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Reinforcement Magnitude Modulates the Rate-Dependent Effects of Fluvoxamine and Desipramine on Fixed-Interval Responding in the Pigeon

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Abstract

Some doses of fluvoxamine can decrease ethanol-maintained behavior more than food-maintained behavior. This might be explained by differences in reinforcement magnitude. In a previous study, fluvoxamine's effects on Fixed-Ratio responding did not depend upon reinforcement magnitude. However, response rates differed with reinforcement magnitude. These differences in response rate might explain the failure to observe differences in the potency of fluvoxamine with changes in reinforcement magnitude.

Methods—We examined if the effects of fluvoxamine and desipramine depend on reinforcement magnitude and response rate by administering these drugs to pigeons responding under a multiple Fixed-Interval schedule in which responding in three components was maintained by differing durations of food presentation (2-, 4-, & 8-sec).

Results—Fluvoxamine and desipramine's effects depended jointly on control rate, reinforcement magnitude, and dose. Low fluvoxamine doses had rate-dependent effects in all three components, --increasing lower rates more than higher rates; as dose increased these rate-dependent effects became greater for components maintained by 2- or 4-sec of food presentation, while declining in the component maintained by 8-sec. Low desipramine doses had rate-dependent effects only in the component maintained by 2-sec; whereas higher doses had rate-dependent effects in components maintained by 2- or 4-sec. Still higher doses had rate-dependent effects in all three components.

Conclusions—While the effects of fluvoxamine and desipramine may not depend upon reinforcement magnitude when studied under Fixed-Ratio schedules, reinforcement magnitude can modulate their effects when studied over a wider range of control response rates.

Keywords

fluvoxamine; desipramine; fixed-interval; rate-dependency; reinforcement magnitude

We often study the effects of drugs on behavior to learn more about the biological basis of a particular behavior. For instance, we might study the effects of a drug on ethanol self-administration in order to learn more about the biological basis of ethanol reinforcement. Selective serotonin reuptake inhibitors, such as fluvoxamine, can decrease ethanol-maintained behavior (e.g. Lamb & Järbe, 2001). Of course, one might expect that a sufficient dose of any drug would decrease ethanol-maintained behavior. For instance, it would be very surprising if an anesthetic dose of halothane did not decrease ethanol-

maintained behavior. Thus, it seems necessary, but not sufficient, if we are to conclude that serotonin modulates ethanol-reinforcement to show that fluvoxamine not only decreases ethanol-maintained behavior, but that fluvoxamine does so at lower doses than those needed to decrease responding maintained by some other event; in other words some level of specificity for ethanol-maintained behavior must be demonstrated. In fact, fluvoxamine can decrease ethanol-maintained behavior at lower doses than those needed to decrease food-maintained behavior (Lamb & Järbe, 2001). Of course, this is only the beginning of demonstrating specificity, or of demonstrating that it is ethanol-reinforcement that is being affected, rather than some other process. For instance, fluvoxamine could be interacting synergistically with the self-administered ethanol to decrease behavior in general. However, this does not seem to be a viable hypothesis for two reasons. First, when ethanol and fluvoxamine are administered jointly by the experimenter, these two drugs do not have synergistic effects (Lamb & Järbe, 2001); and second, when a multiple schedule is used in which a component of ethanol self-administration is placed between two components in which the rat works for food, the effects of fluvoxamine in the first food component before ethanol self-administration are similar to fluvoxamine's effects in the second food component after ethanol self-administration (Ginsburg et al 2005). Similarly, when fluvoxamine effects on ethanol self-administration in one group are compared to fluvoxamine effects on food-maintained behavior in another group, specificity could be a result of chronic ethanol exposure in the ethanol self-administering group rather than the event maintaining behavior. However, the experiment by Ginsburg and coworkers (2005) eliminates this explanation. In their experiment, a multiple schedule was used in which each animal responded for both food and ethanol in separate components; thus, ethanol exposure history was equated, but fluvoxamine still decreased ethanol-maintained behavior more than food-maintained behavior.

One criticism that can and has been made about such findings is that the magnitude of food and ethanol reinforcement may not be necessarily equated, and that behavior maintained by a higher magnitude of reinforcement might be more resistant to disruption than behavior maintained by a lower magnitude of reinforcement. In other words, that it was a quantitative difference in the amount of reinforcement rather than a qualitative difference in the event that reinforced behavior (food vs. ethanol) that explains the observed selectivity. For instance, Nevin (1974) examined the disruptive effects of response-independent food presentations on the responding of pigeons maintained under a multiple VI 3 min schedule in which responding in one component of the schedule was maintained by 2.5 sec of food presentation and responding in the other component was maintained by 7.5 sec of food presentation. Response-independent food decreased responding in the component maintained by 2.5 sec of food presentation more than responding in the component maintained by 7.5 sec of food presentation. Thus, if ethanol reinforcement in the previous studies was of functionally lower magnitude than food reinforcement, then this might explain the results of these previous findings with fluvoxamine. Several findings, however, argue against such an interpretation. First, while there are exceptions (e.g., quinpirole in Harper, 1999), in most cases increased reinforcement density has not made behavior more resistant to disruption by drugs (see Cohen, 1985; Harper, 1999). Second, the potency of fluvoxamine is relatively unaltered across behavior maintained by a range of ethanol concentrations (Lamb & Järbe 2001; Ginsburg et al 2005), which presumably represent a range of magnitudes of ethanol reinforcement (see Gomez & Meisch 2003; and Stewart et al 2002); and thirdly, the potency of fluvoxamine at decreasing FR responding in pigeons does not vary with the duration of food presentation used to maintain responding (Lamb & Ginsburg, 2005), i.e., fluvoxamine did not have effects on FR responding that appeared to depend upon the magnitude of reinforcement that was maintaining behavior. Thus, in this study using fluvoxamine and the studies by Cohen (1986) and by Harper (1999) using a range of drugs, the disruption seen following drug administration does not appear to depend

on the magnitude of reinforcement, unlike the study mentioned earlier by Nevin (1974) and many other similar studies using extinction or changes in food deprivation.

In the study with fluvoxamine, responding was maintained under a mult FR 30 schedule in which responding in the three components of the schedule was maintained by either 2, 4, or 8-sec of food presentation. While the potency of fluvoxamine did not vary across components, the rate of responding did vary across components with longer durations of food presentation maintaining higher rates of responding. This creates another potential confound, differing response rates. As higher rates of responding are often decreased more or at lower doses of drug than lower response rates (see Dews & Wenger, 1977), then any reinforcement magnitude dependent effect that would be expected to operate in the opposite direction might be obscured by these response rate differences. In fact, Harper (1999) suggested that other effects of drugs, in particular disruption of stimulus control, might have obscured how the effects of these drugs on behavior do depend upon reinforcement magnitude or frequency. Rate of responding may have similarly obscured reinforcement magnitude dependent effects in the studies by Cohen (1986) and by Harper (1999). Cohen studied rate-decreasing doses of *d*-amphetamine, pentobarbital and haloperidol, and higher reinforcement densities were associated with higher response-rates in these studies. The rate-dependent effects of these drugs would make higher response-rates more likely to be disrupted, an effect in opposition to the increased behavioral momentum associated with the higher reinforcement rate. Harper studied doses of *d*-amphetamine and fluoxetine that produced either increased rates of behavior or had little effect on behavior; and in this study because increased reinforcement density was accomplished by non-contingent food-delivery, higher reinforcement density was associated with lower response-rates. As lower response-rates are more likely to be increased by drugs with rate-dependent actions, once again the rate-dependent effects of the test drugs may be countering any increased behavioral momentum produced by increasing the reinforcement density.

In this experiment, we tried to separately examine the influences of reinforcement magnitude and response rates on the effects of fluvoxamine and as a comparison desipramine, a selective norepinephrine reuptake inhibitor, by examining the effects of these two drugs on the responding of pigeons under a multiple FI 300 sec schedule in which responding in the three components is maintained by either 2, 4, or 8-sec of food presentation. Response rates within an FI component accelerate from very low rates at the beginning of the FI to high rates near the end of the FI (Ferster & Skinner, 1957). FI schedules have been frequently used to examine the rate-dependent effects of drugs (see Dews & Wenger 1977). Drugs often have effects on responding within FI schedules that at a given dose are well described as a linear relationship between the log of the rate seen following drug administration expressed as a percent of the control-rate of responding regressed upon the log of the control-rate of responding with lower rates of responding being increased more than higher rates of responding. In this experiment as reinforcement magnitude varied across FI components and response rate varies within FI components, this may permit us to examine how the effects of fluvoxamine and desipramine vary with reinforcement magnitude while also taking into account any effects of the baseline rate of responding. FI schedules have been used less frequently than variable-interval schedules to study behavioral momentum. One relevant study is the work reported by Grace & Nevin (2000). In this study, they used a peak timing procedure that involved the use of FI schedules that were sometimes run longer than the FI and not reinforced. In this procedure, disruptors such as extinction, pre-feeding and food delivery in the time-outs between FI components tended to affect the overall rate of FI responding maintained by different magnitudes of reinforcement similarly, but affected the temporal patterning of responding and the terminal rate of responding more when behavior was maintained by smaller magnitudes of reinforcement.

While our study was motivated by studies initially performed in rats, the present study was conducted in pigeons. The effects of reinforcement density on behavioral momentum are similar in rats and pigeons (Cohen et al 1993), but there are perhaps reasons to suspect that the rate-dependent effects of antidepressants such as fluvoxamine and desipramine do vary between the two species with antidepressants being more likely to exhibit rate-dependent effects in the pigeon than in the rat (compare results with rats and pigeons in Lamb & McMillan, 1986, 1989; Leander & Carter, 1984; Rastogi & McMillan, 1985). As the evidence against reinforcement magnitude explaining the specificity observed in rat ethanol self-administration studies comes from experiments in pigeons, it is important to examine if the potential (but not readily observed) rate-dependent effects of fluvoxamine in pigeons might explain the lack of modulation of fluvoxamine's rate decreasing effects by reinforcement magnitude. If the rate-dependent effects of fluvoxamine explain the failure of increasing reinforcement magnitude to attenuate its disruptive effects on FR-responding, then this would make the earlier evidence against the reinforcement magnitude hypothesis less compelling. Thus, this study was designed to examine if and how reinforcement magnitude might modulate any rate-dependent effects of fluvoxamine and as a comparison desipramine.

Methods

Animals

Six adult male White Carneaux Pigeons (Palmento Pigeon Plant, Sumter, SC) were used in these experiments. They were maintained at 80% of their free-feeding weights by food obtained during the experimental sessions and post-session feedings. Pigeons had free access to water and grit outside of the experimental sessions. All pigeons were housed under a 12 h light/12 h dark cycle of illumination, and were tested during the light phase. All pigeons were experimentally naïve before the beginning of the experiment. All experimental procedures were approved by the Institutional Animal Care and Use Committee of the University of Texas Health Science Center at San Antonio.

Apparatus

Experimental sessions were conducted in Gerbrands G7410S test chambers (Alderston, MA). These chambers measure 27.5 cm by 26.4 cm by 27.5 cm and are constructed of Plexiglas® and aluminum with a grid floor. Three response keys were distributed across one wall 18 cm above the floor. Only the center key was used. It could be transilluminated either white, red, or green. Below this key was a hopper in which pigeon chow (Purina Checkers; Purina Mills, St. Louis, MO) could be presented. Test chambers were enclosed within Gerbrands G7211 sound and light attenuating chambers equipped with an exhaust fan. Experimental contingencies were controlled and data were collected by a computer running Med-PC software (Med Associates, Georgia, VT).

Procedure

The pigeons were initially trained to peck for food presentations and subsequently trained to respond under a multiple fixed-interval 300-second (mult FI 300) schedule under which completion of the response requirement in each of the three components resulted in a different duration of food presentation. The beginnings of the fixed-interval components were signaled by illumination of the houselight and of the key. In the presence of a green key light, the first keypeck 300-sec after illumination of the key light resulted in presentation of food and illumination of the hopper light for 2-sec. In the presence of a white key light, the first keypeck 300-sec after illumination of the key light resulted in presentation of food and illumination of the hopper light for 4-sec. In the presence of a red key light, the first keypeck 300-sec after illumination of the key light resulted in presentation of food and

illumination of the hopper light for 8-sec. Each component had a 60-sec limited-hold: if the pigeon did not make a keypeck within 60-sec of the end of the fixed-interval, the component ended. Completion of the fixed-interval requirement or elapse of the limited-hold was followed by a 60-sec time-out. During the time-out both the houselight and the key light were turned off and responses had no programmed consequences. At the end of the time-out, a new FI component began. Which FI component began on any occasion was randomized by choosing without replacement from the set of six possible orders that small, medium and large could occur in repeatedly through out the session. Experimental sessions consisted of four presentations of each component.

Drugs

Fluvoxamine maleate was a gift from Solvay Pharmaceuticals (Weesp, The Netherlands) and was dissolved in saline so that the injection volume was 1 ml/kg. Desipramine HCl was purchased from Sigma Chemicals (St. Louis, MO) and was dissolved in saline so that the injection volume was 1 ml/kg. Both drugs were injected into the pectoral muscle 30 min before the beginning of experimental sessions during this waiting period pigeons remained in their home cage. Drugs were administered on Tuesdays and Fridays, and saline was injected on Thursdays. Injections of saline were also given on some Tuesdays and Fridays to serve as control values. Pigeon R27 died during the experiment and no data for this pigeon with desipramine doses of 0.56, 1.8 and 5.6 m/kg were collected.

Analysis

Each dose of drug was tested at least twice in each pigeon, and the mean of these multiple determinations used in all calculations. Saline vehicle controls on Tuesdays and Fridays were also determined twice during each drug series. These values were normalized to a percent of each individual pigeon's Thursday saline values. Mean individual values obtained following saline given on Tuesday or Friday were used as a control. Responding in each tenth of the fixed-interval was recorded and these values were used for calculating for rate-dependency regressions. These regressions were conducted as suggested by Lorch and Meyers (1990) using JMP statistical software for the Macintosh, so as to take into account the within subject correlations of the values from each subject. Log of ((drug rate/control rate) $\times$ 100) was regressed on log control rate. Points with control rates of less than 0.01 response/sec were excluded as statistically unreliable as increases in these rates would produce large statistical influences in the regression. Points with drug rates of zero were also excluded as these points would be undefined.

Control Responding

Response rates in each FI component for each pigeon are shown in Figure 1. Longer hopper times tended to maintain higher response rates, and the mean rate maintained by 2-sec of grain presentation was lower than the mean rate maintained by 2-sec of grain presentation, which in turn was lower than the rate maintained by 8-sec of grain presentation (paired t-tests: $t=4.19$, $df=5$, $p<.05$; $t=2.98$, $df=5$, $p<0.05$; respectively). In summary, longer hopper times tended to maintain higher rates of responding than shorter hopper times.

Fluvoxamine Effects

In Figure 2, the effects of fluvoxamine and vehicle injections (normal saline) on response rate is plotted as a percent of the rate of responding on the Thursdays during the time when the fluvoxamine dose-response curve was determined. Fluvoxamine dose-dependently and similarly decreased responding across all three hopper times, and no comparison of the rate of responding as percent of the control rate at any dose differed between components (paired t-tests, all $ps>0.05$). The lowest two doses of fluvoxamine (1 & 3 mg/kg) did not decrease

the mean rate of responding below vehicle values. The two highest doses (30 & 56 mg/kg) substantially decreased the mean rate of responding in all three components to levels well below the vehicle value. At 10 mg/kg, the mean rate of responding in the component with responding maintained by 2-sec grain presentations was reduced below the vehicle value (paired t-test: $t=2.96$, $df=5$, $p<0.05$). This was not the case for responding maintained by either 4 or 8-sec of grain presentations ($t=2.08$, $df=5$, $p=.09$; $t=1.98$, $df=5$, $p=.11$). However as mentioned earlier, the rates of responding were not statistically different across components following 10 mg/kg fluvoxamine (paired t-tests, $p>0.10$). The ED50s for fluvoxamine, also, were similar across components 12.9, 12.8 and 13.2 mg/kg and did not differ significantly from each other. Thus, fluvoxamine dose-dependently and similarly decreased fixed-interval rate of responding maintained by 2, 4, or 8 seconds of food presentation.

Grace & Nevin (2000) found that disruptors affected the terminal rate of responding in an FI timing procedure, but not the overall rate of responding. The terminal rates of responding presented in the same manner as used by Grace & Nevin, $\log(\text{disrupted-rate}/\text{control-rate})$, are shown in Table 1. Fluvoxamine dose-dependently and similarly decreased response rate in the last tenth of the FI in which maximal rates of responding occurred across all three hopper times.

In Table 2, the results of regression analyses to assess the rate-dependent effects of fluvoxamine are shown, and the results of some of these regressions are plotted in Figure 3. These results show two things. First, that fluvoxamine has modest rate-dependent effects, and second, that these rate-dependent effects are greatest when behavior is maintained by shorter hopper times. As expected, there is no overall significant effect of regressing log rate after saline injection on Mondays or Fridays on log of the mean rate on Thursdays. This was also true of behavior following 3 mg/kg fluvoxamine. However, the overall regressions following 1 mg/kg, 10 mg/kg and 30 mg/kg were significant and the results of regressions following these doses of fluvoxamine for behavior maintained by each of the three hopper times are shown in Table 1. Following 1 mg/kg fluvoxamine, the slope of the regression line was significantly different from zero for behavior maintained by all three hopper-times. With the possible exception of the comparison between the slope for behavior maintained by the 2-sec hopper-time compared to the slope for behavior maintained by the 4-sec hopper-time, slopes did not differ. The intercepts for all three hopper-times were similar. Following 10 and 30 mg/kg fluvoxamine, the slope of the regression line was significantly different from zero for behavior maintained by the 2- and the 4- sec hopper-times, but not for behavior maintained by the 8-sec hopper time. The slopes for the regression on behavior maintained by the 2- and the 4- sec hopper-times did not differ significantly from each other following either 10 or 30 mg/kg fluvoxamine, but did differ significantly from the slope for behavior maintained by the 8-sec hopper-time. However, the intercepts for all these regressions were similar after a given dose of fluvoxamine. Thus, fluvoxamine had effects that could depend modestly on the control response rate and the degree to which fluvoxamine's effects depended on the control response rate was an inverse function of the magnitude of reinforcement maintaining behavior. Additionally, there was a tendency for the slope of the regression line to become increasingly negative as fluvoxamine dose increased for the two shorter hopper-times, while the converse was true for the longest hopper-time.

Desipramine Effects

As can be seen in Figure 4, desipramine tended to affect overall rates of responding similarly in all three components; as in only one instance was the comparison between rates of responding in one component significantly different from the rate of responding in

another component following a dose of desipramine: Desipramine decreased response rate to 62.9% of the Thursday control value in the component in which responding was maintained by 8-sec of food presentation compared to 89.8% of control in the component in which responding was maintained by 4-sec of food presentation ($t=4.39$, $df=5$, $p<0.05$).

Low to intermediate doses of desipramine tended to increase responding and this was most reliable for responding in the component maintained by 2-sec of food presentation occurring at doses of 0.3, 0.56, & 1.0 mg/kg in this component ($t=2.99$ $df=5$, $p<0.05$; $t=3.66$, $df=4$, $p<0.05$; $t=3.48$, $df=5$, $p<0.05$). Responding was not increased above that seen following vehicle in administration in the component in which responding was maintained by 4-sec of food presentation, and responding was only increased following 0.56 mg/kg desipramine in the component maintained by 8-sec of food presentation ($t=2.84$, $df=4$, $p<0.05$). In no case, however, were the rates of responding different between components.

High doses of desipramine tended to decrease responding. However, responding in one of the six birds tested was not decreased below control levels by any dose of desipramine tested in any of the three components. When this bird is excluded from the analysis doses of 5.6 & 10.0 mg/kg desipramine decreased responding significantly and to near zero levels in all three components. The mean ED50s of desipramine were 3.3, 2.8, and 2.9 mg/kg in the components maintained by 2-, 4-, and 8-sec of food presentation respectively and these values did not differ from each other.

As can be seen in Table 1, desipramine dose-dependently and similarly decreased responding in the last tenth of the FI in which maximal rates of responding occurred across all three hopper times.

In Table 2, the results of regression analyses to assess the rate-dependent effects of desipramine are shown, and some of these are plotted in Figure 5. These results show two things: First, that desipramine has rate-dependent effects, and second, that these rate-dependent effects are greatest when behavior is maintained by shorter hopper times. Doses of 1–3 mg/kg have clear rate dependent effects at all hopper times. At a dose of 0.56 mg/kg, the slope is different from zero for the 2- and 4- sec hopper times, but not for the 8-sec hopper time. At 0.3 mg/kg desipramine, slope is different from zero only for the 2-sec hopper time. At 1 mg/kg desipramine slopes for the 2- and 4- sec hopper times were similar and more negative than the slope for the 8-sec hopper time. At 1.8 mg/kg desipramine, slope for the 2-sec hopper time was more negative than the slope for the 4-sec hopper time which was in turn more negative than the slope for the 8-sec hopper time. At 3 mg/kg desipramine slopes for the 2- and the 4- sec hopper times were again similar, and both were more negative than the slope for the 8-sec hopper time. Intercept values were similar across components at the various doses, and as expected tended to decrease with dose.

Discussion

Reinforcement magnitude did not appear to modulate the effects of fluvoxamine nor of desipramine on overall response rates with some limited exceptions, e.g., desipramine appeared slightly more likely to increase the overall rate of FI responding in components maintained by the shortest duration of food presentation. However, reinforcement magnitude clearly does modulate the effects of fluvoxamine and of desipramine on FI responding when the effects of fluvoxamine and desipramine on rates of responding within the FI are examined. At lower magnitudes of reinforcement, control rates of responding within the FI appeared to be a determinant of the effects of both fluvoxamine's and desipramine's behavioral effects. However, these rate-dependent effects are attenuated when behavior is maintained by larger magnitudes of reinforcement.

Lamb and McMillan (1986) reported the effects of fluvoxamine on responding by pigeons under a mult FR 30, FI 600-sec schedule and under an mult FI 200-sec, FI 200-sec schedule in which responding in one component was punished by a mild electric shock. In this study by Lamb and McMillan, responding in all components of both schedules were dose-dependently decreased by fluvoxamine, and there was little indication that the control rates of responding under these schedules influenced the effects of fluvoxamine. In this study responding was maintained either by 4-sec (mult FR, FI) or 5-sec (mult FI, FI) of grain presentation. These magnitudes of reinforcement and the less powerful statistical procedures used probably account for the lack of rate-dependent effects observed for fluvoxamine in that study.

Desipramine has previously been reported to sometimes (Leander & Carter, 1984), but not always (Lamb & McMillan, 1989) increase overall rates of FI responding in the pigeon. Results consistent with these were observed in the present study. The present study also indicated that these overall response rate increases may be easier to see when responding occurs in the component of the multiple schedule providing the smallest magnitude of reinforcement. In both of these previous studies and the present study desipramine had effects on behavior that appear to depend upon the control rate of behavior. Typically, desipramine increased low rates of responding that occurred at the beginning of the FI proportionally more than higher rates that occurred at the end of the FI. The present study extends these previous findings by showing that these rate-dependent effects of desipramine may be greater and more likely to be observed when the magnitude of reinforcement used to maintain behavior is small compared to when the magnitude of reinforcement used to maintain behavior is large.

These observations that the effects of fluvoxamine and desipramine are more likely to depend upon the rate of responding within the FI when behavior is maintained by shorter durations of food presentation are consistent with the observations of Grace & Nevin (2000). They found that the effects of other disruptors such as extinction and pre-feeding on the pattern of responding within a peak timing procedure increased with shorter durations of food presentation.

Previously, we reported that the effects of fluvoxamine and desipramine on FR responding in the pigeon did not appear to depend on reinforcement magnitude in an experiment analogous to this experiment (Lamb & Ginsburg, 2005). The results of the present experiment are wholly consistent with the results of this experiment. When the response rates maintained by the various components of the mult FR schedule are placed into the regression equations for the rate dependency plots produced from the results of this experiment, there is little indication either drug would be expected to show effects that appear to depend on reinforcement magnitude in any orderly way. Similarly, in this experiment, the effects of fluvoxamine or desipramine on the terminal rates of responding in the FI did not appear to depend upon the duration of food presentation used to maintain behavior. These results contrast with the findings by Nevin & Grace (2000) showing that disruption of maximal-rates of responding under a peak-timing procedure was less with longer durations of food presentation. Our results show that while behavioral momentum or reinforcement magnitude can attenuate the effects of drugs as disruptors, this attenuation may be modulated by other effects of the drug (see Cohen, 1986 and Harper 1999 for other examples of studies of this issue with drugs).

While these experiments demonstrate that reinforcement magnitude modulates how the effects of fluvoxamine and desipramine depend upon the control rate of responding, it does not appear that these modulatory effects of reinforcement magnitude can adequately explain any of the differences in the effects of fluvoxamine on ethanol and food-maintained

behavior seen in our earlier experiments. In several experiments described in the introduction, we observed that fluvoxamine decreased ethanol maintained behavior more than food maintained behavior at some doses of fluvoxamine. In one of these experiments (Lamb & Järbe, 2001), ethanol-maintained behavior occurred at a lower rate than food maintained behavior, and based on the differential ratios required to equate ethanol and food maintained behavior under a concurrent schedule (Ginsburg & Lamb, 2006), ethanol-maintained behavior was likely to be the more weakly reinforced behavior. This weaker ethanol-reinforcement, if anything, should have decreased the potential selectivity of fluvoxamine based on the present results. In the other experiment (Ginsburg et al 2005), response rates were relatively well equated and high for both food and ethanol maintained behavior. As with the earlier pigeon experiment using different durations of food access (Lamb & Ginsburg, 2005), the results of the present experiment would predict that the effects seen on these high rate behaviors would be relatively independent of any reinforcement magnitude effects. Finally, in a more recent experiment (Ginsburg & Lamb, 2006), we found that when ethanol and food are available concurrently, i.e., at the same time, and food maintained responding is occurring at higher rate than ethanol maintained responding, fluvoxamine has the opposite selectivity to that we had observed previously, fluvoxamine decreases food-maintained responding more and at lower doses than ethanol-maintained responding. While in this case, the direction of the observed selectivity would be predicted based on the results of this experiment, the magnitude of effect seen in this earlier experiment is greater than would be predicted from this experiment. However, for several reasons the possible influence of reinforcement magnitude on fluvoxamine selectivity will require more direct experimental investigation.

One reason that further experimental investigation is required is that the effects of antidepressants are often qualitatively different in rats and pigeons. In particular, rate dependent effects, particularly with norepinephrine uptake inhibitors, are frequently seen in pigeons (e.g., Leander & Carter, 1984; Lamb & McMillan, 1989), but not in rats (Rastogi & McMillan, 1985; Lamb & McMillan, 1989). These species differences limit the extent to which reinforcement magnitude modulation of the rate dependent effects of fluvoxamine or desipramine should be directly extended from the pigeon to the rat without more direct investigation.

The original hypothesis that this experiment and our earlier similar experiment with FR behavior (Lamb & Ginsburg, 2005) were designed to address was most simply stated as behavior reinforced by lower magnitudes of reinforcement would be more easily disrupted by fluvoxamine than behavior maintained by larger magnitudes of reinforcement. This notion derives both from the idea that this would increase survival fitness and from the empirical and theoretical work of Nevin on behavioral momentum (see Nevin & Grace 2000 for a review of this work). Our expectation originally based on this hypothesis was that this effect of reinforcement magnitude would operate predominantly on overall response rate. This expectation was clearly not seen. Rather, reinforcement magnitude modulated how fluvoxamine and desipramine affected local rates of responding. This is consistent with the observation by Grace & Nevin (2000) that disruption of the pattern of responding by extinction was more clearly attenuated by increasing the duration of food presentation used to maintain behavior than was overall decreases in response rate. The rate-dependency regressions were modulated by reinforcement magnitude mainly by changes in slope. This results in fluvoxamine and desipramine having effects on low rate behaviors that are influenced by reinforcement magnitude, while the actions of these drugs on high rate behaviors, like those at the end of the FI or under an FR schedule, appear little influenced by reinforcement magnitude. Our results contrast with other findings by Grace & Nevin using prefeeding and extinction as disruptors in a peak-timing procedures, in which they found that the effects of these disruptors on maximal rates of responding was attenuated in

behavior maintained by longer durations of food presentation. In the present experiment, decreases in maximal rates of responding at the end of the FI by fluvoxamine and desipramine were not attenuated by increasing reinforcement magnitude. As the high rates at the end of the FI account for most of the responses made during the FI, this results in fluvoxamine and desipramine having effects on the overall rate of FI responding that do not appear to be greatly influenced by reinforcement magnitude. The attenuation of the rate dependent effects of fluvoxamine and desipramine with increasing reinforcement magnitude can be interpreted as increasing reinforcement magnitude decreasing the effects of these two drugs on disrupting FI patterning. This interpretation would be consistent in some ways with the ideas of behavioral momentum, and at least partially consistent with the observations of Grace & Nevin (2000) on the effects of other disruptors on the peak timing procedure. In that study, the effects of these disruptors on the distribution of responding and peak response rate, but not overall response rate, were attenuated when behavior was maintained by longer durations of food presentation.

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References

- Cohen SL. A pharmacological examination of the resistance-to-change hypothesis of response strength. *J Exp Anal Behav.* 1986; 46:363–379. [PubMed: 3805976]
- Cohen SL, Riley DS, Weigle PA. Tests of behavior momentum in simple and multiple schedules with rats and pigeons. *J Exp Anal Behav.* 1993; 60:255–291. [PubMed: 8409822]
- Dews PD, Wenger GR. Rate-dependency of the behavioral effects of amphetamine. *Adv Behav Pharmacol.* 1977; 1:167–227.
- Ferster, CB.; Skinner, BF. *Schedules of Reinforcement.* Englewood, NJ: Prentice-Hall Inc; 1957.
- Ginsburg B, Koek W, Javors MA, Lamb RJ. Effects of fluvoxamine on a multiple schedule of ethanol- and food- maintained behavior in two rat strains. *Psychopharmacol.* 2005; 180:249–257.
- Ginsburg BC, Lamb RJ. Fluvoxamine effects on concurrent ethanol- and food-maintained behaviors. *Exp Clin Psychopharmacol.* 2006; 14:483–492. [PubMed: 17115876]
- Gomez TH, Meisch RA. Relationship between choice of ethanol concentration and response rates under progressive- and fixed-ratio schedules: studies with rhesus monkeys. *Psychopharmacol.* 2003; 170:1–8.
- Grace RC, Nevin JA. Response strength and temporal control in fixed-interval schedules. *Animal Learn Behav.* 2000; 28:313–331.
- Harper DN. Drug-induced changes in responding are dependent on baseline stimulus-reinforcer contingencies. *Psychobiology.* 1999; 27:95–104.
- Lamb RJ, Ginsburg BC. Fluvoxamine and desipramine on fixed-ratio responding: Effects of reinforcement magnitude. *Behav Pharmacol.* 2005; 16:573–578. [PubMed: 16170234]
- Lamb RJ, Järbe TUC. Effects of fluvoxamine on ethanol-reinforced behavior in the rat. *J Pharmacol Exp Therap.* 2001; 297:1001–1009. [PubMed: 11356922]
- Lamb RJ, McMillan DE. The effects of some putative antidepressant agents on the schedule-controlled behavior of the pigeon. *Psychopharmacol.* 1986; 88:368–373.
- Lamb RJ, McMillan DE. Some effects of desmethylinipramine and amitriptyline on the schedule-controlled behavior of pigeons and rats. *Arch internat Pharmacol.* 1989; 302:49–67.
- Leander JD, Carter RB. Effects of norepinephrine and serotonin uptake inhibitors on the schedule-controlled behavior of the pigeon. *Pharmacol Biochem Behav.* 1984; 20:391–395. [PubMed: 6608736]
- Lorch RF, Myers JL. Regression analysis of repeated measures data in cognitive research. *J Exp Psychol Learn Mem Cog.* 1990; 16:149–157.

- Nevin JA. Response strength in multiple schedules. *J Exp Anal Behav.* 1974; 21:389–408. [PubMed: 16811752]
- Nevin JA, Grace RC. Behavioral momentum and the law of effect. *Behav Brain Sci.* 2000; 23:73–130. [PubMed: 11303339]
- Rastogi SK, McMillan DE. Effects of some typical and atypical antidepressants on schedule-controlled responding in rats. *Drug Develop Res.* 1985; 5:243–250.
- Stewart RB, Wang HS, Bass AA, Meisch RA. Relative reinforcing effects of different oral ethanol doses in rhesus monkeys. *J Exp Anal Behav.* 2002; 77:49–64. [PubMed: 11831783]

Figure 1.

The median rate of responding on Thursdays in responses per second for each pigeon for each component during the period when the effects of fluvoxamine were determined. Data for each pigeon is shown sequentially as a set of connect points for behavior maintained by 2, 4 or 8-sec of food presentation.

Figure 2.

Effects of fluvoxamine on the mean rate of responding: Y-axis is response rate as a percent of the Thursday control values. X-axis is fluvoxamine dose on a log scale; points above 'V' represent the effects of vehicle injections given on a Tuesday or a Friday. Circles represent values for the component in which behavior was maintained with 2-sec of food presentation, squares by 4-sec of food presentation, and triangles by 8-sec of food presentation. Error bars are standard errors of the mean

Figure 3.

Rate-dependency plots of the effects of selected fluvoxamine doses: The Y-axes are the rate of responding after drug as a percentage of the control rate plotted on a log scale. The X-axes are the control rate plotted on a log scale. Each color represents a different pigeon, and each point represents the effects of fluvoxamine in a particular tenth of the fixed-interval. The left column represents the effects of 1 mg/kg of fluvoxamine, the middle column the effects of 10 mg/kg fluvoxamine, and the right column the effects of 30 mg/kg. The top row represents the effects seen on behavior in the component maintained by 2-sec of food presentation, the middle row by 4-sec of food presentation, and the bottom row by 8-sec.

Figure 4.

Effects of desipramine on the mean rate of responding: Y-axis is mean response rate as a percent of the Thursday control values. X-axis is desipramine dose on a log scale; points above 'V' represent the effects of vehicle injections on a Tuesday or Friday. Circles represent values for the component in which behavior was maintained with 2-sec of food presentation, squares by 4-sec of food presentation, and triangles points by 8-sec of food presentation.

Figure 5.

Rate-dependency plots of the effects of selected desipramine doses: The Y-axes are the rate of responding after drug as a percentage of the control rate plotted on a log scale. The X-axes are the control rate plotted on a log scale. Each color represents a different pigeon, and each point represents the effects of desipramine in a particular tenth of the fixed-interval. The left column represents the effects of 0.3 mg/kg of desipramine, the middle column the effects of 0.56 mg/kg desipramine, and the right column the effects of 1.8 mg/kg. The top row represents the effects seen on behavior in the component maintained by 2-sec of food presentation, the middle row by 4-sec of food presentation, and the bottom row by 8-sec.

Effects of Fuvoxamine & Desipramine on Response Rate during the last tenth of the Fixed-Interval maintained by either 2-, 4- or 8-sec of food presentation

Table 1

dose (mg/kg)	log(drug-rate/vehicle-rate)			
	hopper time		hopper time	
fluvoxamine	2-sec	4-sec	8-sec	
1	-0.01 (0.03)	0.02 (0.05)	-0.02 (0.02)	
3	-0.08 (0.06)	-0.10 (0.05)	-0.08 (0.03)	
10	-0.26 (0.07)	-0.22 (0.05)	-0.22 (0.04)	
30	-0.82 (0.18)	-1.12 (0.37)	-0.61 (0.11)	
desipramine	2-sec	4-sec	8-sec	
0.30	0.05 (0.05)	-0.04 (0.05)	-0.01 (0.04)	
0.56	-0.03 (0.08)	-0.03 (0.03)	0.00 (0.03)	
1.00	0.00 (0.03)	-0.09 (0.07)	-0.09 (0.05)	
1.80	-0.37 (0.17)	-0.56 (0.23)	-0.51 (0.23)	
3.00	-0.36 (0.13)	-0.26 (0.05)	-0.33 (0.10)	

N=6 for all, points except 30 mg/kg fluvoxamine (N=3), and 0.56 and 1.8 mg/kg desipramine (N=5).

Table 2

Results of Rate-Dependency Regressions (log rate following drug as a percent of the control-rate on log of the control-rate)

Hopper time	Antilog Intercept	Intercept	(SEM)	Slope	(SEM)	P slope = 0
Saline						
2-sec						
4-sec						
8-sec						
OVERALL REGRESSION NON-SIGNIFICANT						
1 mg/kg Fluvoxamine						
2-sec	109	2.037	0.034	-0.257	0.039	<0.0001
4-sec	92	1.962	0.051	-0.138	0.058	0.0220
8-sec	95	1.979	0.046	-0.170	0.066	0.0134
3 mg/kg Fluvoxamine						
2-sec						
4-sec						
8-sec						
OVERALL REGRESSION NON-SIGNIFICANT						
10 mg/kg Fluvoxamine						
2-sec	52	1.722	0.051	-0.310	0.059	<0.0001
4-sec	71	1.851	0.044	-0.361	0.053	<0.0001
8-sec	66	1.821	0.091	-0.089	0.047	0.659
30 mg/kg Fluvoxamine						
2-sec	20	1.302	0.066	-0.553	0.078	<0.0001
4-sec	6	0.790	0.111	-0.660	0.141	0.0003
8-sec	28	1.452	0.036	0.030	0.041	0.7144
0.3 mg/kg Desipramine						
2-sec	97	1.988	0.043	-0.312	0.054	<0.0001
4-sec	105	2.019	0.057	-0.099	0.070	0.163
8-sec	87	1.940	0.046	0.035	0.067	0.611
0.56 mg/kg Desipramine						
2-sec	108	2.032	0.044	-0.455	0.057	<0.0001
4-sec	87	1.938	0.059	-0.419	0.063	<0.0001
8-sec	109	2.037	0.047	-0.010	0.060	0.816

Hopper time	Antilog Intercept	Intercept	(SEM)	Slope	(SEM)	P slope = 0
1 mg/kg Desipramine						
2-sec	83	1.919	0.042	-0.549	0.050	<0.0001
4-sec	78	1.892	0.026	-0.566	0.031	<0.0001
8-sec	71	1.849	0.038	-0.437	0.049	<0.0001
1.8 mg/kg Desipramine						
2-sec	52	1.717	0.041	-0.677	0.050	<0.0001
4-sec	39	1.586	0.035	-0.446	0.042	<0.0001
8-sec	40	1.603	0.063	-0.213	0.085	0.0168
3 mg/kg Desipramine						
2-sec	43	1.628	0.035	-0.679	0.043	<0.0001
4-sec	62	1.795	0.025	-0.619	0.028	<0.0001
8-sec	45	1.657	0.028	-0.388	0.039	<0.0001