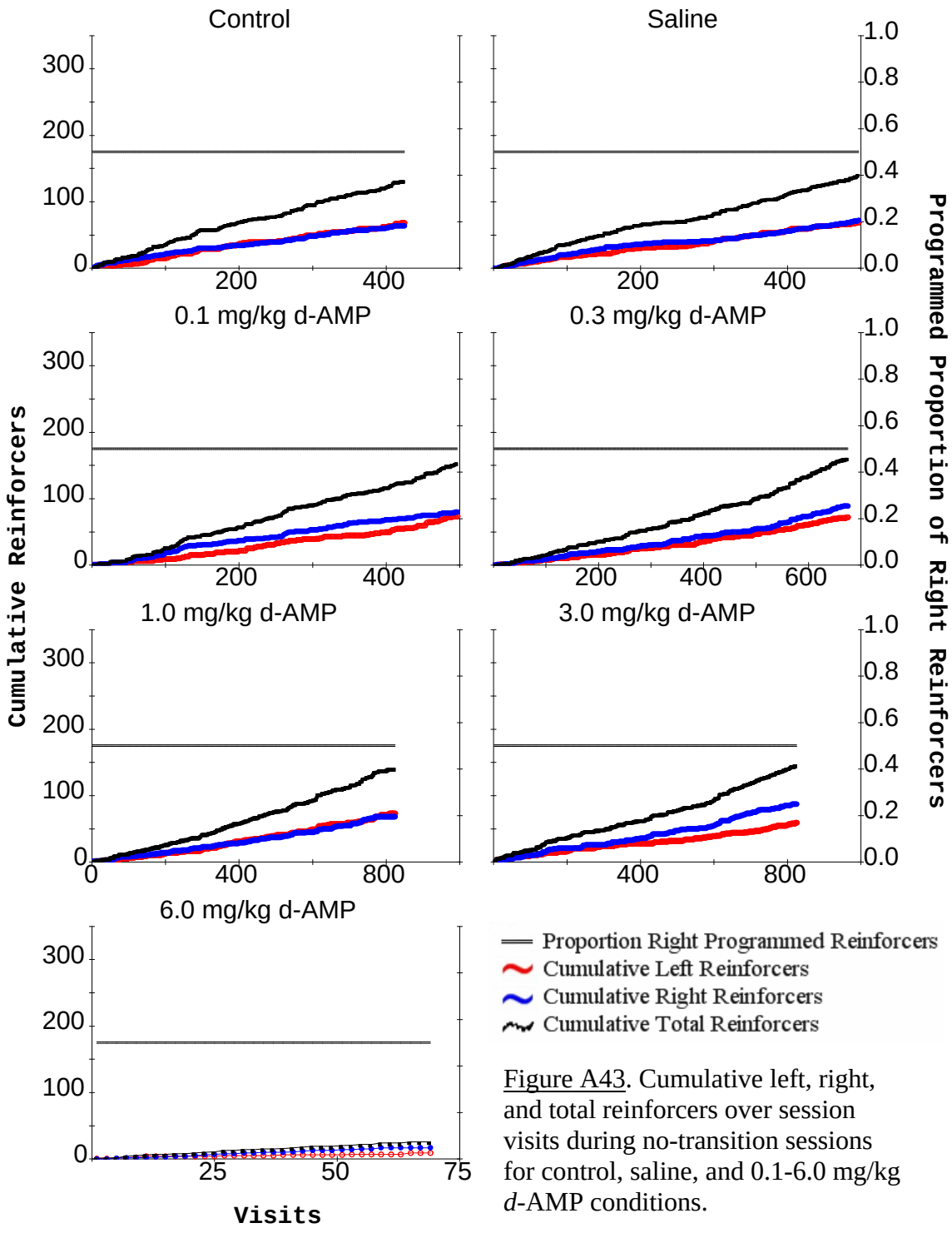
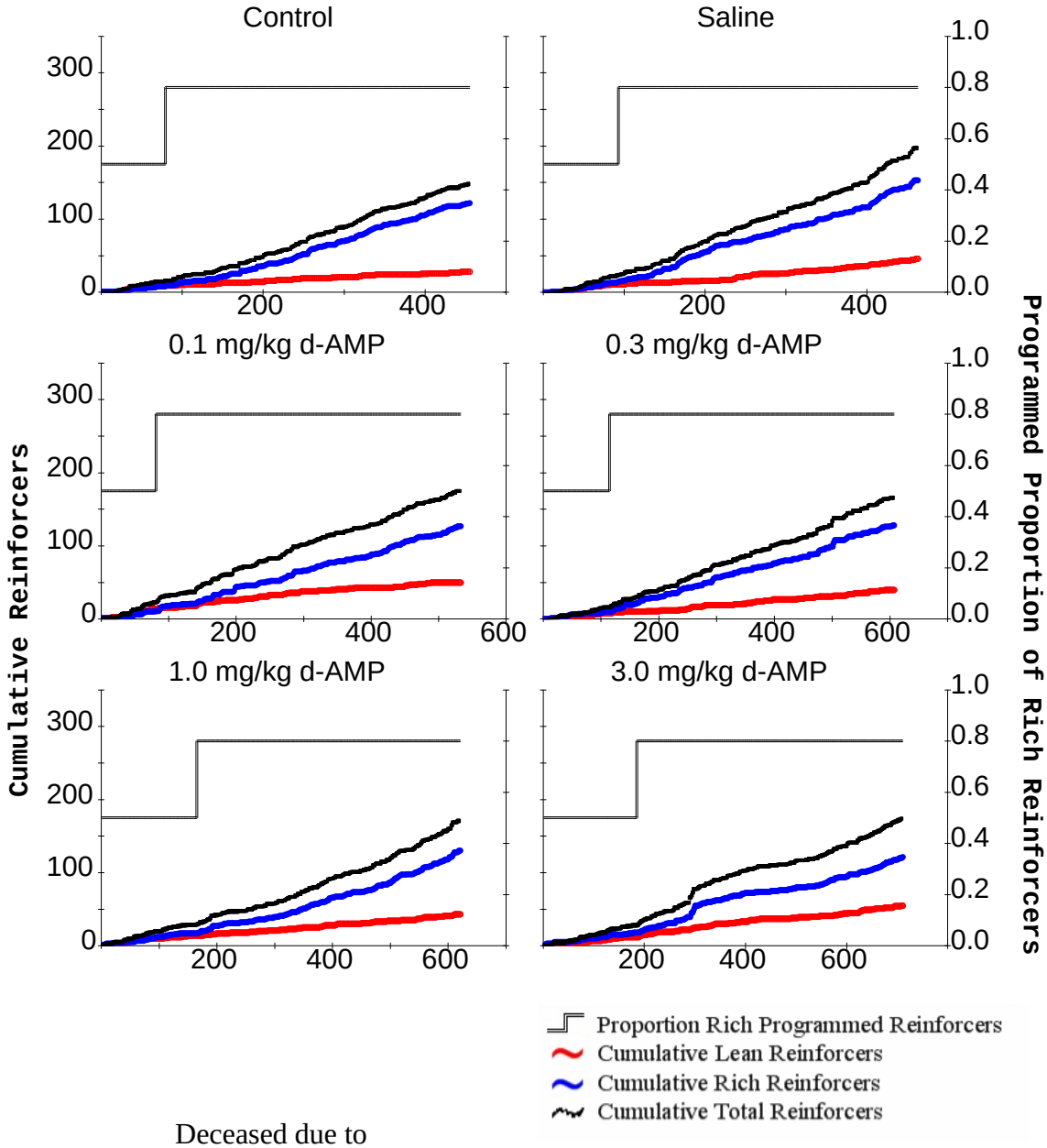


Figure A43. Cumulative left, right, and total reinforcers over session visits during no-transition sessions for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

Cumulative Lean, Rich, and Total Reinforcers through Sessions in which the Left Lever Became Rich for Subject 131



Deceased due to Natural Causes -- No 6.0 mg/kg session.

Figure A44. Cumulative lean, rich, and total reinforcers over session visits during transition sessions in which the left lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

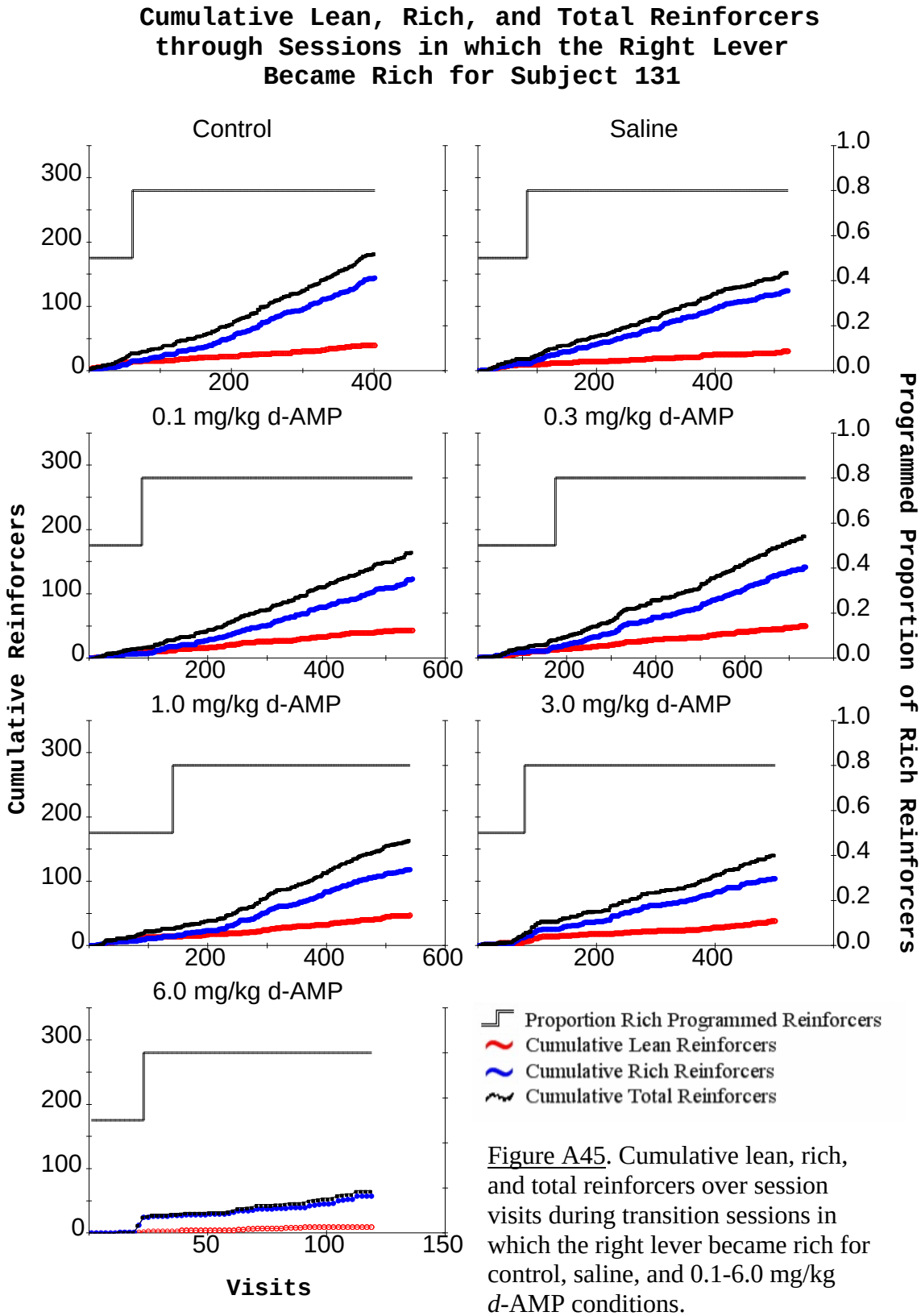


Figure A45. Cumulative lean, rich, and total reinforcers over session visits during transition sessions in which the right lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

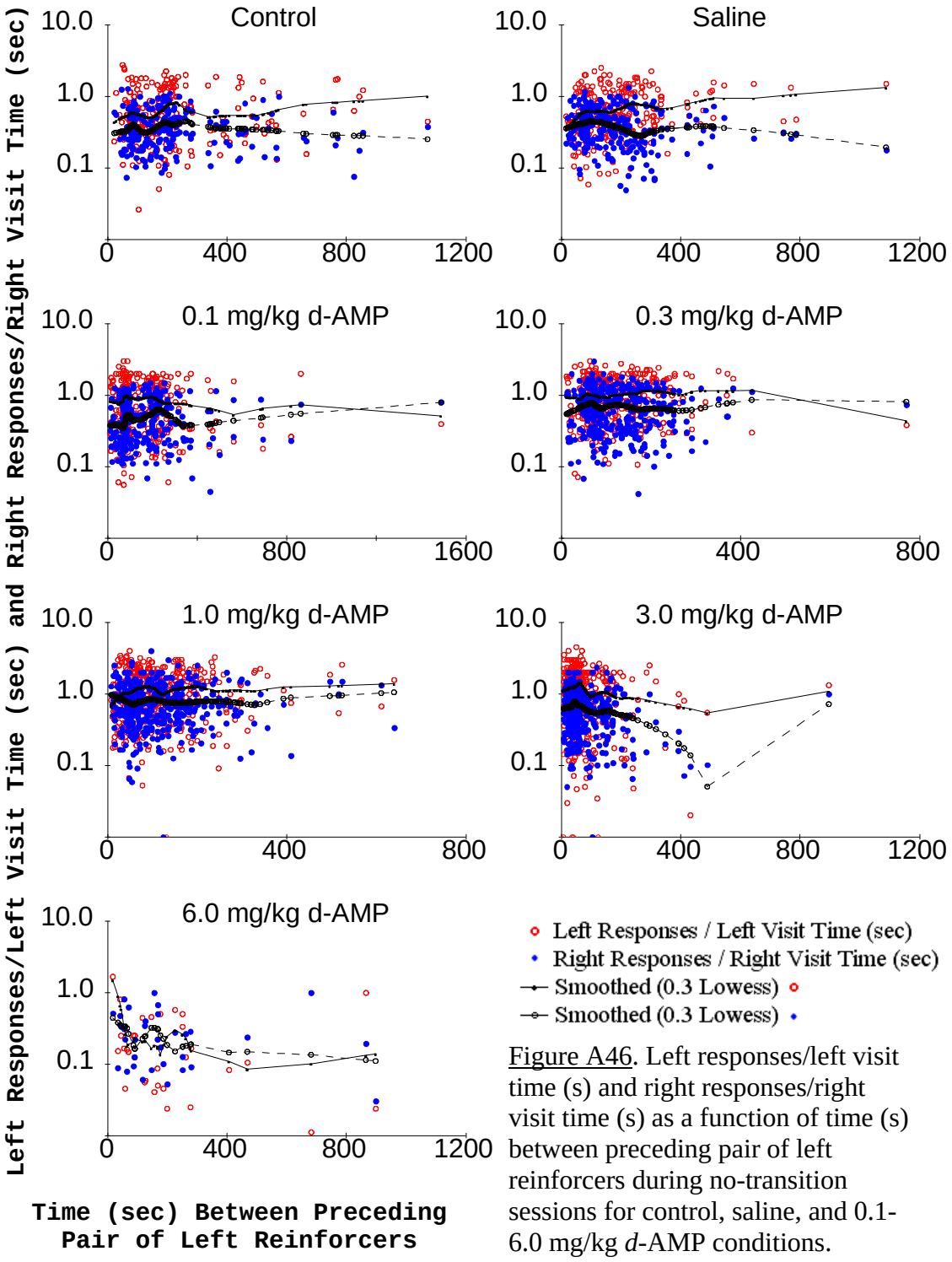
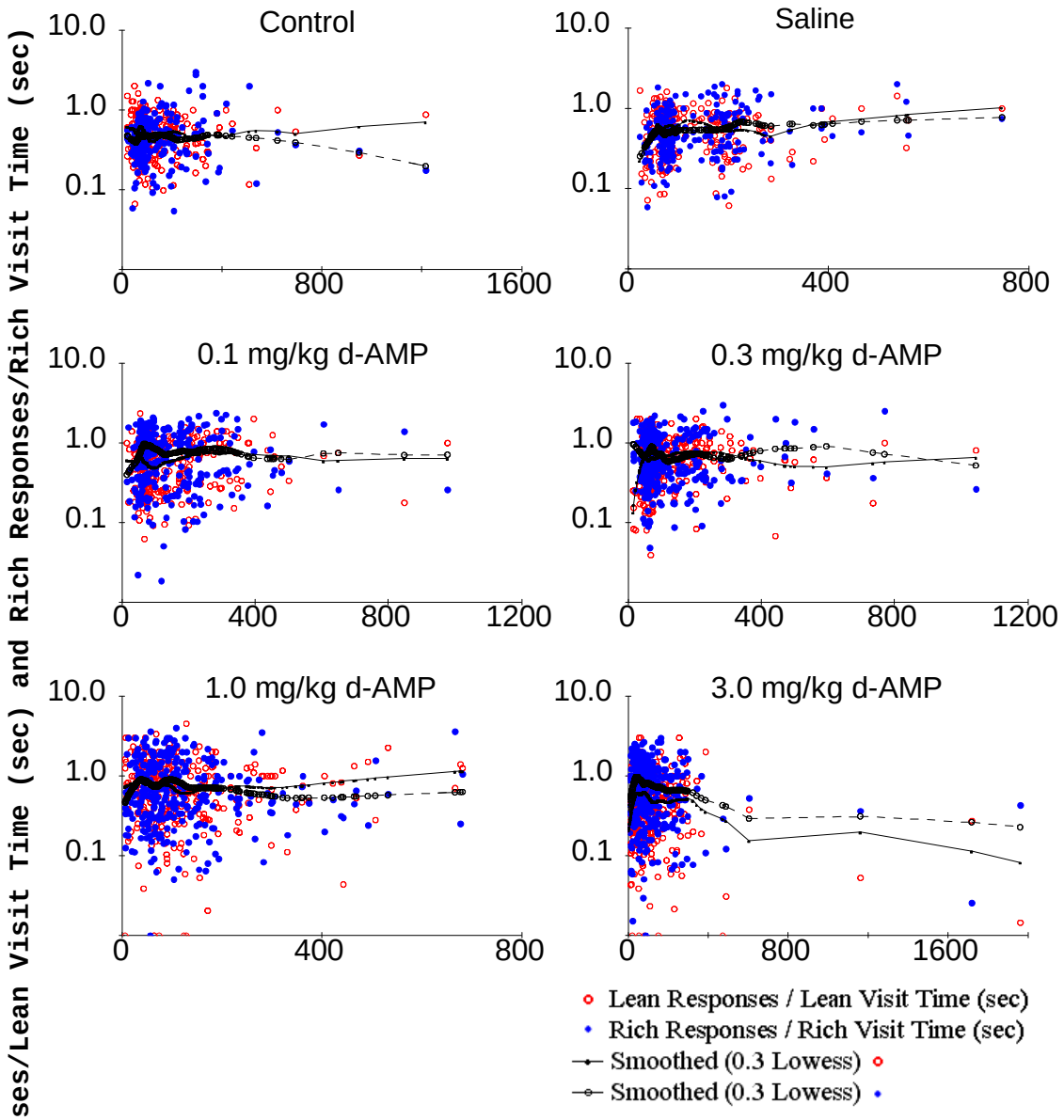


Figure A46. Left responses/left visit time (s) and right responses/right visit time (s) as a function of time (s) between preceding pair of left reinforcers during no-transition sessions for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.



Deceased due to
Natural Causes --
No 6.0 mg/kg session.

Figure A47. Lean responses/lean visit time (s) and rich responses/rich visit time (s) as a function of time (s) between preceding pair of lean reinforcers during transition sessions in which the left lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

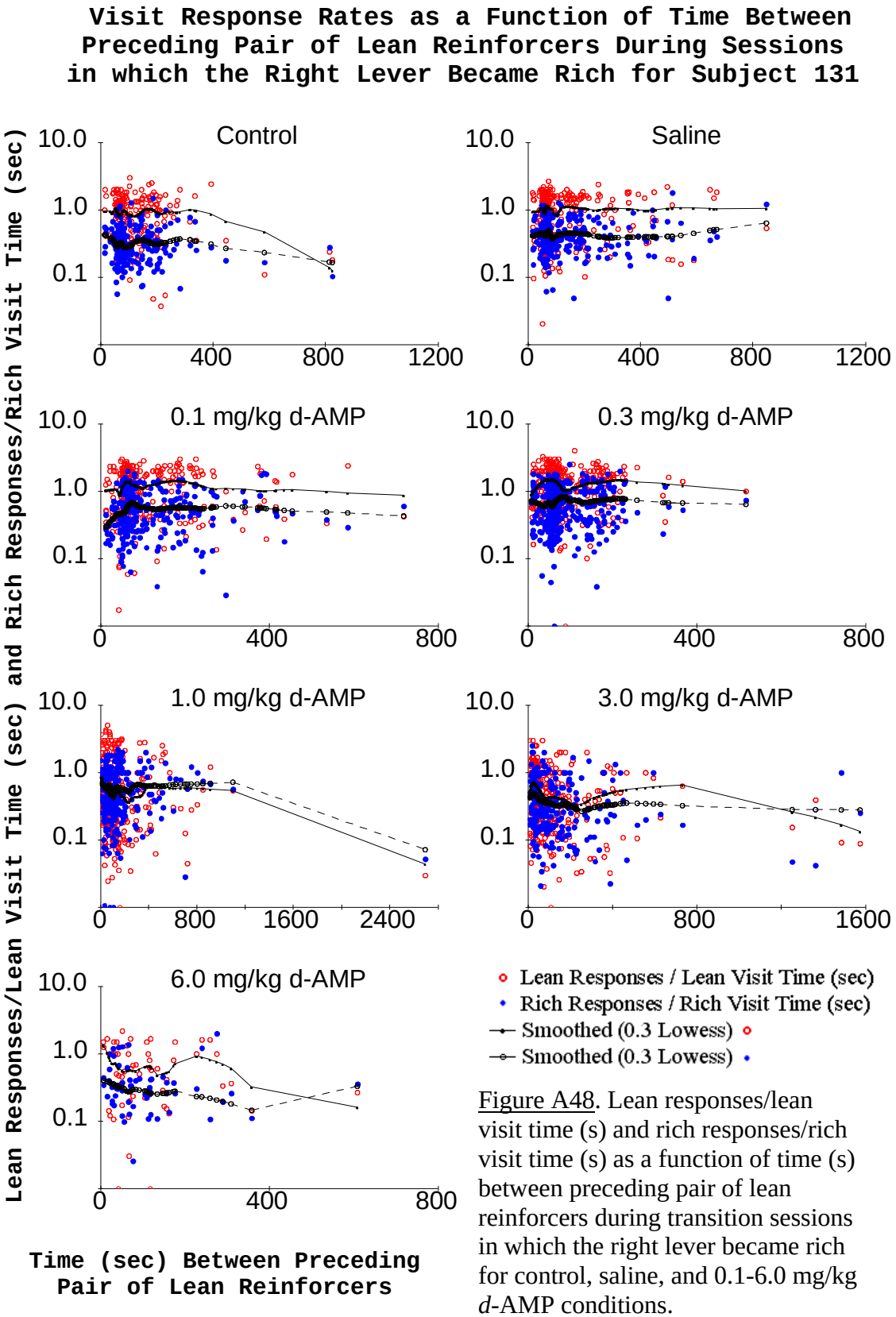
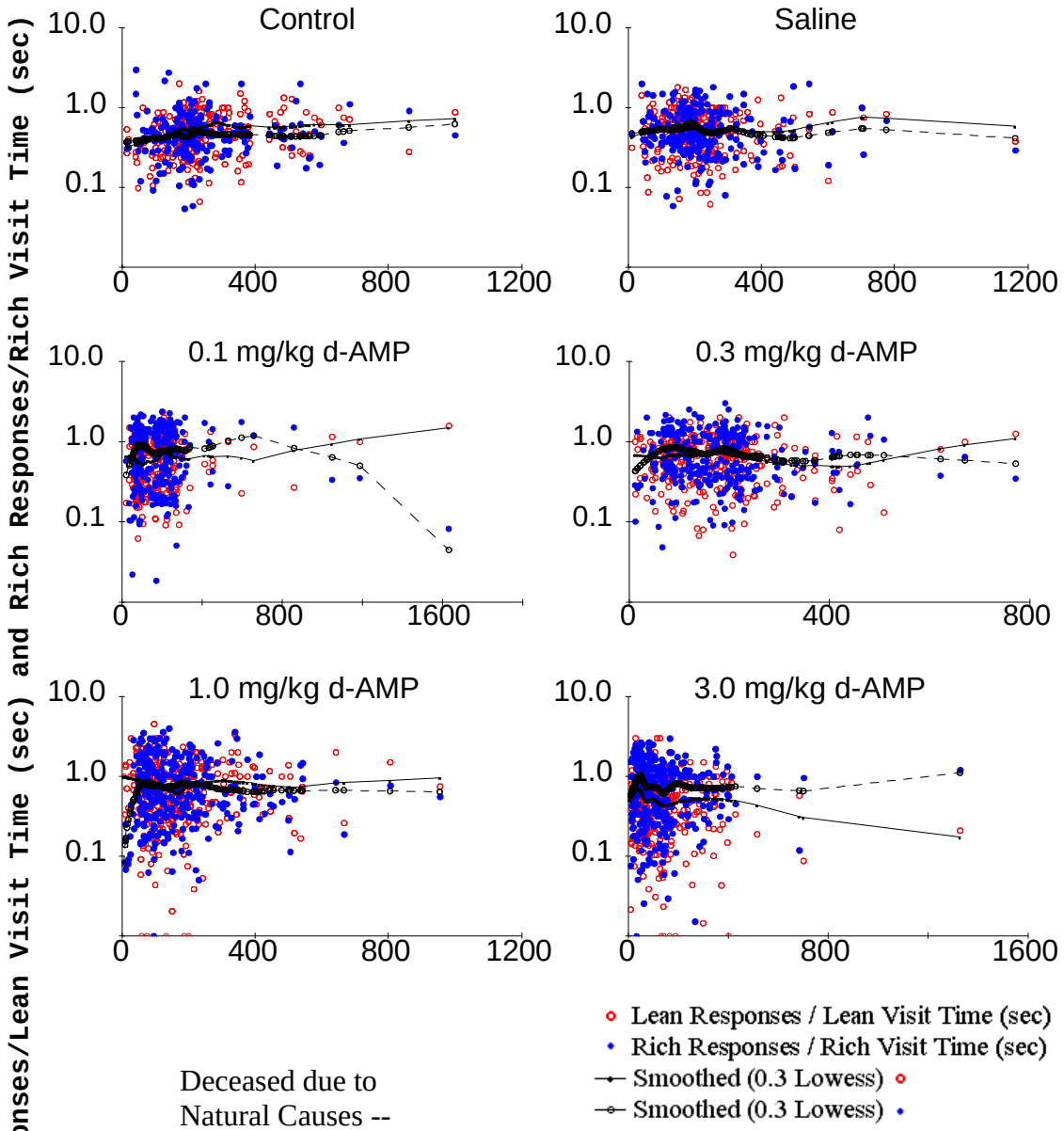


Figure A48. Lean responses/lean visit time (s) and rich responses/rich visit time (s) as a function of time (s) between preceding pair of lean reinforcers during transition sessions in which the right lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.



Deceased due to
Natural Causes --
No 6.0 mg/kg session.

Figure A49. Lean responses/lean visit time (s) and rich responses/rich visit time (s) as a function of time (s) between preceding pair of rich reinforcers during transition sessions in which the left lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

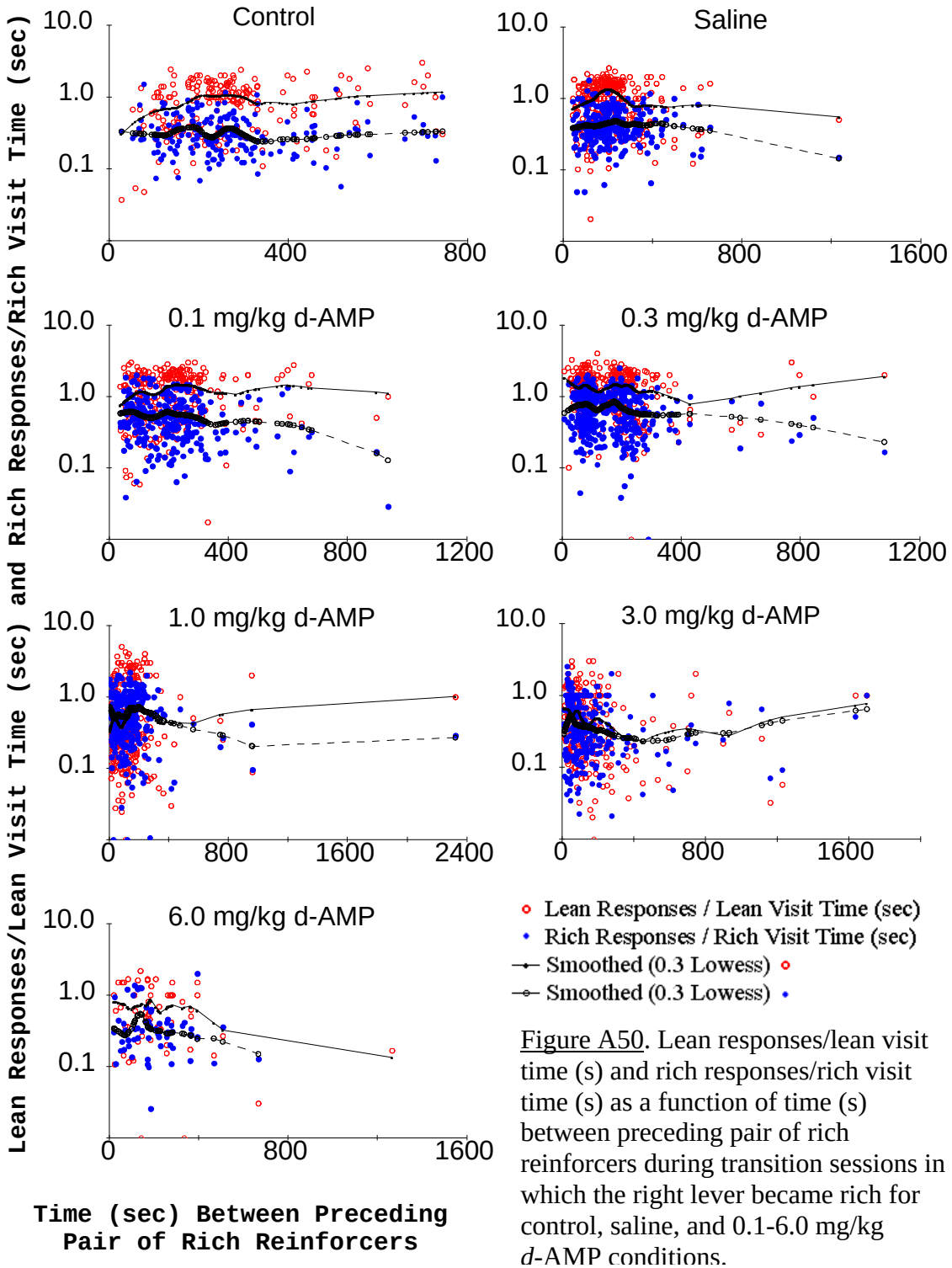


Figure A50. Lean responses/lean visit time (s) and rich responses/rich visit time (s) as a function of time (s) between preceding pair of rich reinforcers during transition sessions in which the right lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

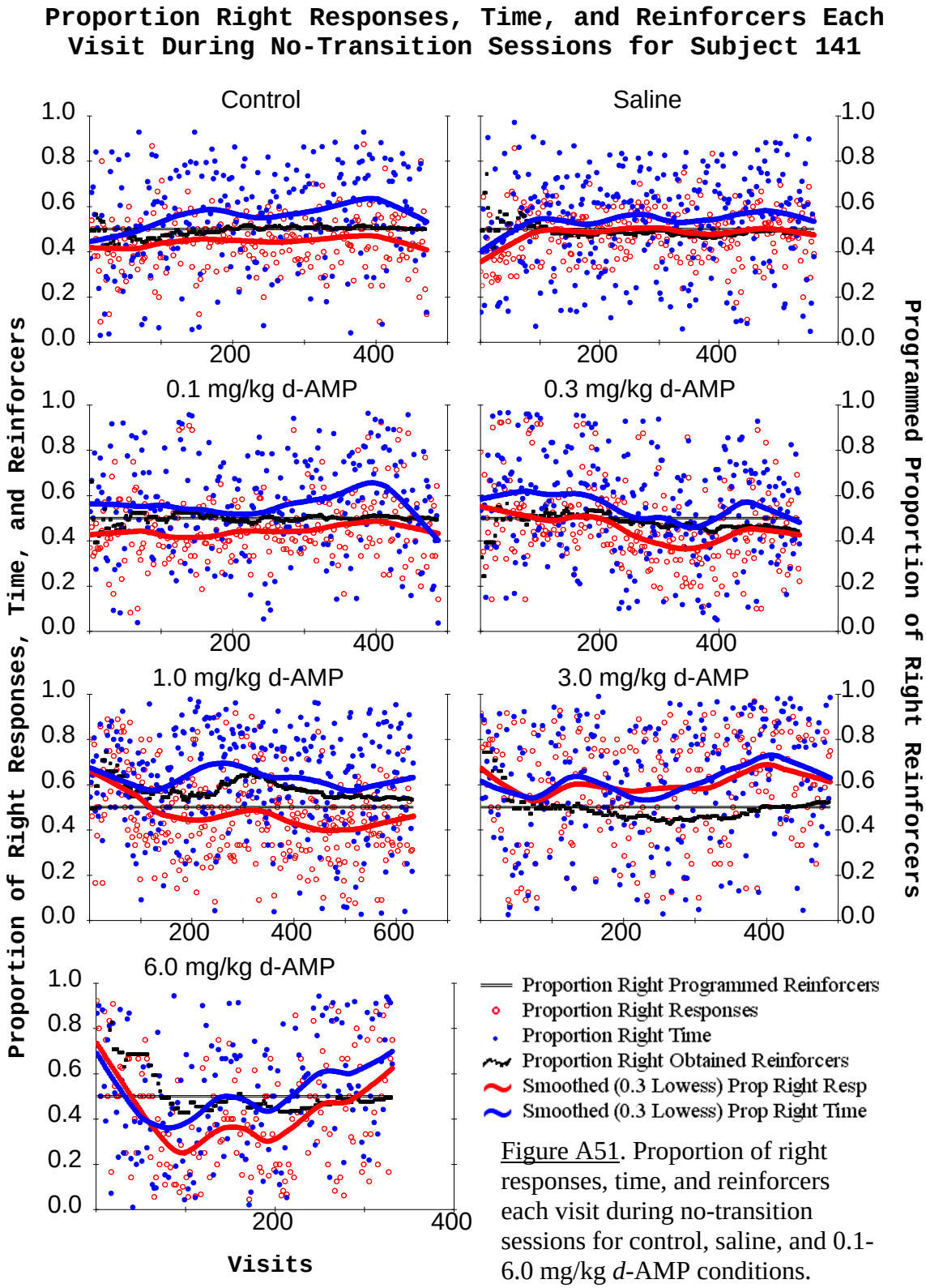


Figure A51. Proportion of right responses, time, and reinforcers each visit during no-transition sessions for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

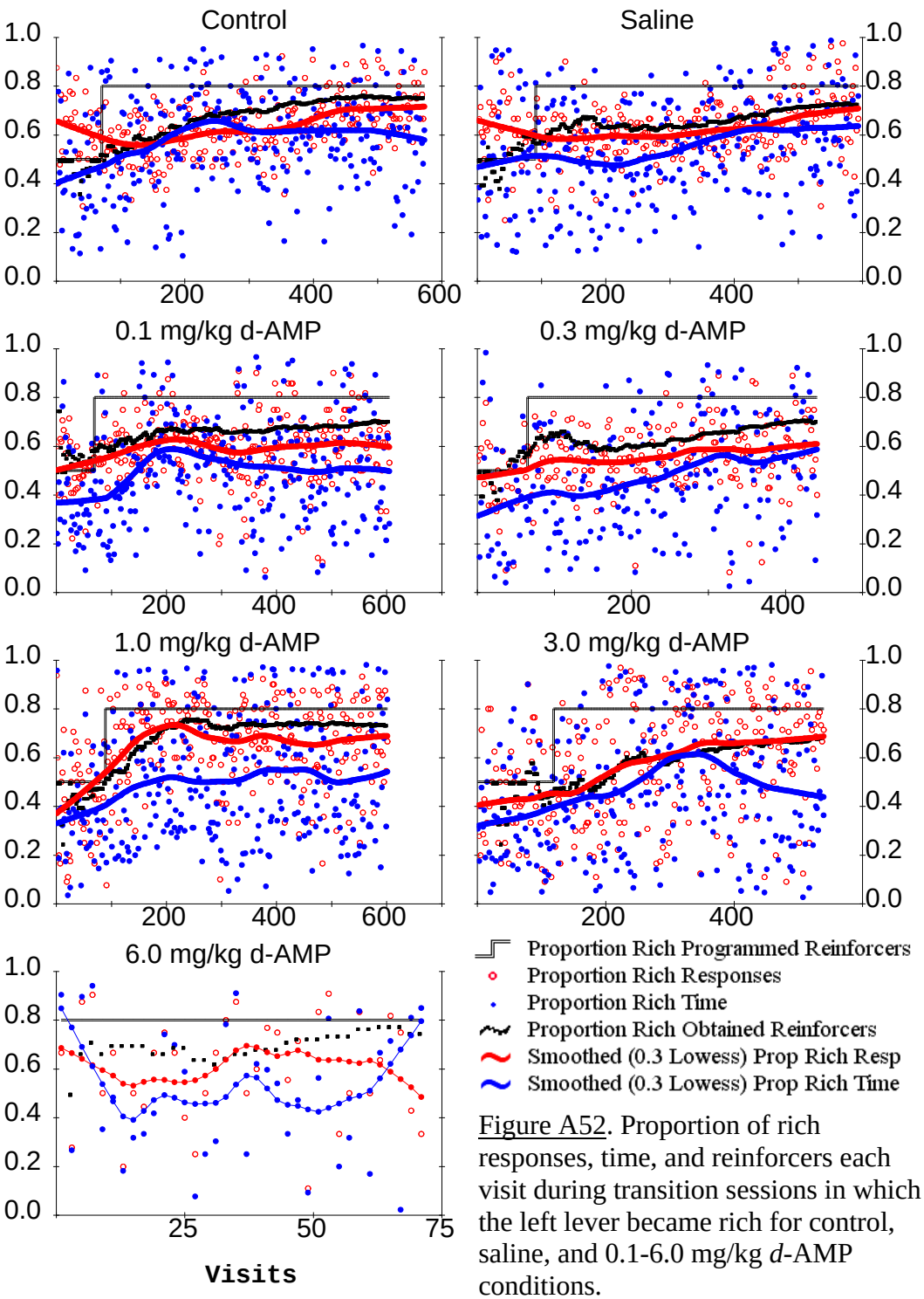


Figure A52. Proportion of rich responses, time, and reinforcers each visit during transition sessions in which the left lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

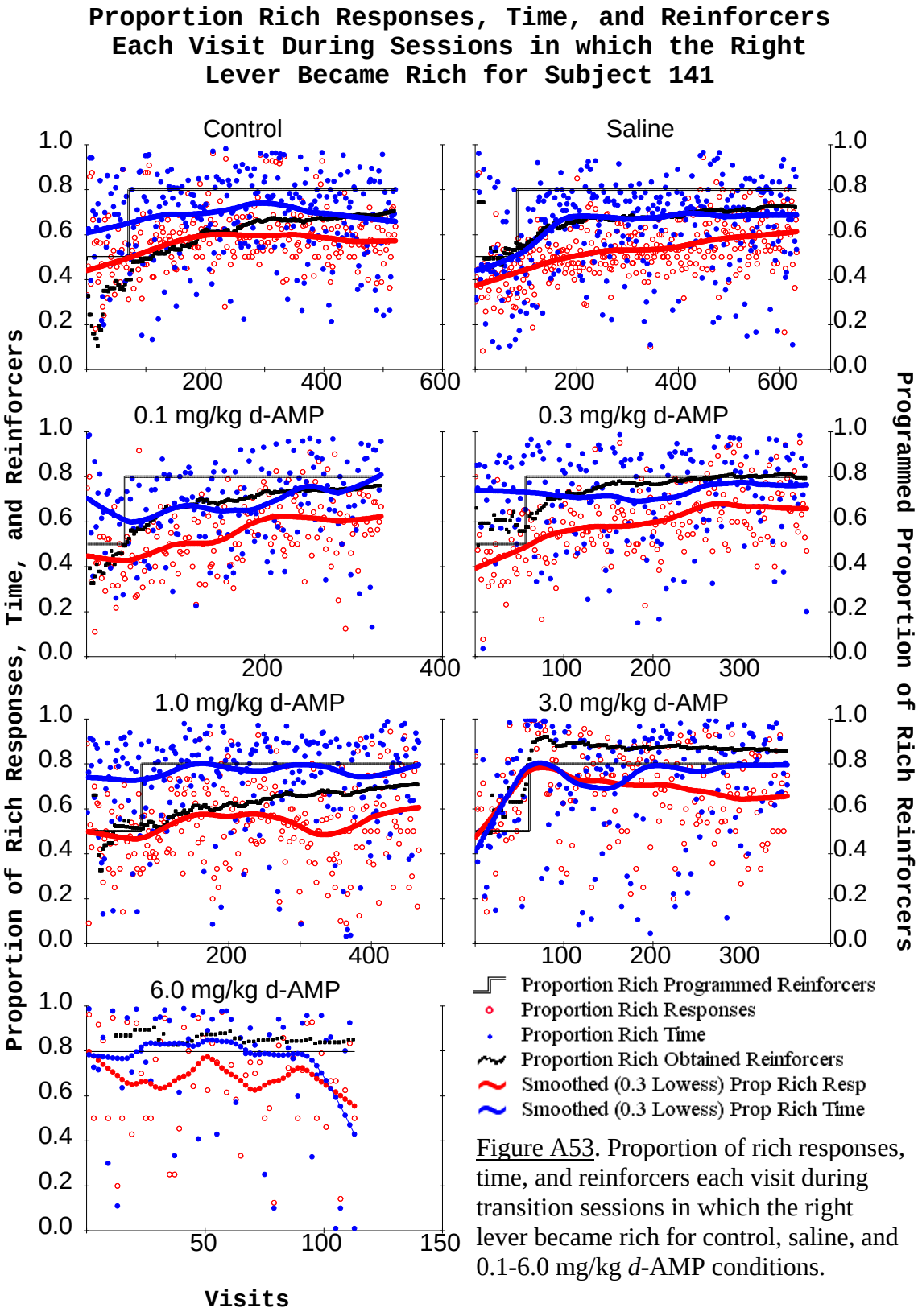


Figure A53. Proportion of rich responses, time, and reinforcers each visit during transition sessions in which the right lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

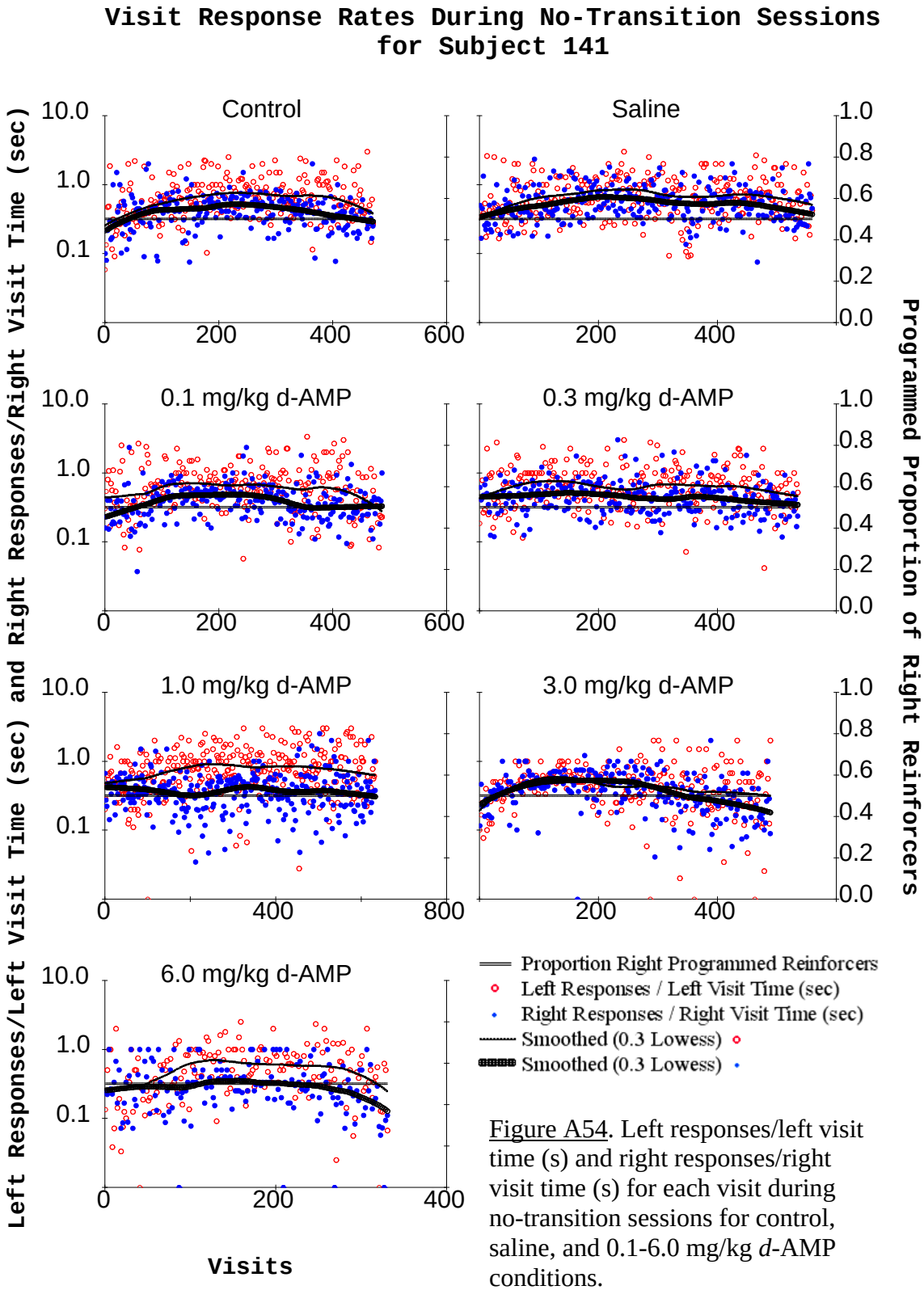


Figure A54. Left responses/left visit time (s) and right responses/right visit time (s) for each visit during no-transition sessions for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

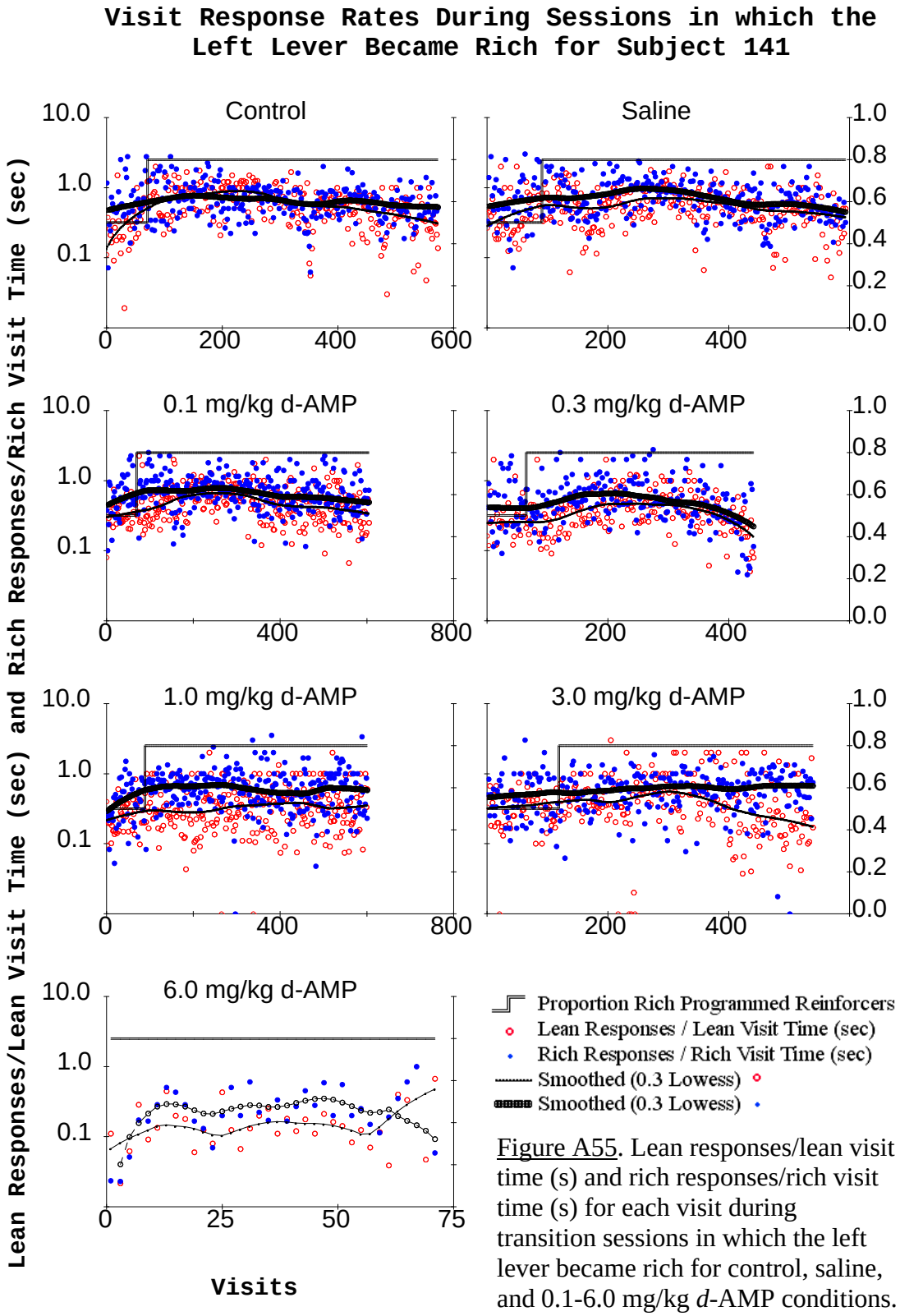


Figure A55. Lean responses/lean visit time (s) and rich responses/rich visit time (s) for each visit during transition sessions in which the left lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

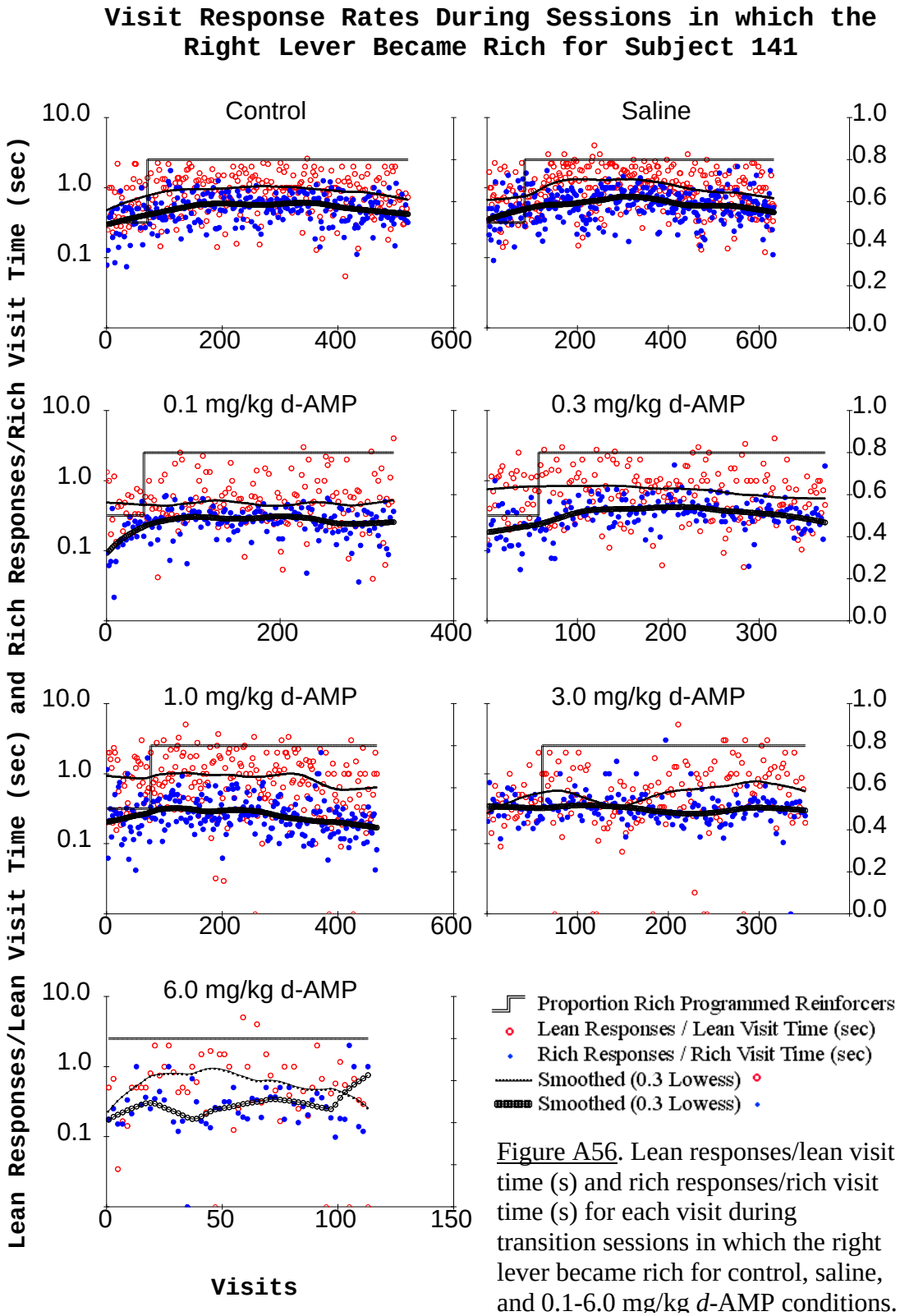


Figure A56. Lean responses/lean visit time (s) and rich responses/rich visit time (s) for each visit during transition sessions in which the right lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

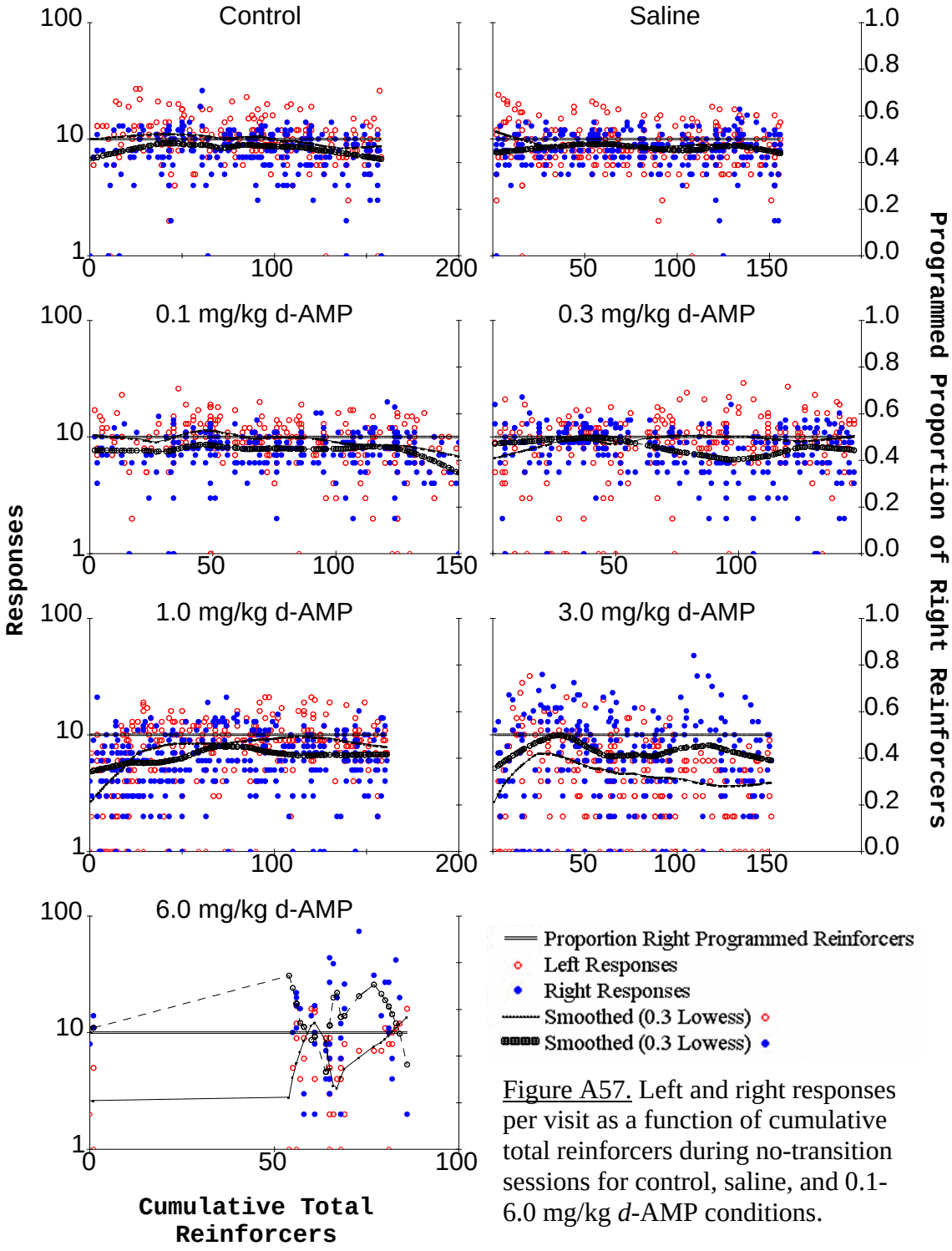


Figure A57. Left and right responses per visit as a function of cumulative total reinforcers during no-transition sessions for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

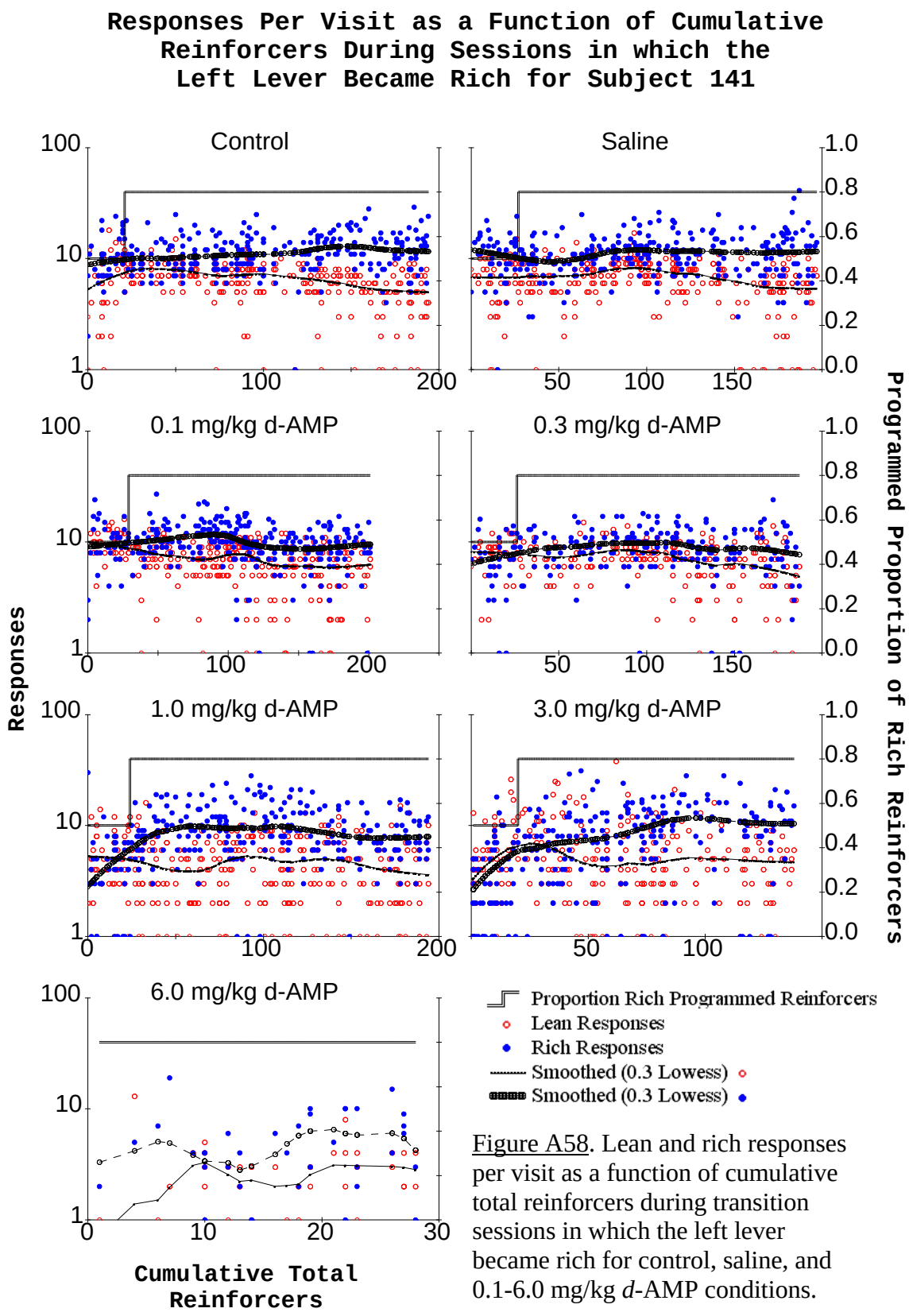


Figure A58. Lean and rich responses per visit as a function of cumulative total reinforcers during transition sessions in which the left lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

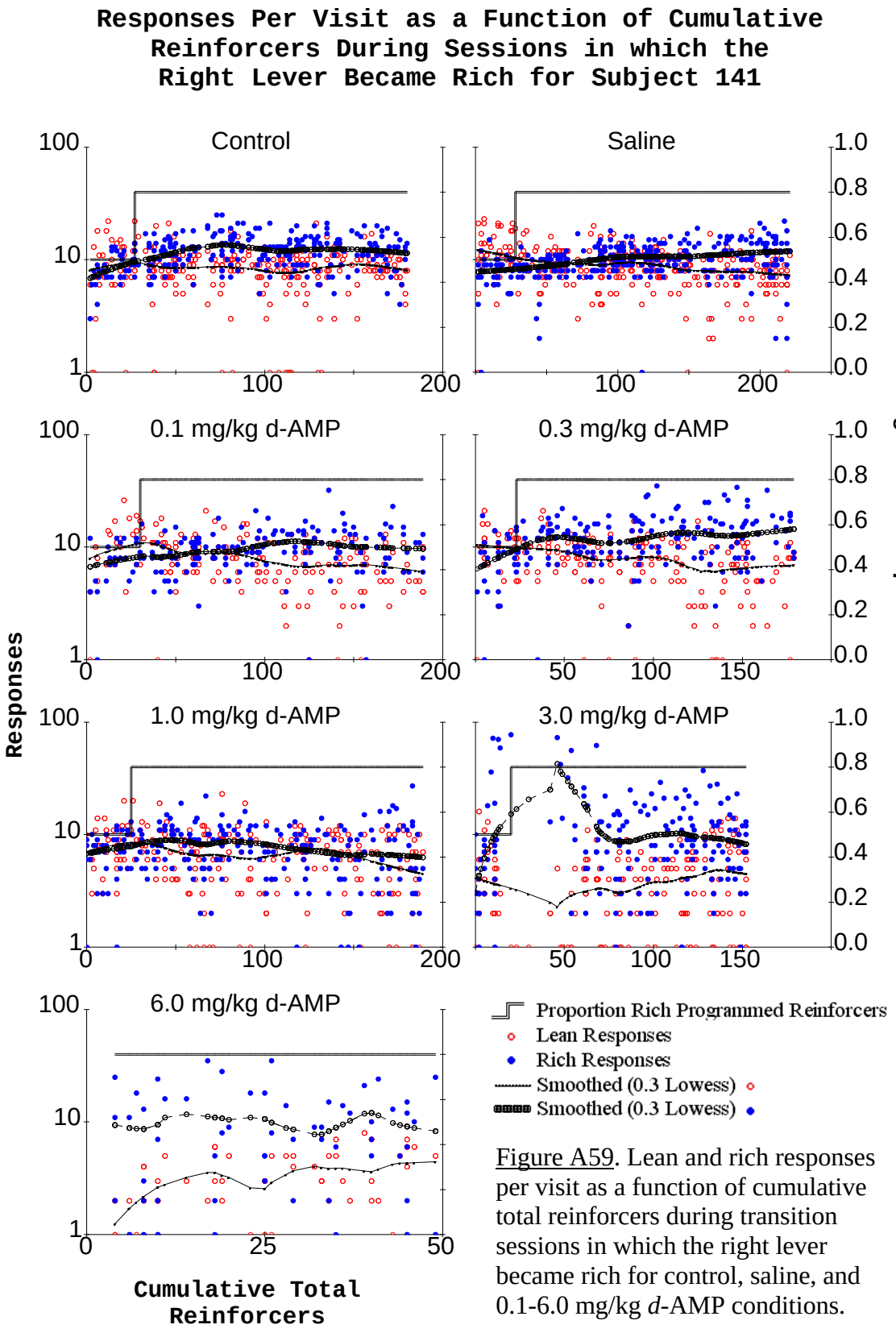


Figure A59. Lean and rich responses per visit as a function of cumulative total reinforcers during transition sessions in which the right lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

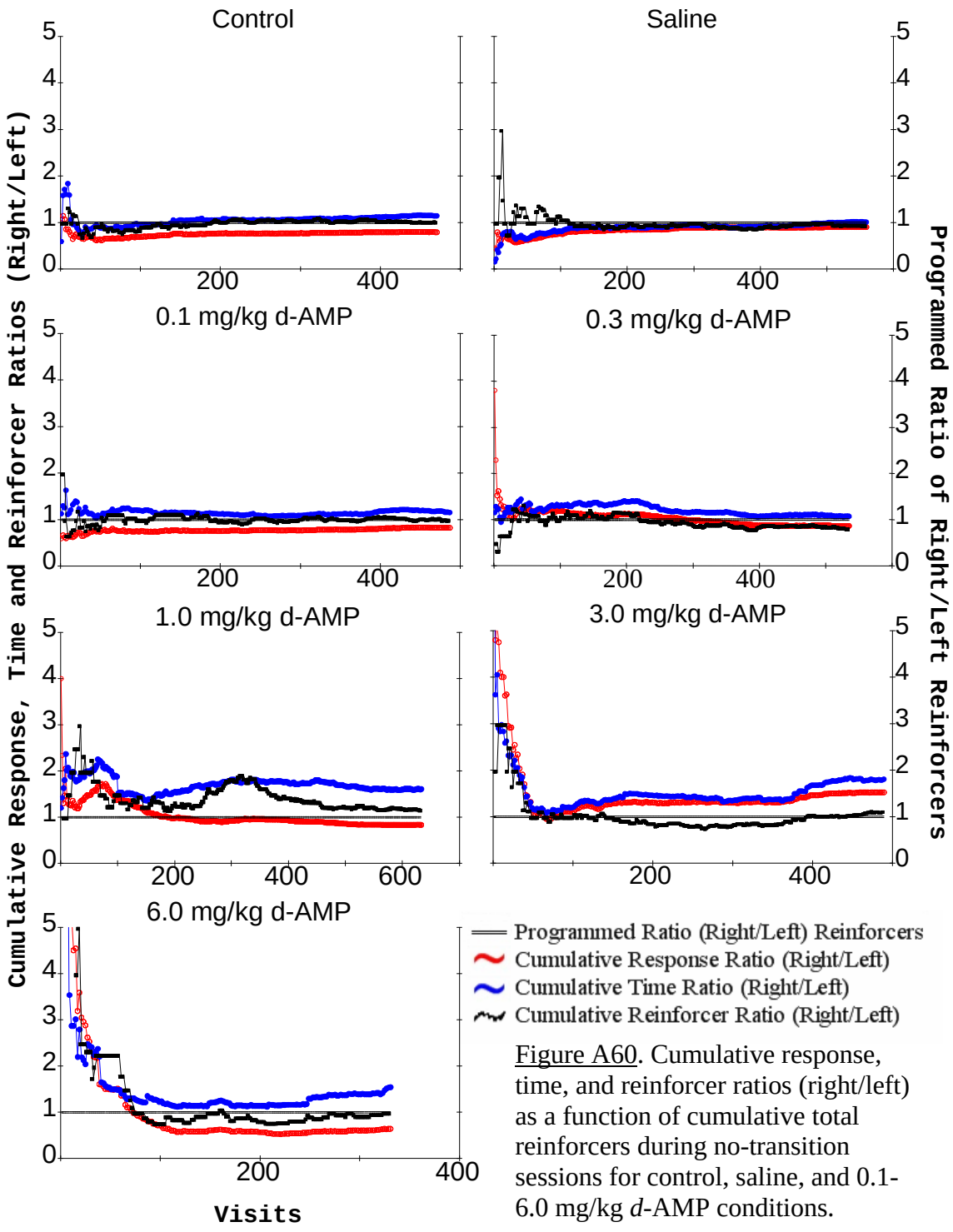


Figure A60. Cumulative response, time, and reinforcer ratios (right/left) as a function of cumulative total reinforcers during no-transition sessions for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

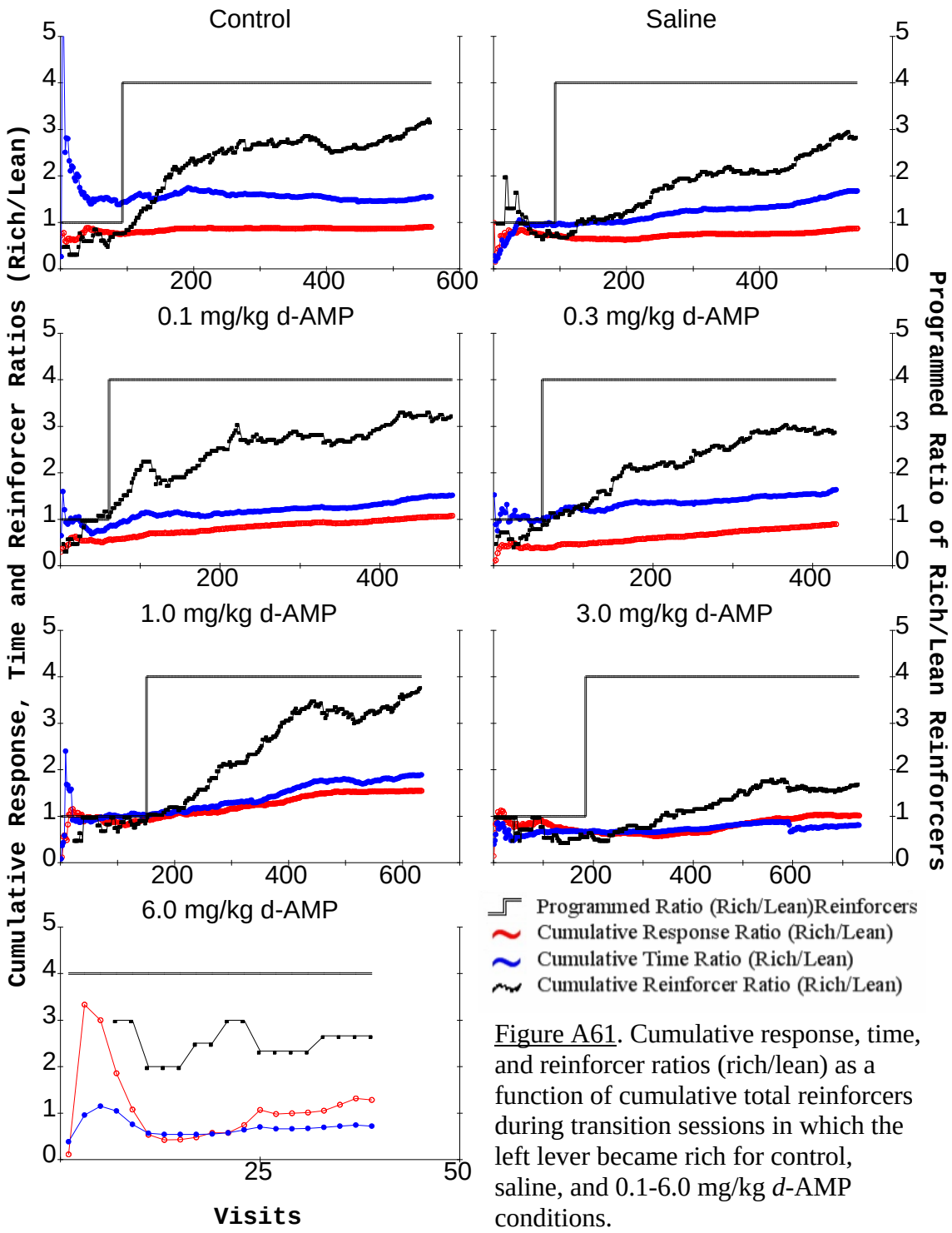


Figure A61. Cumulative response, time, and reinforcer ratios (rich/lean) as a function of cumulative total reinforcers during transition sessions in which the left lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

Cumulative Response, Time, and Reinforcer Ratios (Rich/Lean) During Sessions in which the Left Lever Became Rich for Subject 141

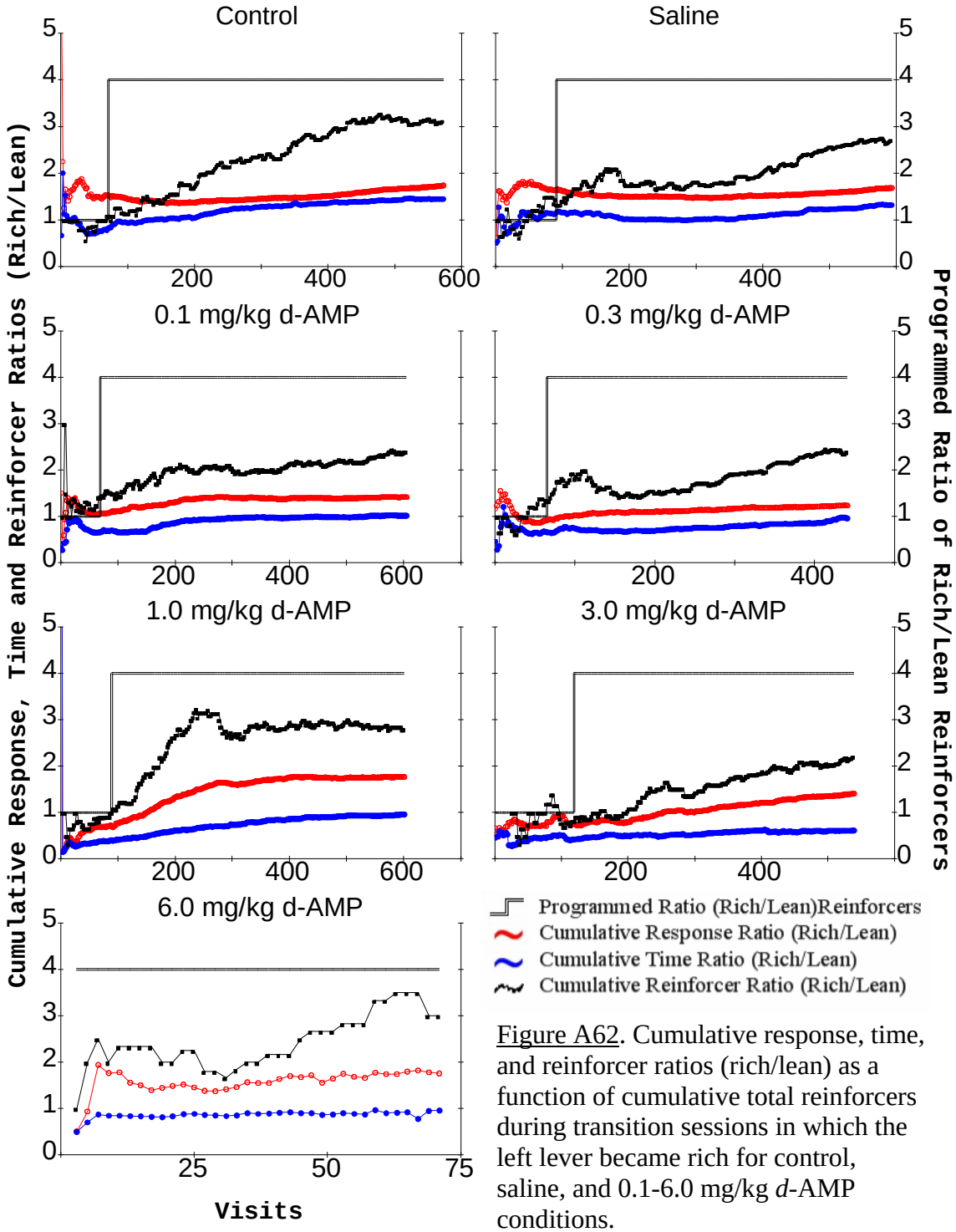


Figure A62. Cumulative response, time, and reinforcer ratios (rich/lean) as a function of cumulative total reinforcers during transition sessions in which the left lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

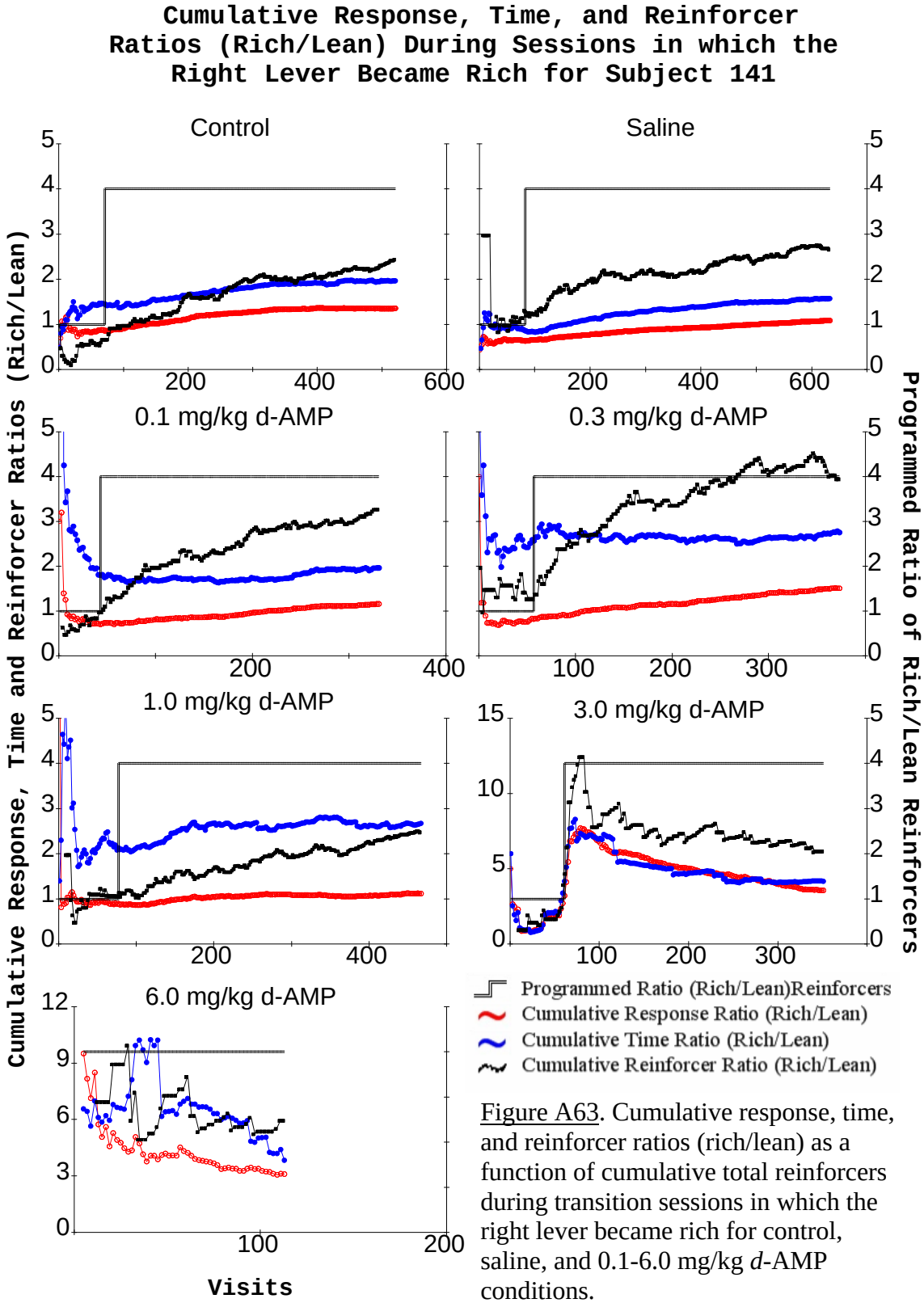


Figure A63. Cumulative response, time, and reinforcer ratios (rich/lean) as a function of cumulative total reinforcers during transition sessions in which the right lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

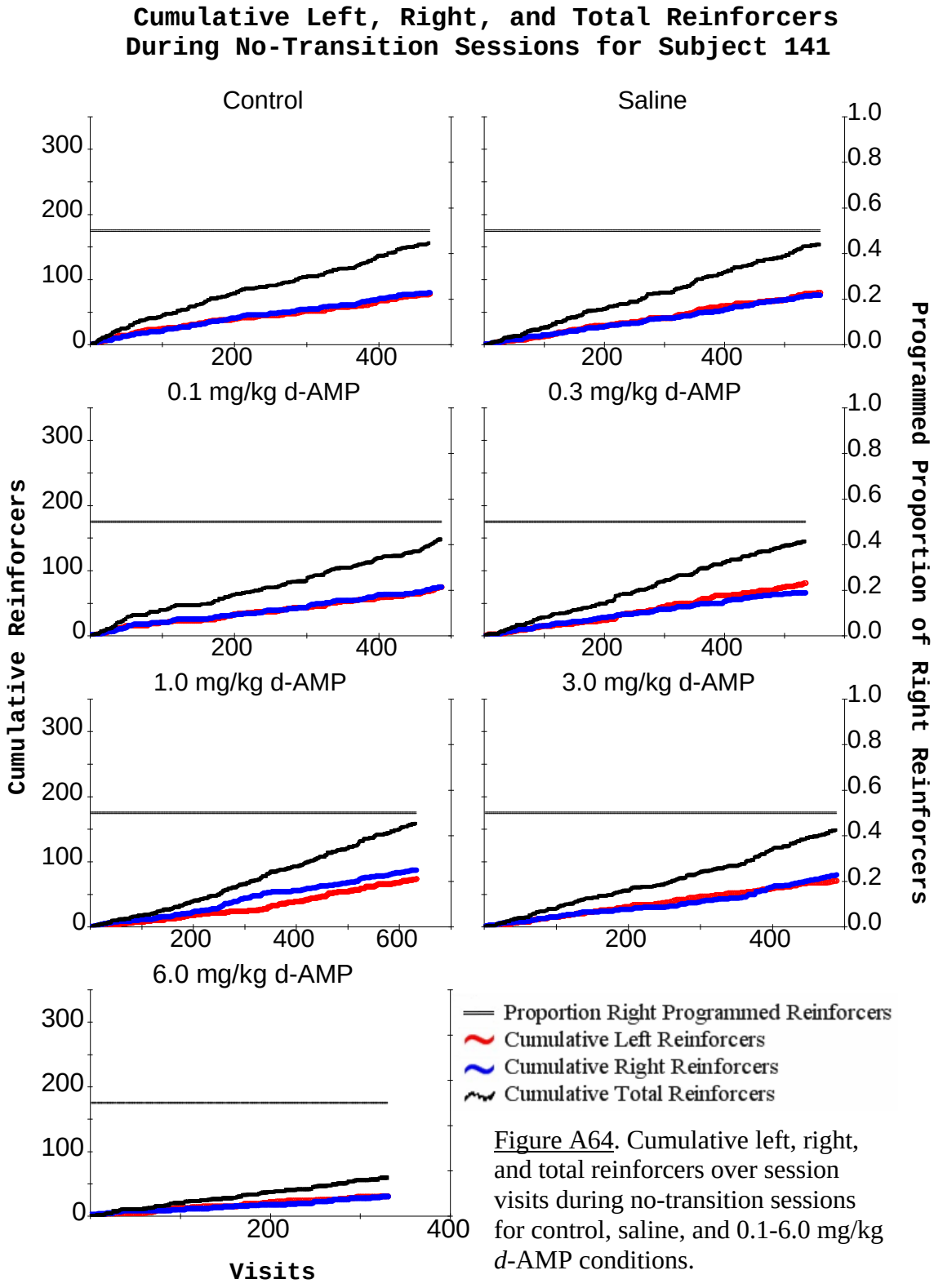


Figure A64. Cumulative left, right, and total reinforcers over session visits during no-transition sessions for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

Cumulative Lean, Rich, and Total Reinforcers through Sessions in which the Left Lever Became Rich for Subject 141

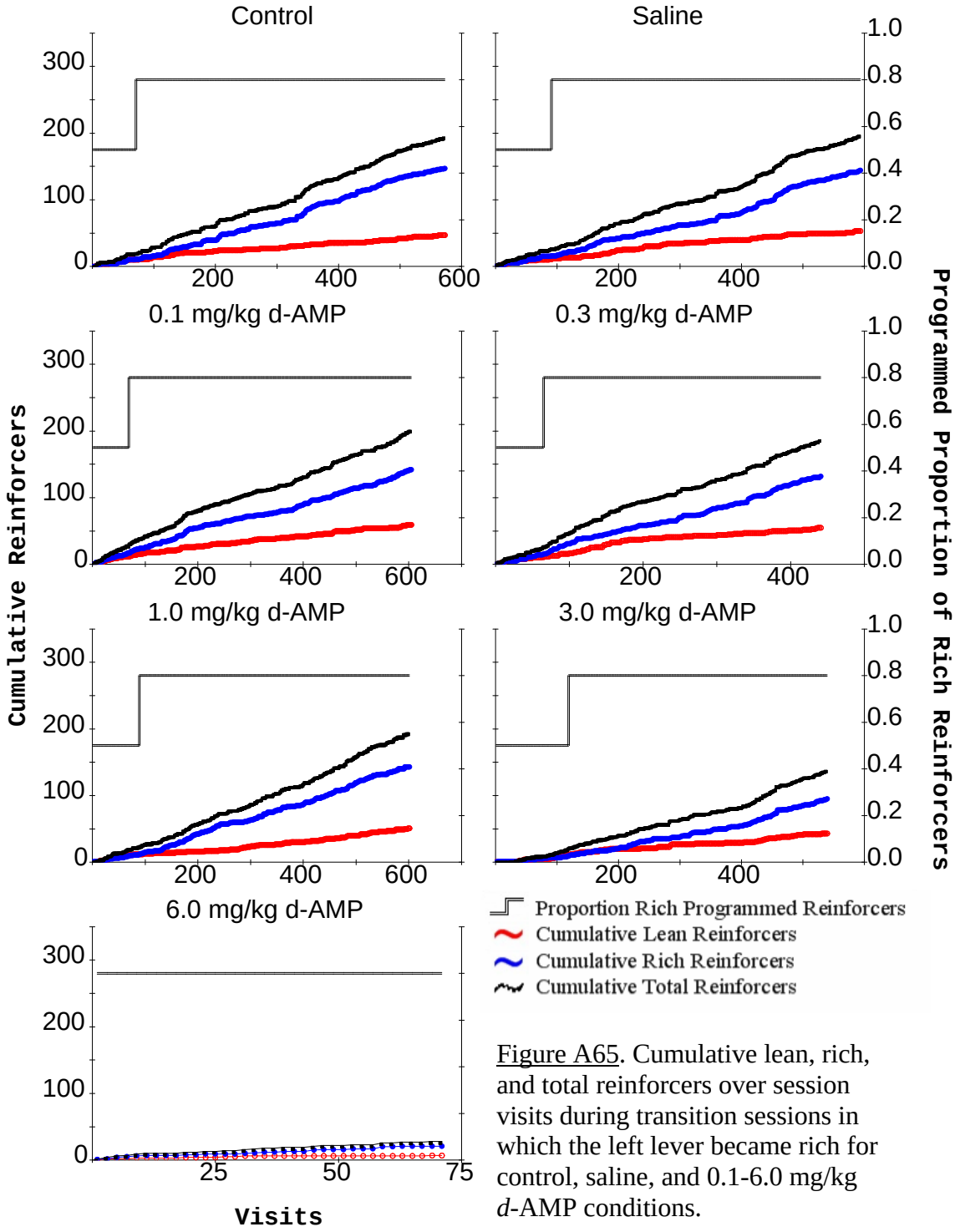


Figure A65. Cumulative lean, rich, and total reinforcers over session visits during transition sessions in which the left lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

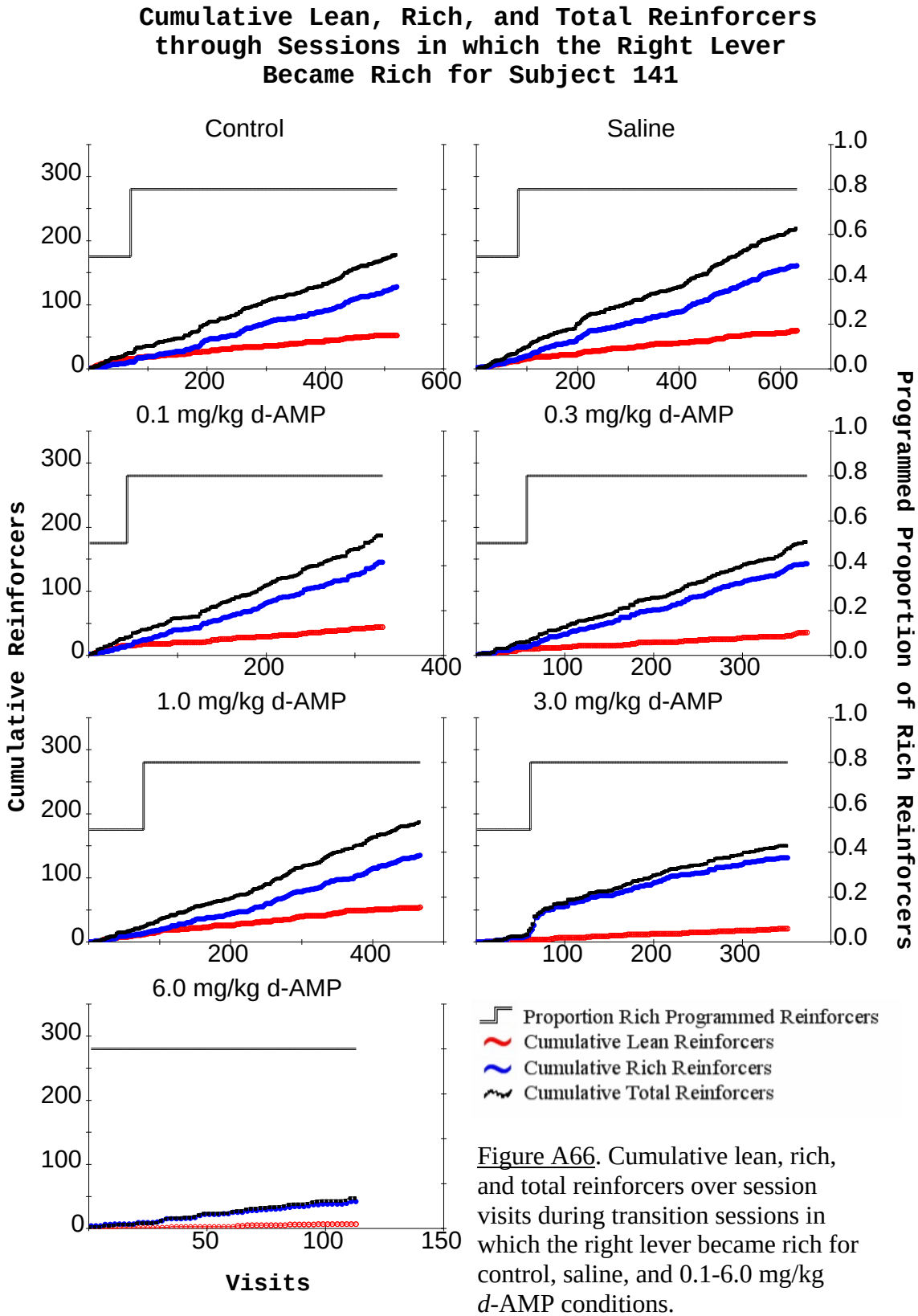


Figure A66. Cumulative lean, rich, and total reinforcers over session visits during transition sessions in which the right lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

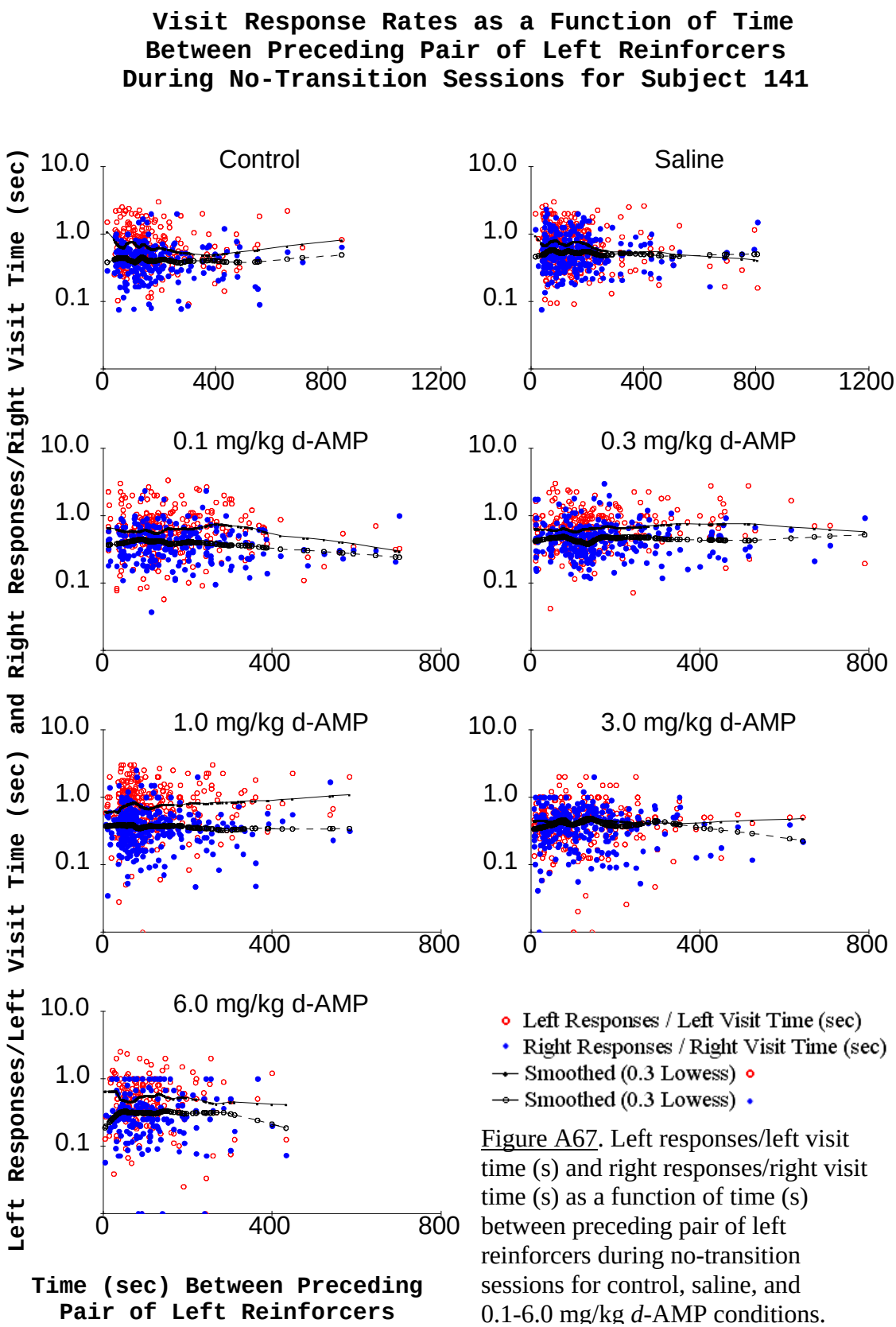


Figure A67. Left responses/left visit time (s) and right responses/right visit time (s) as a function of time (s) between preceding pair of left reinforcers during no-transition sessions for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

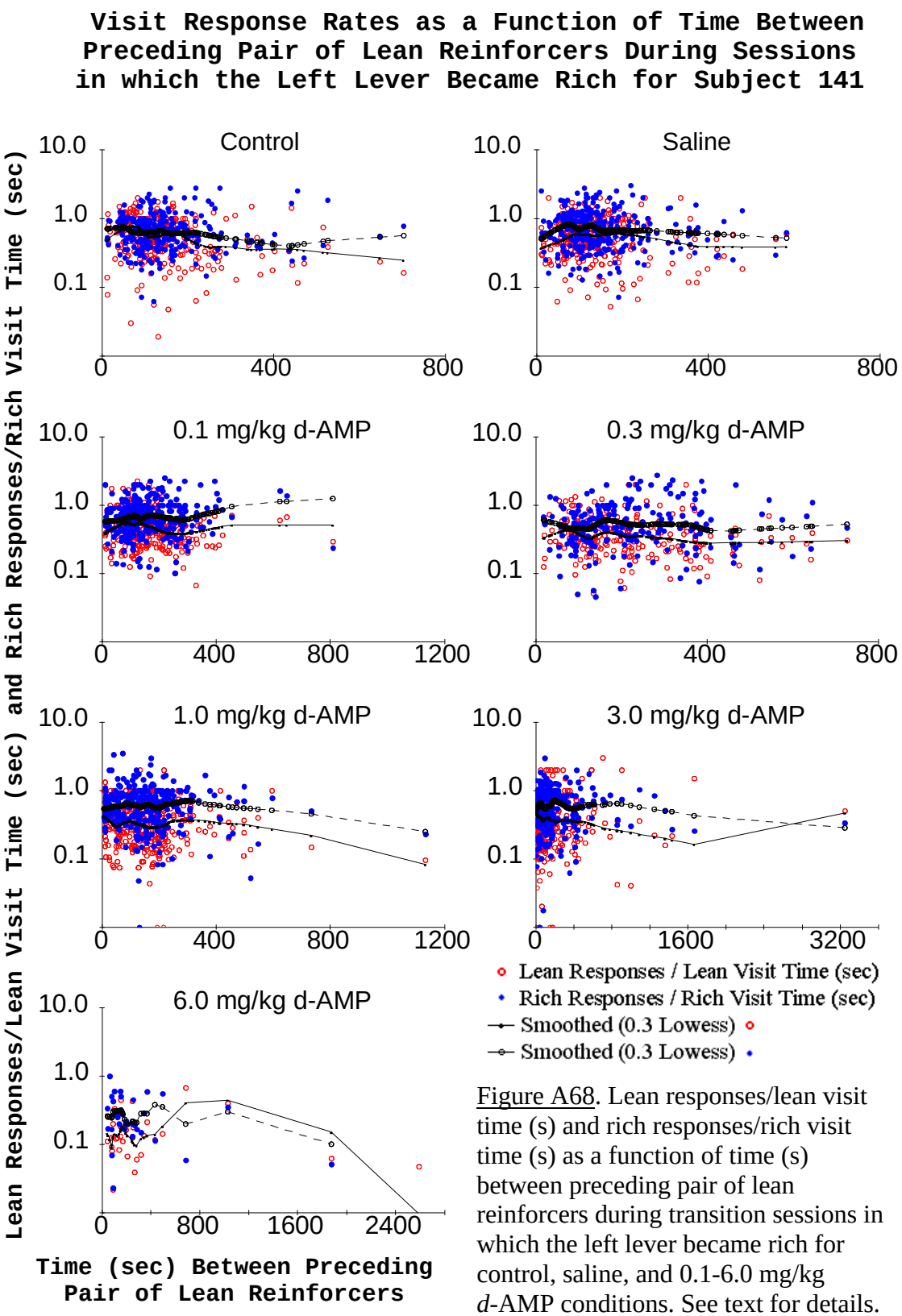


Figure A68. Lean responses/lean visit time (s) and rich responses/rich visit time (s) as a function of time (s) between preceding pair of lean reinforcers during transition sessions in which the left lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions. See text for details.

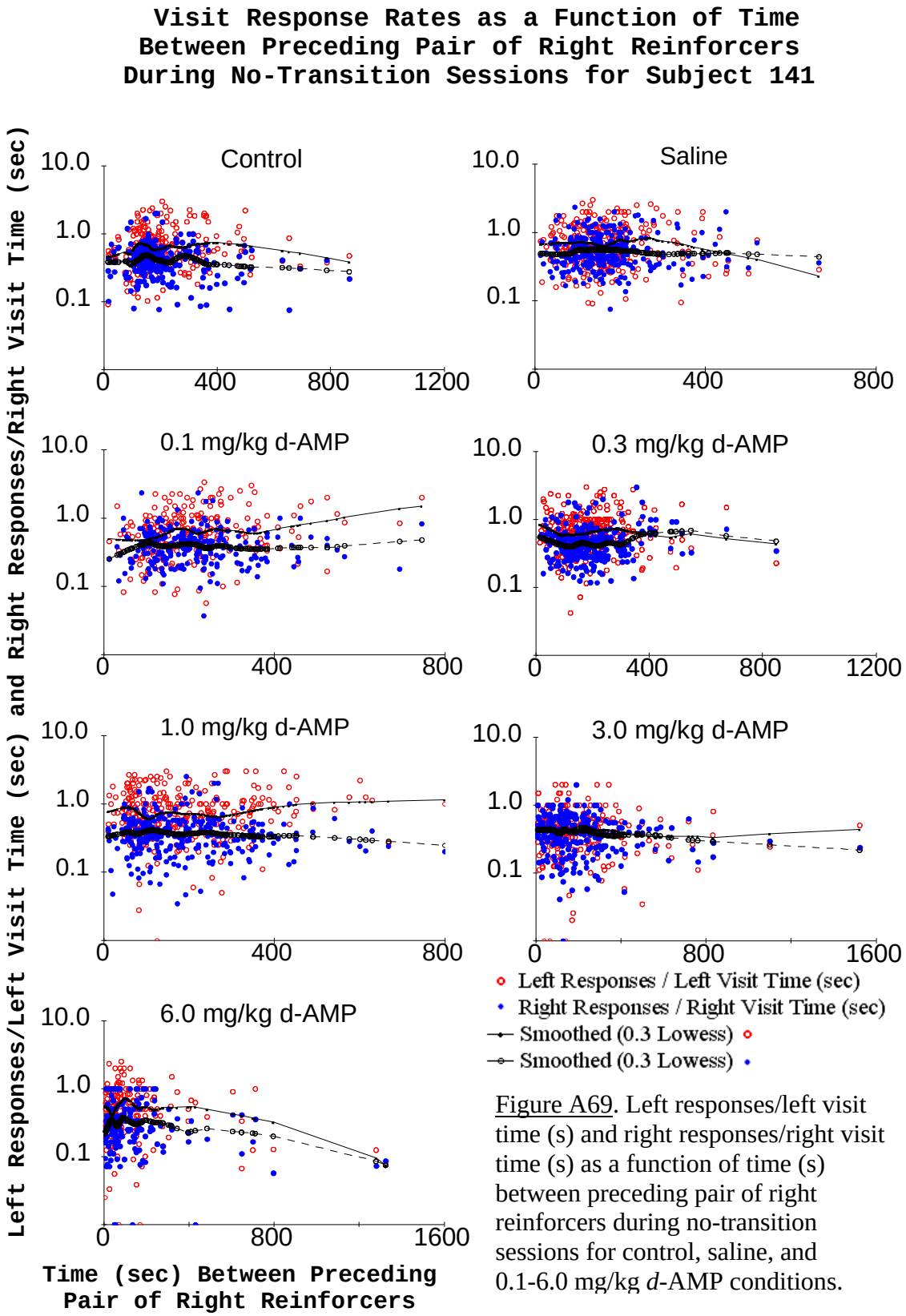


Figure A69. Left responses/left visit time (s) and right responses/right visit time (s) as a function of time (s) between preceding pair of right reinforcers during no-transition sessions for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

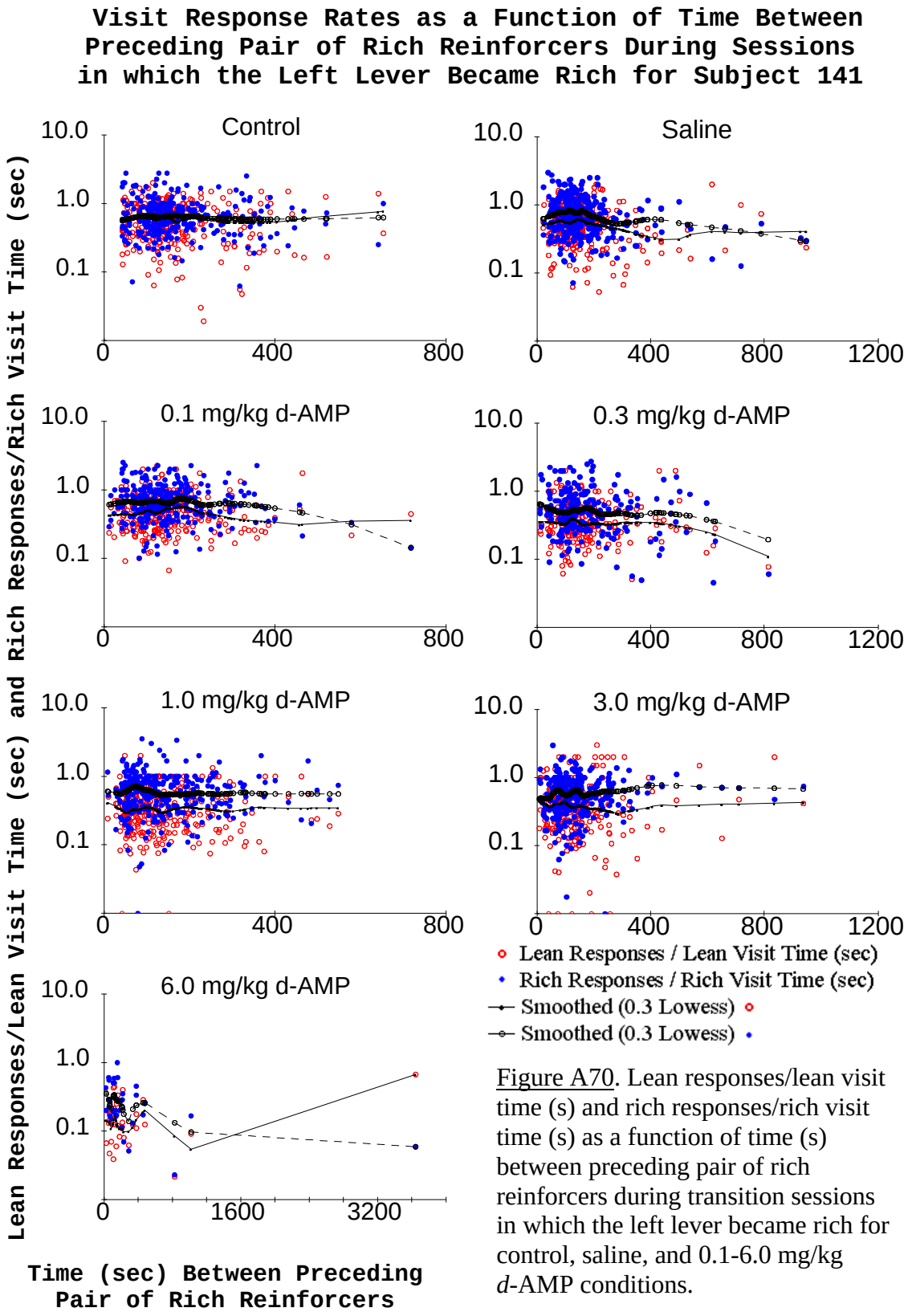


Figure A70. Lean responses/lean visit time (s) and rich responses/rich visit time (s) as a function of time (s) between preceding pair of rich reinforcers during transition sessions in which the left lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.

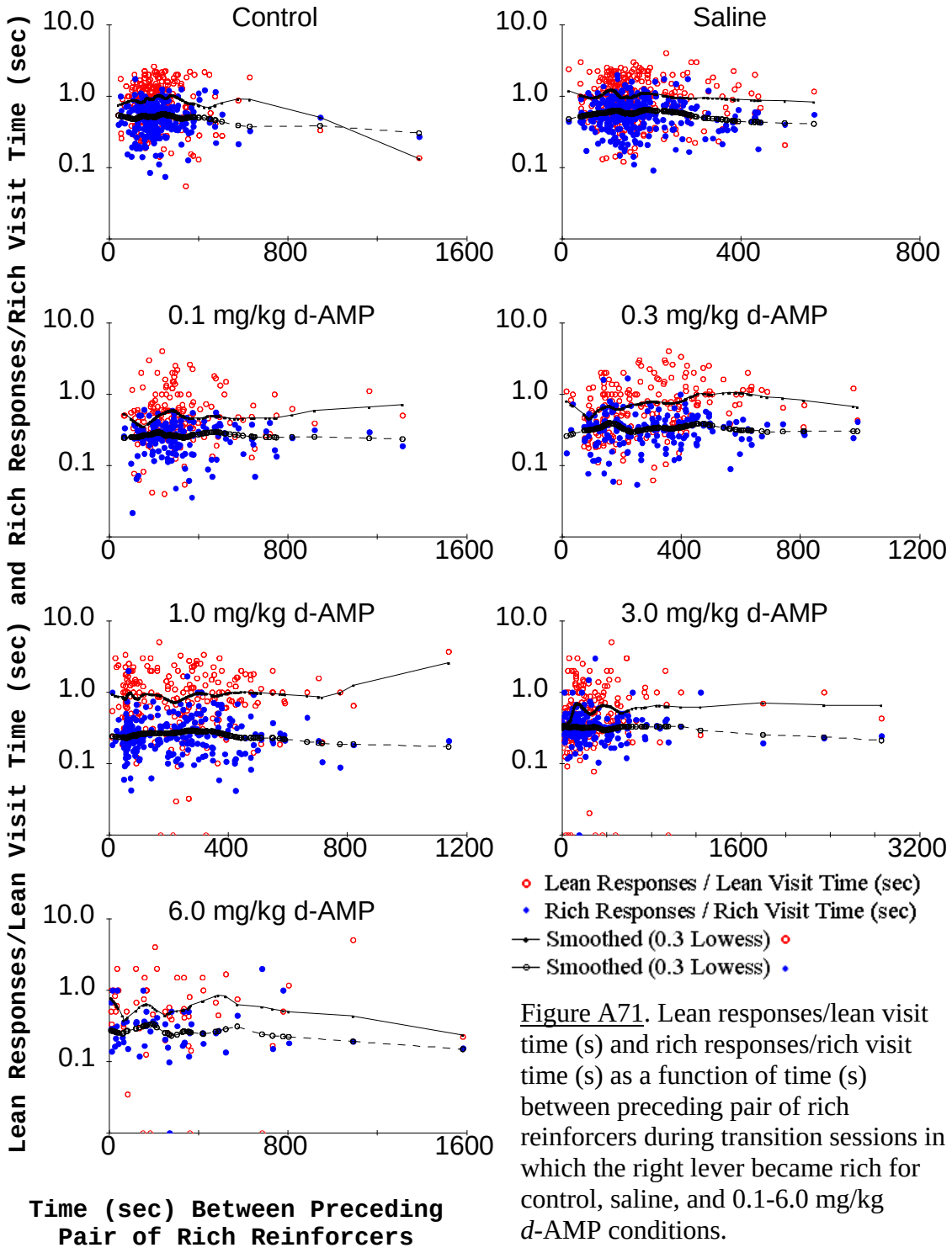


Figure A71. Lean responses/lean visit time (s) and rich responses/rich visit time (s) as a function of time (s) between preceding pair of rich reinforcers during transition sessions in which the right lever became rich for control, saline, and 0.1-6.0 mg/kg *d*-AMP conditions.