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The effects of lipopolysaccharide on positive reinforcement in rats

Daamoon Ghahari

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Abstract

Lipopolysaccharide (LPS), a bacterial endotoxin which has potent immune activating properties, has been widely used to study the effects of neuroinflammation in animal models. Previous studies have demonstrated that LPS increases the stress response, reduces operant responding, and causes anhedonia and anorexia in rats. Most of these studies have demonstrated the behavioural effects of LPS through decreases in palatable solution consumption or self-administration of pleasurable electrical brain stimulation (EBS), however a more detailed study exploring the differences between appetitive and consummatory behaviours is needed to truly understand the impact of neuroinflammation on food-motivated behaviour. The current study injected 23 male Long Evans rats with either LPS (200 μg/kg; n = 8), scopolamine hydrobromide (SH; 1 mg/kg; n = 7) or a saline control (0.9% saline; n = 8), and assessed bar pressing performance under an FR-1 schedule in a Skinner box. Measures on latency time to begin bar pressing (LT), rate of responding (RR), horizontal movements (HM), and vertical movements (VM) were collected during a 14 min test day session, incremented in 2 min time blocks. Additionally, the number of total bar presses (TBP) was recorded during baseline and testing sessions. The study's hypothesis that LPS-injected rats would display impaired response to positive reinforcements in the Skinner box was supported; LPS rats underperformed the saline control in all bar pressing measures, including LT, RR, and TBP. However, decreases in LPS rats' HM and VM suggest that reduction in bar pressing is not solely due to reduced motivation. Future research should further examine the mechanism of LPS effects on appetitive behaviour, and attempt to isolate deficits in locomotor behaviour from reduced food intake.

The effects of lipopolysaccharide on positive reinforcement in rats

Lipopolysaccharide (LPS), a non-infectious endotoxin purified from gram-negative bacterial cell wall, induces monocytes and macrophages to express and release pro-inflammatory cytokines, including interleukin-1 (IL-1β; Zuckerman, Shellhaas & Butler, 1989). Both LPS and IL-1β have been demonstrated to affect central nervous system functioning in a variety of ways, including increased activity of the hypothalamic-pituitary-adrenal axis, an important regulator in stress response (Beishuizen & Thijs, 2003). Thus, the systemic administration of LPS is a widely accepted model for inducing neuroinflammation in animal models and studying the effects of immune-challenge on behaviour. When administered peripherally, LPS and IL-1β may result in various behavioural changes termed "sickness behaviours". These sickness behaviours are characterized in rodent species as reduced social interaction, exploration, locomotor activity, and food and water intake (Dantzer et al., 1998).

An additional aspect of LPS-induced sickness behaviour in rats is anhedonia, or the loss of interest in pleasurable activities. This can be observed in the diminished consumption of sucrose or saccharin solutions and decreased self-administration of pleasurable electrical brain stimulation (EBS) after immune activation in rats (Kent, Ossenkopp & Kavaliers, 1999; Yirmiya, 1996; Anisman, Kokkinidis & Merali, 1996). The current study will examine the effects of LPS sickness behaviours using a different positive reinforcement model, rather than palatable solution consumption or EBS. Assessing the latency to first response, rate of responding and total responses of food-deprived rats on bar pressing for food rewards will help determine if LPS exerts similar negative effects across various measures of positive reinforcements.

Numerous studies have demonstrated anorectic effects, or pronounced reductions in food intake after LPS or cytokine administration (Langhans, Balkowski, & Savoldelli, 1991; Larson,

Romanoff, Dunn, & Glowa, 2002). In one such study, peripheral administration of IL-1β induced anorexia in fasted rats and rats fed ad libitum, demonstrated by decreased operant responding and food-motivated behaviour (Plata-Salamán, Oomura & Kai, 1988). However, several studies have further described that using an operant response, such as bar pressing, to measure food or water intake involves both appetitive and consummatory behaviour (Roberts, Kavaliers & Ossenkopp, 2003). Additionally, distinct effects of LPS on these two behaviours have been established. Kent, Kavaliers and Ossenkopp (2000) described that systemic LPS administration decreased voluntary water intake (appetitive behaviour), but increased ingestive behaviours during brief intraoral water infusions (consummatory behaviour). These results challenge past findings that have attributed decreased bar pressing entirely to decreased food-motivated behaviour. Appetitive behaviours rely on subjects orienting and moving themselves towards a food reinforcer or paired stimulus, and would be inherently disrupted due to impairments in locomotor activity. This study will measure locomotion to assess if LPS-induced anorectic effects are influenced by a disruption to appetitive behaviour.

In addition to sickness behaviours, rodents injected with LPS have demonstrated alterations in other cognitive functions such as memory and learning. Although cytokine IL-1 receptors are greatly spread throughout the brain, higher densities have been reported in the dentate gyrus of the hippocampus (Farrar, Kilian, Ruff, Hill, & Pert, 1987), implying that the hippocampus may be selectively disrupted during LPS/IL-1β administration. In fact, Kranjac et al. (2012) demonstrated that mice administered with LPS, up to 2 hr post-training, were impaired in memory consolidation processes involved with storing conditioned contextual fear. However, results on LPS-induced memory impairment are mixed, and may or may not play a role in the reduction of bar presses. Larson (2006) displayed that LPS and IL-1gβ administration in rats did

not disrupt the expression of place preference, a learned response. Thus, LPS may work by disrupting specific forms of memory, such as contextual fear, but not others.

The current study will use a Skinner box to assess bar pressing and positive reinforcement in rats injected with either LPS, scopolamine hydrobromide (SH), or a saline control (SC). Scopolamine hydrobromide (SH), an acetylcholine antagonist, is a known memory blocker that will be used in this study as a positive control (Newman & Gold, 2016). If LPS-induced rats are impaired in memory and learning, they should perform similar to SH rats in bar pressing measures. The latency to begin bar pressing will be a measure used to assess how food-motivated behaviour is impacted by drug treatments. Additionally, the anorectic effects of drug treatments on positive reinforcement will be measured by the rate of responding, or the number of bar presses made every 2 min in a 14 min test day session. The total number of bar presses made in the test day session will be compared to a similar baseline session when rats are drug-free. Locomotor activity will be measured on test day by recording the number of horizontal and vertical movements made across the seven 2-min time blocks; the effects of drug treatment on these movements will provide further insight into the expected anorectic behaviours. This study hypothesizes that LPS will have a negative effect on bar pressing in rats being assessed in the Skinner box. Specifically, this study predicts an increase in latency time and a decrease in the rate of responding, total responses, and horizontal and vertical movements in LPS rats when compared to the saline control. Additionally, this study predicts that LPS does not induce similar memory impairment as SH on bar pressing; LPS rats will not perform similar to SH injected rats on the above measures.

Methods

Subjects

Twenty-three male Long Evans rats (375-400 g) were housed in pairs in polypropylene cages (21 ± 1°C) under a 12:12 light/dark cycle (lights on at 07:00 hr). Subjects were randomly assigned to 3 groups (n = 7-8/group) and were habituated to a food deprivation schedule for one week prior to testing. Rats were maintained at 90% pre-deprivation weight. All animals were handled and tested according to the guidelines set out by the Canadian Council on Animal Care.

Apparatus

A Skinner box (43 cm X 35 cm X 30 cm, plywood with a clear Plexiglas front panel) was used for operant conditioning and collection of behavioural data. The floor of the chamber was divided into six equally sized squares and the walls were vertically bisected with black marker. Inside the chamber was a retractable lever beside the food pellet dispenser, designed to provide reinforcement for every bar press under a fixed-ratio schedule (FR-1). The pellet dispenser was also controlled by a remote that experimenters could use to reinforce behaviour. The apparatus recorded the number of reinforcements provided by experimenters and the number of rewards gained by successful bar presses.

Procedure

Drug Condition. Rats were injected with either 200 μg/kg lipopolysaccharide (LPS; from *Escherichia coli* 0111:B4, L-2630; Sigma, St. Louis, MO) dissolved in 0.9% saline (n = 8), 1 mg/kg of scopolamine hydrobromide (SH; Sigma, St. Louis, MO) dissolved in 0.9% saline (n = 7), or a control (SC) of 0.9% saline vehicle (n = 8). All injections were made in a volume of 1.0 ml/kg and administered intraperitoneally. LPS and SC were given 2 hr prior to behavioural testing, whereas SH was given 20 min prior to behavioural testing.

Test Condition. Subjects were randomly assigned to one of three treatment groups: LPS (200 μg/kg), SH (1mg/kg), or SC (0.9% saline). Rats received three habituation sessions in the apparatus to familiarize them with eating the reinforcer (food pellets, Test Diet purified rodent table 5TUL). Experimenters (blind to treatment conditions) trained and weighed subjects for 5 consecutive days, with each rat being trained for a minimum of 15-20 min/day. Training sessions shaped the subjects' behaviour by reinforcing successful approximations towards bar pressing. As training progressed, rats were gradually required to perform more specific behaviours such as sniffing or placing a paw on the lever to receive the reinforcer. The shaping eventually resulted in subjects repeatedly bar pressing to receive food rewards. One day after the 5-day training period, rats received a baseline session where they were placed in the apparatus for 14 min and the total number of bar presses was recorded. The test day session occurred two days after the baseline. Subjects were injected with their respective drug treatment and tested in the apparatus for a total of 14 min, incremented in 2 min time blocks. For every subject a maximum of two experimenters independently recorded data on (a) latency time (LT), the amount of time taken to make the first bar press; (b) total bar presses (TBP), recorded at the end of the 14 min; (c) rate of responding (RR), the number of bar presses per time block; (d) horizontal movements (HM), every time a rat's front two paws crossed the same line or crossed into a diagonal square on the floor; and (e) vertical movements (VM), every time a rat's front two paws were lifted off the floor and its snout crossed the vertical bisector.

Results

Pearson correlations were used to determine the inter-rater reliability for HM and VM, $r(61) = 0.96$ and $r(61) = 0.92$, respectively. Thus, only one rater's data was necessary for HM and VM statistical analysis. A series of separate mixed-design ANOVAs were performed on BP,

RR, HM, and VM to determine the significant effects ($\alpha < .05$) of LPS treatment and time blocks (or testing session) on positive reinforcement. For BP the between-subjects measure of drug treatment and the within-subjects measure of testing session consisted of three levels (LPS, SH and SC) and two levels (baseline and test day session), respectively. For RR, HM and VM the between-subjects measure of drug treatment and the within-subjects measure of time blocks consisted of three levels (LPS, SH and SC) and seven levels (seven time blocks, 2 min/time block), respectively. A one-way ANOVA was performed on LT to determine the significance of drug treatment, a between-subjects measure which consisted of three levels (LPS, SH and SC).

LT significantly differed across drug treatments groups, $F(2, 20) = 6.83$, $p = .005$. Rats in the LPS group displayed a significantly greater LT than SC rats, and a significantly lower LT than SH rats (Figure 1).

TBP significantly varied across drug treatment groups, $F(2, 20) = 24.53$, $p < .001$, with LPS rats demonstrating a lower number of TBP when compared to the SC group. However, rats in the LPS group displayed a significantly greater number of TBP when compared to the SH group (Figure 2). The number of TBP significantly decreased between the baseline and test day session, $F(1, 20) = 17.68$, $p < .001$. Additionally, a significant interaction between drug treatment and testing session affected TBP, $F(2, 20) = 10.29$, $p = .001$; rats in the LPS group demonstrated a greater decrease in TBP across testing sessions when compared to the SC group. LPS and SC rats demonstrated a less pronounced decrease in TBP across testing sessions when compared to SH rats.

LPS rats demonstrated a significantly lower RR when compared to the SC group, $F(2, 20) = 5.76$, $p = .01$, however they also demonstrated a significantly greater RR than SH rats (Figure 3). RR significantly decreased over the seven time blocks, $F(6, 120) = 14.21$, $p < .001$. A

significant interaction between drug treatment and time blocks also affected RR, $F(12, 120) = 2.39$, $p = .008$; LPS rats demonstrated a greater decline in their RR which began earlier when compared to SH and SC rats. Additionally, SH and SC rats displayed a similar decline in their RR across time blocks.

LPS rats displayed a significantly lower number of HM when compared to the SH and SC rats, $F(2, 20) = 3.90$, $p = .037$, however SH rats did not significantly vary from SC rats (Figure 4). HM significantly decreased over the seven time blocks, $F(6, 120) = 22.72$, $p < .001$. An interaction between drug treatment and time blocks also significantly affected HM, $F(12, 120) = 2.32$, $p = .011$; rats in the LPS group demonstrated less of a decline in HM across time blocks when compared to SH and SC group. Additionally, SH and SC rats displayed a similar decline in HM across time blocks.

Rats in the LPS group demonstrated a significantly lower number of VM when compared to the SC and SH group, $F(2, 20) = 7.06$, $p = .005$ (Figure 5). VM significantly decreased across the seven time blocks, $F(6, 120) = 15.83$, $p < .001$. A significant interaction between drug treatment and time blocks affected VM, $F(12, 120) = 2.16$, $p = .026$; rats in the LPS group demonstrated less of a decline in VM throughout time blocks when compared to SC and SH rats.

Discussion

LPS injected rats displayed a significant deficit in bar pressing responses when compared to the saline control group, measured by their greater LT and reduced RR and TBP in the Skinner box. LPS rats significantly differed on all bar pressing measures when compared to SH rats, displaying a reduced LT and greater RR and TBP. These results support the hypothesis and indicate that LPS decreases responses to positive reinforcement and leads to anorexic effects, which cannot be fully attributed to memory and learning impairments; LPS rats consistently

underperformed the saline control rats and outperformed the SH group on all bar pressing measures. The LPS group also revealed a significantly lower locomotor activity, measured by HM and VM, when compared to both saline control and SH rats. This suggests that LT increases and RR and TBP decreases in LPS rats are also influenced by impaired appetitive behaviour rather than just decreased food-motivated behaviour. Additionally, a significant interaction revealed a greater decrease in the RR across time blocks in LPS rats when compared to the saline control and SH group, suggesting that LPS diminishes food-motivated behaviour at a quicker rate. To further support the hypothesis of this study, LPS rats displayed a greater TBP reduction across baseline and test sessions when compared to the SC group, however SH rats experienced the greatest reduction. This indicates LPS rats became less motivated to bar press across sessions to a greater degree than saline control rats, but were not impaired to the extent of SH rats. Thus, the presence of supporting evidence suggests that LPS impairs bar pressing and leads to anorexia, interfering with locomotion and food-motivation. These results also demonstrate that attributing decreases in bar pressing to impaired memory is challenging, as LPS rats do not demonstrate the same level of deficit exhibited by SH rats.

McCarthy, Kluger and Vander (1986) also demonstrated that a peripheral intravenous dose of LPS significantly suppressed food intake in food deprived rats, paralleling the results described in this study. Additionally, Larson et al. (2002) displayed no difference in the expression of a place preference when animals were pretreated with LPS, IL-1β or saline control, even though LPS and IL-1β reduced consumption of sucrose solution. Place preference is a positively reinforced behaviour that was previously learned; these findings largely support the current study's finding that memory impairment is not the entire mechanism for reduced bar pressing in LPS treated rats. Furthermore, Larson et al. (2002) demonstrated that a reduction in

food intake is still present even when memory is intact, suggesting the presence of another underlying mechanism of LPS-induce anorexia, such as reduced food-motivated behaviour or impaired appetitive behaviour.

Roberts et al. (2003) evaluated the effects of LPS on feeding behaviour in rats and reported a pronounced reduction in voluntary intake of the sucrose solution, but when the same solution was infused directly the rat's mouth, no decreases in intake were displayed. These findings challenge previous studies which equate decreased bar pressing with a decrease in food-motivated behaviour. Instead, the researchers explain that it is the appetitive behavioural component which is adversely effected and results in the observed anorexia. The decreased locomotor activity described in the current study suggests a possible mechanism of LPS-induced impaired appetitive behaviour.

One limitation of the current study is the behavioural paradigm used to assess LPS effects on positive reinforcement. Since rats are required to be constantly orienting and moving themselves from lever to food reward, LPS-induced locomotor deficits towards appetitive behaviour make drawing conclusions about food-motivated behaviour very difficult. Although measuring locomotion helps to alleviate this confound, accurate interpretations of reduced food intake is still challenging. Intracranial self-stimulation (ICSS) or intraoral infusions are paradigms which would allow for better evaluation of LPS effects on positive reinforcement, greatly reducing the dependence on locomotor activity to generate a response. An additional limitation is the use of a single low effort and low reward FR-1 schedule to assess LPS effects on positive reinforcement. Vichaya, Hunt and Dantzer (2014) demonstrated that LPS only reduces reinforced responses for low rewards on FR-1 schedule, but actually results in an increase the percentage of responses for high rewards (chocolate-flavoured) on a FR-10 schedule. Thus, using

an incremented reward schedule with different rewards, could further reveal how LPS affects positive reinforcement when more than one choice is available.

In conclusion, the hypothesis that LPS-injected rats would be impaired in responding to a positive reinforcement was supported by the results; LPS rats underperformed SC rats in all measures of bar pressing including LT, TBP, and RR. Additionally, reduced locomotor activity, measured by HM and VM, demonstrated that rats may display anorexia due to impaired appetitive behaviour. These findings challenge some of the current literature's interpretation of LPS as reducing food-motivation. Future research should examine LPS' exact mechanism of action on isolated appetitive and consummatory behaviours involved in feeding and drinking. Additionally, assessing the effects of LPS on non-ingestive forms of positive reinforcement that do not depend on locomotor activity, such as ICSS, could reveal a clearer influence on positive reinforcement. Finally, future research on the effects of LPS on select memory tasks could further reveal its differential influence.

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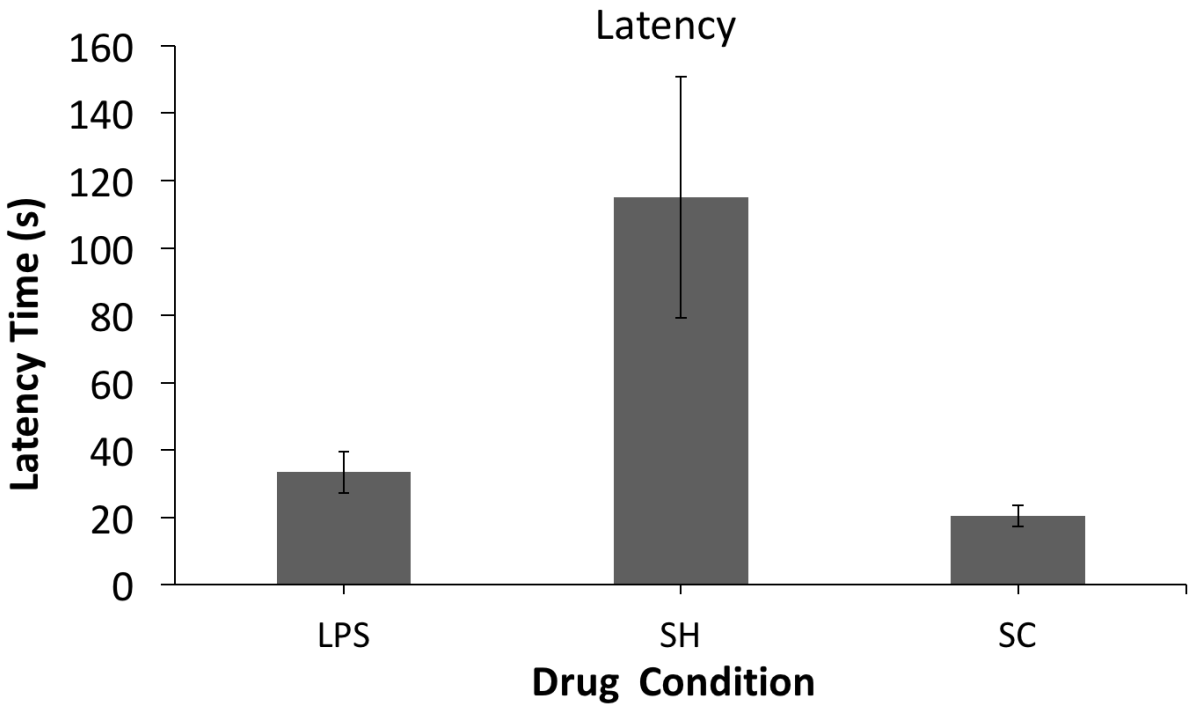

Figure 1. The average (± SEM) latency time (s) measured on test day for rats injected with either lipopolysaccharide (LPS; 200 μg/kg dissolved in 0.9% saline; $n = 8$), scopolamine hydrobromide (SH; 1mg/kg dissolved in 0.9% saline; $n = 7$), or a saline control (SC; 0.9% saline; $n = 8$). Rats in the LPS group demonstrated a significantly greater latency time when compared to the SC group. LPS rats displayed a significantly lower latency time than SH rats.

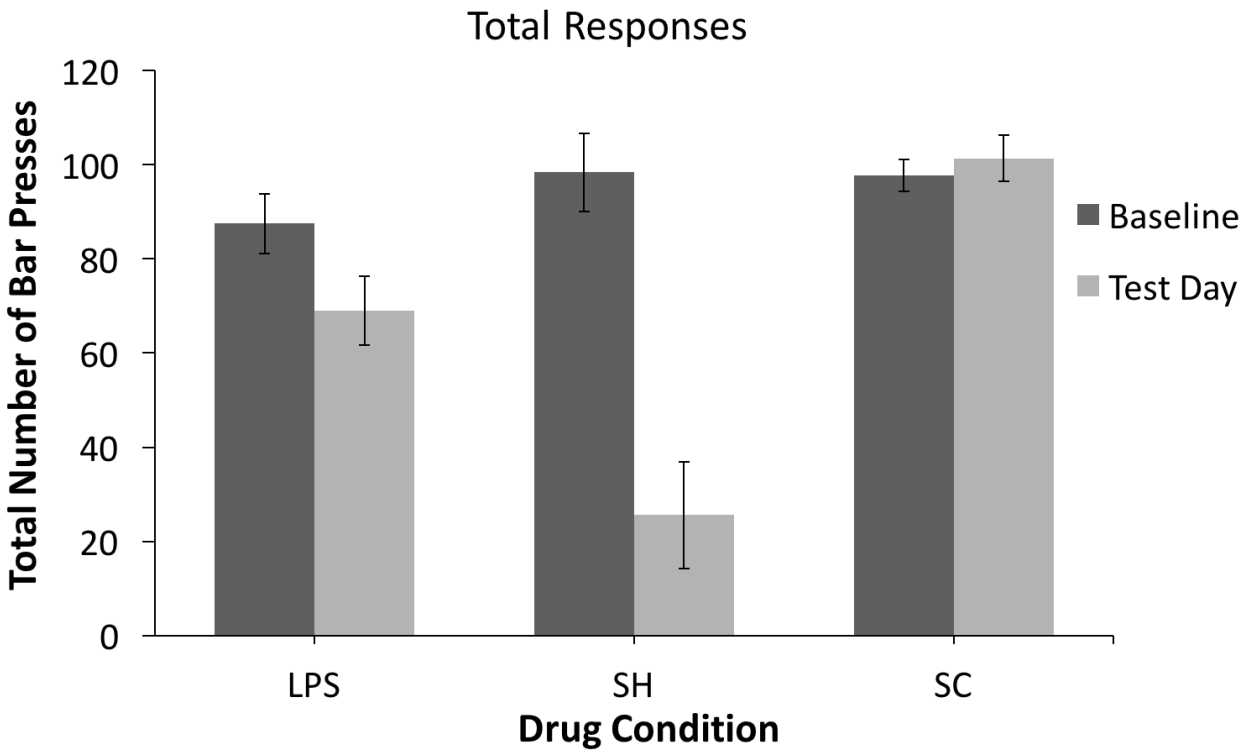

Figure 2. The average (± SEM) number of total bar presses (TBP) measured across baseline and test day sessions for rats injected with either lipopolysaccharide (LPS; 200 μg/kg dissolved in 0.9% saline; $n = 8$), scopolamine hydrobromide (SH; 1mg/kg dissolved in 0.9% saline; $n = 7$), or a saline control (SC; 0.9% saline; $n = 8$). LPS rats demonstrated a significantly lower number of TBP when compared to the SC group. LPS rats also displayed a significantly greater number of TBP when compared to the SH group. TBP significantly decreased between the baseline and test day session. Rats in the LPS group demonstrated a significantly greater decrease in TBP across testing sessions when compared to the SC group.

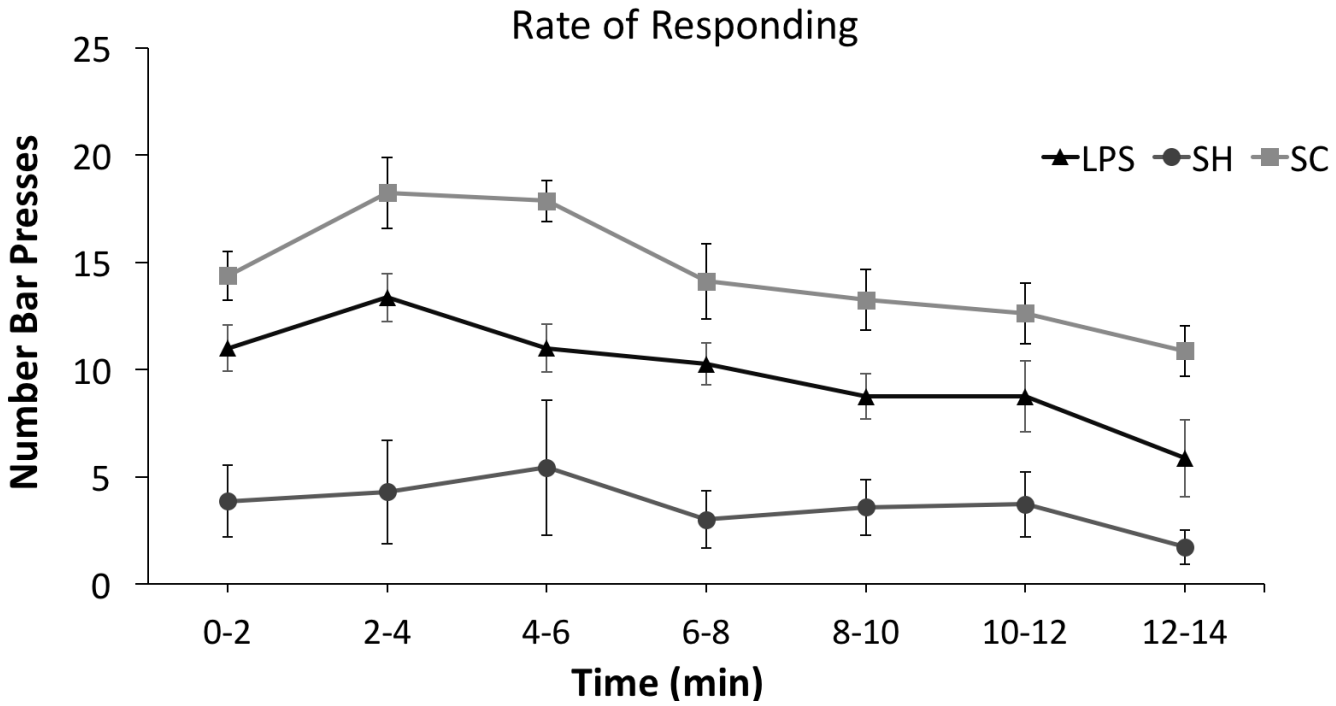

Figure 3. The average (± SEM) number of bar presses measured across seven 2-min time blocks for rats injected with either lipopolysaccharide (LPS; 200 μg/kg dissolved in 0.9% saline; *n* = 8), scopolamine hydrobromide (SH; 1mg/kg dissolved in 0.9% saline; *n* = 7), or a saline control (SC; 0.9% saline; *n* = 8). Rats in the LPS group demonstrated a significantly lower rate of responding when compared to SC rats, but displayed a significantly greater rate of responding when compared to SH rats. Additionally, rats in the LPS group demonstrated a greater decline in their rate of responding which began earlier when compared to SC and SH rats.

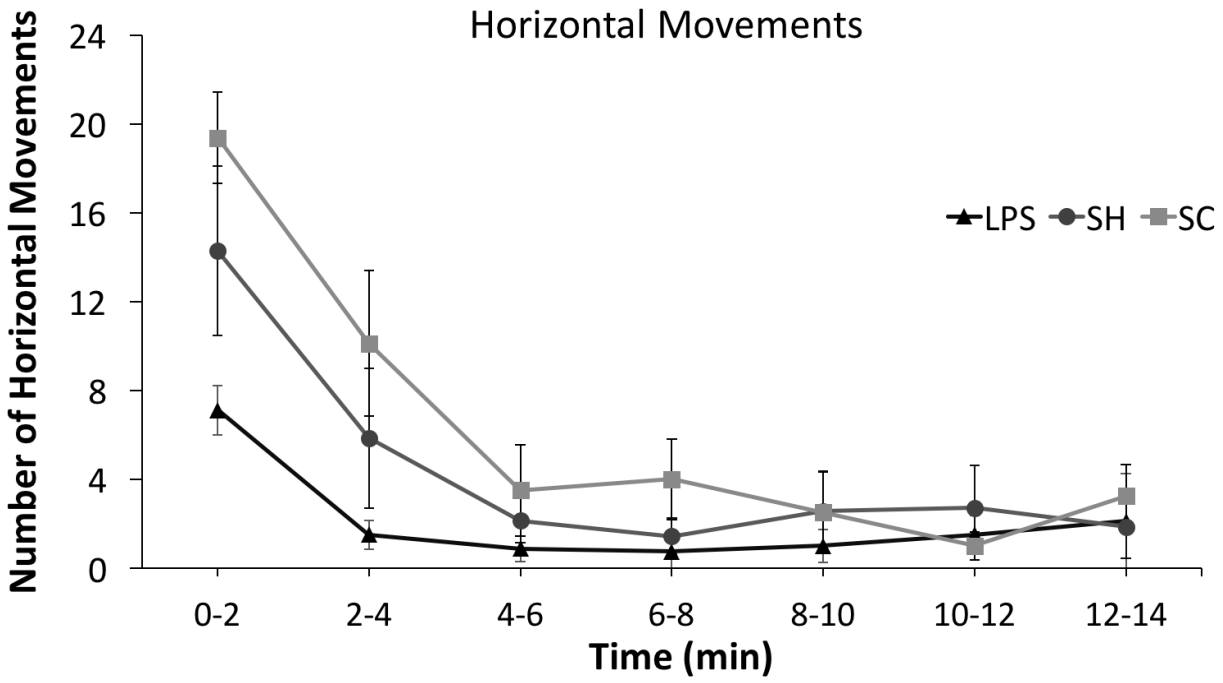

Figure 4. The average (± SEM) number of horizontal movements (HM) across seven 2-min time blocks for rats injected with either lipopolysaccharide (LPS; 200 μg/kg dissolved in 0.9% saline; *n* = 8), scopolamine hydrobromide (SH; 1mg/kg dissolved in 0.9% saline; *n* = 7), or a saline control (SC; 0.9% saline; *n* = 8). Rats in the LPS group demonstrated a significantly lower number of HM than SC and SH rats. HM significantly decreased across time blocks. Rats in the LPS group demonstrated a significantly slower decline in HM when compared to SH and SC rats.

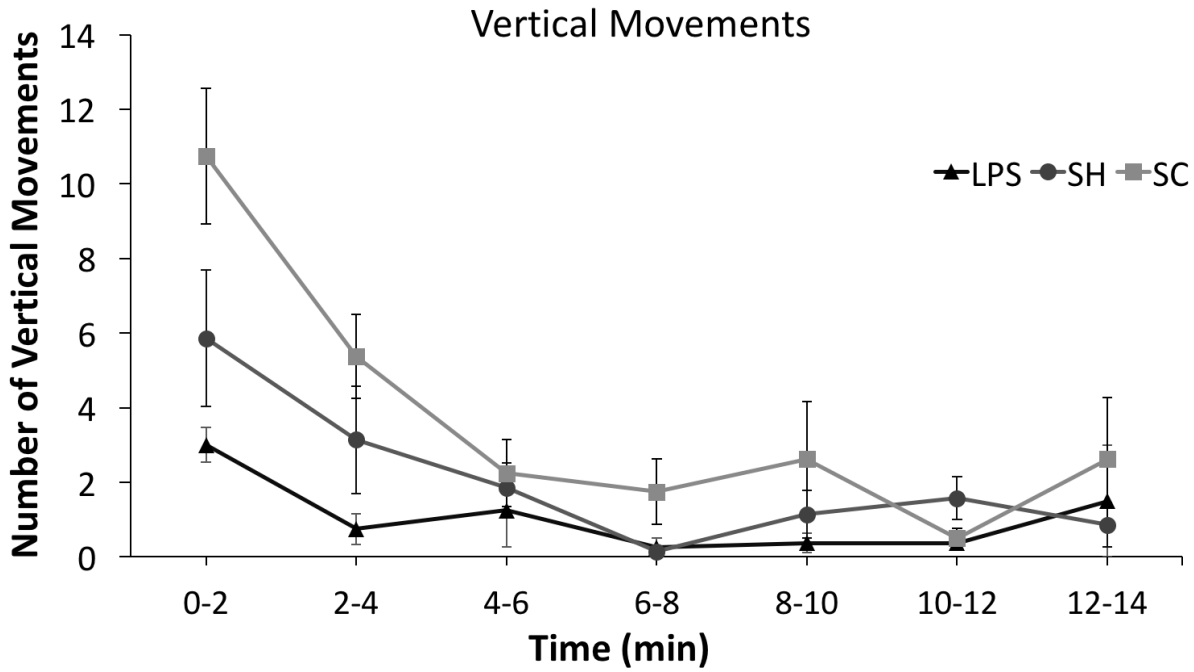

Figure 5. The average (± SEM) number of vertical movements (VM) across seven 2-min time blocks for rats injected with either lipopolysaccharide (LPS; 200 μg/kg dissolved in 0.9% saline; *n* = 8), scopolamine hydrobromide (SH; 1mg/kg dissolved in 0.9% saline; *n* = 7), or a saline control (SC; 0.9% saline; *n* = 8). Rats in the LPS group demonstrated a significantly lower number of VM than SH and SC rats. VM significantly decreased across time blocks. Rats in the LPS group demonstrated a significantly slower decline in HM when compared to SH and SC rats.