# DEVELOPMENT AND TEMPORAL ORGANIZATION OF COMPULSIVE CHECKING INDUCED BY REPEATED INJECTIONS OF THE DOPAMINE AGONIST QUINPIROLE IN AN ANIMAL MODEL OF OBSESSIVE-COMPULSIVE DISORDER

*Anna Dvorkin[1], Melissa L. Perreault[2] and Henry Szechtman[2]**

(1) Department of Zoology, Tel-Aviv University, Tel-Aviv, Israel

(2) Department of Psychiatry and Behavioural Neurosciences, McMaster University, 1200 Main St. West, Hamilton, Ontario, Canada L8N 3Z5

*Correspondence:

Dr. Henry Szechtman

Department of Psychiatry and Behavioural Neurosciences, HSC 4N82, McMaster University, 1200 Main St. West, Hamilton, Ontario, CANADA L8N 3Z5; Tel: (905) 525-9140 ext 22201; FAX: (905) 522-8804; E-mail: szechtma@mcmaster.ca

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**ABSTRACT**

Rats treated chronically with the dopamine D2/D3 receptor agonist quinpirole develop locomotor sensitization and exhibit compulsive checking of specific places in an open-field arena, a behavioral profile that may represent an animal model of obsessive-compulsive disorder. However, it is not known how compulsive checking develops across quinpirole injections nor whether checking behavior possesses a particular temporal structure. Male rats received quinpirole (0.5 mg/kg, twice weekly x 10) or an equivalent regimen of saline and were placed in a large open field for 55 min where their behavior was digitally tracked for subsequent analysis of checking behavior using existing and newly developed computer software. Results showed that the measures of compulsive checking did not follow a singular profile across injections: some remained constant and others changed monotonically reaching their near-maximum levels after about 5-7 quinpirole injections. Moreover, results showed that checking behavior was organized into bouts of checking, with the number of bouts, as well as the rate of checking within a bout, increasing across injections to reach near maximal levels after about 5-7 administrations of quinpirole. Finally, quinpirole-treated rats showed a paucity of long inter-bout intervals. These results suggest that: (a) compulsive checking emerges from the operation of at least two underlying processes: a regulated process, and a process of sensitization that intensifies the performance of checking behavior; and, (b) quinpirole treatment may attenuate a sense of satiety that could underlie the compulsive nature of checking. Finally, because key variables measured using the newly developed algorithms showed the expected profile, the present study provides validation for the use of this methodology for the analysis of checking behavior.

**KEYWORDS**: sensitization - obsessive-compulsive disorder – development – rats - checking bouts – satiety

**INTRODUCTION**

Rats treated chronically with the dopamine D2/D3 receptor agonist quinpirole (QNP) develop locomotor sensitization [2,12,20,26] and exhibit compulsive checking of specific places in an open field arena, a behavioral profile that may represent an animal model of OCD [8,11,19]. The usefulness of this model is further supported by the finding that the clinically effective serotonin uptake inhibitor clomipramine partially attenuates QNP-induced compulsive checking [19].

In the quinpirole model, compulsive checking was evaluated following the 10th drug injection, when the rats were already well sensitized to the locomotor enhancing effects of quinpirole [16,19,20]. Although the morphogenesis of the motor rituals under quinpirole had been described [1], there is no information on the development of checking behavior across sessions and thus it is unknown whether checking behavior is a single phenomenon or the result of several underlying processes. Therefore, the first purpose of the present study was to examine the development of compulsive checking behavior across quinpirole injections.

A second purpose of the present study was to evaluate whether or not checking behavior exhibits a temporal structure. Such information would be particularly relevant in light of a recent theory that described OCD as a disturbance of the security motivation system. In that theory, OCD is seen as the result of a failure to shut down the activated security motivation, a failure that occurs because performance of security-related behaviors such as checking do not generate the normal "satiety" feedback signal that indicates task completion [21,27,28]. The presence of a temporal structure in checking would be informative as to whether or not there is evidence of a satiety-like state produced by security-motivated checking behavior.

Finally, the present study had an additional objective. Thus far measures of checking behavior were obtained in our lab through manual scoring of video tape records of the rats' behavior. Here, we sought to establish whether the same findings would be observed by using an automated method, both by having the videotapes tracked by commercial software [13,15] and by having the obtained tracks analyzed by a combination of available [4] and custom-developed software.

## MATERIALS AND METHODS

### Subjects

Twenty-four experimentally naive male Long-Evans rats (Charles-River, Canada) weighing 200-250 g at the start of treatment were used. Rats were individually housed in a temperature controlled colony room (22°C) under a 12 h light-dark cycle, with free access to food and water. Rats were allowed to acclimatize to the colony room for one week following arrival and were handled two minutes daily for 7 days before the start of the experiment. All treatment and testing was conducted during the light hours. Animals were housed and tested in compliance with the guidelines described in the Guide to the Care and Use of Experimental Animals (Canadian Council on Animal Care, 1993).

### Drugs

Quinpirole hydrochloride (Sigma Aldrich) was dissolved in physiological saline and injected subcutaneously at a dose of 0.5 mg/kg. Rats were injected on a twice weekly schedule (eg, every Monday and Thursday, or every Tuesday and Friday). The particular dose and injection regimen of quinpirole was selected because the 0.5 mg/kg dose of quinpirole is representative of the behavioral effects induced by doses of the drug from 0.25 to 2.5 mg/kg, and because the locomotor effects of chronic treatment reach a plateau after 8-10 drug injections

administered 2 to 8 days apart [7,16,20] and reach the maximum effect at a dose of about 0.2 mg/kg [22].

**Apparatus**

Animals were tested in a large open field similar to the apparatus used previously to assess compulsive checking behavior [19] but consisting of a solid surface top (rather than a mirrored glass) table (160 x 160 and 60 cm high). The table top was constructed of material used in making kitchen counter-tops - it was smooth, non-porous, composed of unsaturated polyester and acrylic resin blends (Acryflek Industries; http://www.acryflek.ca/product/index.shtml), and had a custom blue color to facilitate video detection of dark and white objects. Four small Plexiglas/glass boxes (approximately 8 x 8 x 7.5 cm) were present at the same fixed location of the open field throughout the study: two at corners and two at places near the center of the open field. The open field platform was subdivided into 25 rectangular places (locales) used to define the location of the animal in the field. The open field and objects were wiped clean after each rat with a diluted solution of an antibacterial cleaner (Lysol). Behavior was videotaped continuously by a camera (Ikegami ICD-47) affixed to the ceiling, providing a stationary top view of the entire open field and the rat in it. Videotapes were converted to MPEG files (Canopus MPEGPro EMR realtime MPEG-1 MPEG-2 encoder) and these digitized videos were used to automatically track the trajectories of locomotion in the open field using EthoVision 3.0 (Noldus Information Technology bv, Netherlands) system [13,15]. The spatial sensitivity of the tracking system was 8 mm x 8 mm per pixel, with a temporal resolution of 30 frames per second.

**Design and procedure**

Two groups of rats were tested (N=12/group): the experimental group received injections of quinpirole (QNP), while the control group received a similar regimen of saline injections.

On the day of testing, animals were weighed, transported in their home cage to an adjoining non-colony testing room, and administered the appropriate injection. Immediately afterwards, rats were placed into the open field for 55 minutes and their behavior videotaped for offline analysis. Videotapes from injections 1, 3, 5, 7, 9, and 10, were processed for analysis.

**Behavioral analysis**

*Locomotion in the open field*

Two aspects of locomotor activity in the open field were quantified in the present study: distance traveled and the spatial distribution of locomotor trajectories. Such quantitative information was extracted from the time series of *x,y* coordinates in the EthoVision track files, using a software package designed for analysis of locomotor behavior, the SEE Basic software [4] (available at http://www.tau.ac.il/~ilan99/see/help). In actual practice, measures of locomotor activity are calculated using EthoVision trackfiles that had been pre-processed to remove noise from the digitized tracking data (by applying appropriate filtes to smooth the *x,y* coordinates) and the smoothed *x,y* coordinates subdivided into episodes of forward locomotion (*progression*) and episodes of small movements or immobility (*lingering*). The rationale and detailed description of the relevant methods are described elsewhere [3,4,9,10] and were followed in the present study with the exception of using a transformation of Cubic Root during segmentation and imposing no more than three Gaussians in the Gaussian mixture.

Total distance traveled was calculated as the sum of distances moved in progression segments and lingering episodes. To describe the spatial distribution of locomotor trajectories, two indices were used: *path stereotypy ratio* and *area of 2 standard deviational ellipse*,

computed according to the method detailed elsewhere [5]. The first index, path stereotypy ratio, reflects the relative frequency of repetitions of travel along the same paths while the second index is a measure of the extent of the area covered by the trajectories of locomotion.

*Compulsive checking behavior*

Measures of checking behavior were obtained previously from the time series of *stops* in different locales of the open field [19], where a stop (also referred to as a *visit* to the place) is the interval between two episodes of forward progression [6]. Previously, stops had been scored by an observer watching the video records of behavior in the open field. In the present study, a software algorithm was used to directly identify such stops from EthoVision trackfiles, and automate the scoring and measurement of checking behavior.

To identify the start and end of a stop, it was necessary to introduce an additional criterion to the ones used in SEE for the division of the smoothed *x,y* coordinates into progression and lingering episodes. Specifically, by observing the video records of quinpirole-treated rats, it was noted that while episodes of lingering identified by the software corresponded well to stops scored by an observer, there were brief events, which the observer defined as stops, but the software did not recognize as lingering episodes. On examination, it was found that during these brief events the rat performed either rapid deceleration or slow movement within progression, not reaching a complete stop (zero speed) in both cases. To identify a criterion that would demarcate rapid decelerations, changes in speed within episodes of progression were computed by calculating the ratios of minimal to maximal speeds and a density function of these ratios was plotted. The resultant function was multi-modal and the threshold was set at the appropriate valley to eliminate extremely small changes in speed. The obtained value served to extract the sequence of *x,y* coordinates that defined the extent of each

event. Slow movement within progression was identified using an additional criterion, namely, the presence of low speeds similar to the ones characteristic of lingering episodes. The two types of events identified according to these criteria are referred to as pseudolingering segments. Pseudolingering segments, together with lingering episodes, are defined as stops for the purpose of characterization of checking behavior.

Because checking behavior had been measured previously using a coordinate system of 25 locales (places) that subdivided the open field arena [19], a similar subdivision of the open field was implemented in the present study and the frequency of visits and the duration of stops in each locale computed accordingly. These values were used to identify the home base locale, defined as the place with the maximal cumulative duration of stay [6]. Checking behavior was measured with reference to this home base as done previously [17,23]. The following measurements of checking behavior were computed: absolute and relative frequency of checking the home base, absolute and relative checking recurrence time, number of locales visited before returning to the home base, and mean duration of visit to home base (a visit to home base is often referred to as a *check*). These dependent variables were defined during previous studies of checking behavior [17,19,23], except for *relative checking recurrence time*, a measurement introduced here as an additional index bearing relatively little dependence on the level of hyperactivity; it is computed by normalizing the mean return time to the home base to the mean return time to every place that was visited more than once. As reviewed elsewhere [8,18], these measures are said to reflect two characteristics of compulsive checking – a preoccupation with the performance of the behavior and a reluctance to leave the place/object on which the behavior is focused.

*Bouts of checking behavior*

In the present study, bouts of checking behavior were identified and served as the units to describe dynamics of checking across injections. A bout of behavior is generally defined by examining the distribution of time intervals between behavioral events to locate a natural split between two clusters of inter-event intervals, a split that would separate time intervals into a class of intervals that are between the bouts of behavior (inter-bout intervals) and a class of intervals that belong within a bout of behavior (intra-bout intervals). Several statistical approaches have been described to identify the bout criterion interval, but these methods are dependent on a large sample of inter-event intervals [24,25,29]. Considering the modest size of our sample, we used an approach that is geared more specifically to the present data and is thus less general. A two step process was used to identify the bout criterion threshold. In the first step, because checking behavior is dependent on locomotor activity, bouts of activity were identified and were used as one criterion to delimit bouts of checking behavior. In the second step, a second criterion was employed to identify bouts of checking within the bouts of locomotor activity. Thus, bouts of checking were defined both by the threshold interval for activity bouts and by the threshold interval for checking within locomotor bouts. The same procedure was employed to identify the threshold criteria for locomotor and checking bouts, a procedure that was applied to each individual animal, and regardless of whether it was treated with quinpirole or saline. Specifically, to define locomotor bouts, the distribution of lingering durations (that is, the time intervals between locomotor events) within a test session was used to calculate statistical outliers and so identified long lingering episodes served to divide the sequence of locomotor events into bouts of activity. Similarly, to define checking bouts within bouts of activity, the distribution of return times to the home base was used to calculate statistical outliers and the identified long return times served as the inter-checking bout intervals.

Thus, bouts of checking were separated by long lingering episodes and by long return times, moreover, to avoid spurious artifacts, a bout of checking had to contain at least one visit to the home base and at least two progression segments.

Several measures were computed to characterize checking bouts. These measures included: the number of bouts in a test session, the total time engaged in checking bouts (calculated as the sum of bout durations in the test session), the mean time to next checking bout (calculated as the average duration of inter-bout intervals), as well as the frequency and the rate of checks within a checking bout. The latter two measures were calculated on a per bout basis as the average return frequency to the home base and the average reciprocal return time to the home base, respectively. Unless noted otherwise, each rat contributed a single score for computation of group means; for measures occurring multiple times in a rat (eg, the number of checks in a bout when the rat had several bouts of checking in the test), the score for each rat was the mean of the multiple occurrences.

**Statistics**

For statistical analysis of each dependent variable, a Group x Injections analysis of variance (ANOVA) with repeated measures on the second factor was employed. The Group factor had 2 levels (quinpirole versus saline), and the Injections factor had 7 levels (injections 1, 3, 5, 7, 9 and 10). The chosen level of significance was $P < 0.05$. Calculations were performed using SPSS 13.0 for Windows. Values in graphs are means ± SEM.

**RESULTS**

**Locomotion and spatial dispersion**

Figure 1 shows that the distance travelled by quinpirole-treated rats increased as a function of repeated quinpirole injections, confirming the presence of the expected locomotor

sensitization to quinpirole [16,20]. As shown in Table 1, the fitted asymmetric sigmoid curve suggests that the half-maximum response was reached after 4.1 ($\pm$ 0.3) quinpirole injections, that the maximum response was more than 6-fold of the acute response, and that the slope of the curve was 3.4 ($\pm$ 0.6), values that are within the range of those found in previous studies [14,16,20].

The increase in distance travelled was accompanied by a change in the spatial distribution of locomotion. Specifically, as shown in Figure 2, the trajectories of locomotion became dispersed over a wider area during the course of successive quinpirole injections (*left panel*) while the paths of locomotion became more restricted with animals travelling more and more along the same routes (*right panel*). In contrast, saline rats did not show any changes in either of these measures of spatial distribution. However, the spatial dispersion of locomotion in saline rats was different than in the quinpirole treated animals: saline controls spread their trajectories over a wider area of the open field (Group x Injection interaction, $F(5,110) = 11.3$, $p < .001$) and their routes were less stereotyped compared to quinpirole rats (Group x Injection interaction, $F(5,110) = 4.3$, $p = .001$).

**Measures of checking behavior**

Figure 3 shows the profiles in measures of compulsive checking behavior across successive quinpirole injections. Two patterns are evident: a fairly constant level across injections (fig 3c, d, and e) and a monotonic change during the course of quinpirole treatment (fig 3a, b, f). The measures that showed no significant change across injections – checking recurrence time, relative checking recurrence time, and number of locales visited before returning to home base – were significantly lower in quinpirole treated animals (Group effect, $p < .001$ for each variable), suggesting a restriction on the duration of time that quinpirole animals

spend outside the home base. Moreover, the level of restriction was present from the very first injection of quinpirole and was constant throughout. This suggests that these measures may be controlled variables in the sense that behavior of the animal is so organized as to maintain them at a fixed level. In contrast, the other 3 measures of checking behavior either increased (frequency of checking and relative frequency of checking; Fig 3a, b) or declined (mean duration of visit to home base; Fig 3f) across quinpirole injections, showing the typical profile of sensitization to quinpirole.. As is evident from inspection of the figure and the parameters in Table 1, these measures reached near saturation levels between quinpirole injections 5 and 7.

**Checking bouts**

To examine the nature of the temporal organization of checking behavior, we analyzed the distribution of intervals between successive checks (visits to home base) and identified the longest intervals as the criterion for division of the temporal sequence of checking into bouts (see Methods). Figure 4 illustrates the temporal division into bouts obtained by this method and Fig 5a shows the relative frequency distribution of inter-bout intervals for quinpirole- and saline-treated rats. Because of the limited sample size, the distribution of inter-bout intervals was computed using all data from every rat pooled across injections. As is evident from an inspection of the figure, there was an absence of long inter-bout intervals in quinpirole-treated rats, compared to the saline animals. Instead, there was an excess of short inter-bout intervals in quinpirole rats. A similar picture emerged when the mean inter-bout interval was computed across injections (Fig 5b *right*): this mean time to the next checking bout was significantly shorter in quinpirole rats compared to the saline controls from injection 5 onwards ($p < .05$, t-tests).

The shorter duration of inter-bout intervals in quinpirole rats was accompanied by a greater number of checking bouts during the session (Figure 5b *left*). This higher frequency of bouts became marked during the later injections of quinpirole, as evident by a significant Group by Injection interaction ($F(5,110) = 4.6$, $p = .001$). Surprisingly, the total duration of checking bouts remained constant across injections (Figure 5b *center*), as evident by the presence of only a significant Group effect ($F(1,22) = 41.1$, $p < .001$). However, the lack of an increase may reflect the presence of a ceiling effect, as the duration of the testing session (3300 sec) is very close to the observed total duration of checking bouts.

Figure 6 examines the properties of checks within a bout. As shown in Fig 6 (*left*), the number of checks in a bout increased across quinpirole injections (Group x Injection interaction, $F(5,110) = 3.7$, $p = .004$). Moreover, not only the frequency but also the rate of checks in a bout, increased across quinpirole injections (Group x Injection interaction, $F(5,110) = 5.1$, $p < .001$; Fig 6, *right*). Both the frequency and rate of checks in a bout seem to have reached their near peak levels between quinpirole injections 5 and 7.

**DISCUSSION**

The present study showed that in addition to the well established sensitization of locomotor distance to repeated injections of quinpirole [2,12,20,26], there was also a sensitization of the spatial dispersion and organization of locomotor trajectories. Moreover, the study revealed that compulsive checking behavior underwent orderly changes across injections but the pattern shown by the measures of checking behavior was more complex, with some measures changing monotonically across injections while other measures remaining constant throughout. Finally, the present results showed that checking behavior is organized into bouts that have markedly different properties in quinpirole- and saline-treated rats. Together, these

findings show that there exist levels of organization of checking behavior, having different time courses of development across quinpirole injections. They also suggest that the compulsive nature of checking behavior in quinpirole rats may be related to a diminished sense of satiety that would normally accompany a bout of checking. We elaborate on these points below.

**Sensitization of compulsive checking behaviour**

Previous studies have described compulsive checking behavior in well-sensitized rats following a course of chronic quinpirole treatment [17,19,23]. Considering the gradual change in distance travelled across quinpirole injections, together with a similar profile for the spatial organization of locomotor trajectories, it may be surprising that a similar pattern of sensitization was not shown for compulsive checking behavior. Instead, there was an uncoupling between the different measures of checking behavior. On the one hand, checking recurrence time and the number of locales visited between successive checks remained constant and unchanged across injections, in both quinpirole and saline rats. On the other hand, the number and the duration of checks showed a gradual change across quinpirole injections. Stated another way, the more rapid recurrence of checking and the lower number of locales visited between checks were present in quinpirole rats from the time of their first injection while the appearance of a significant difference in the number and duration of checks required several drug injections. This pattern of results may indicate that there exist distinct processes underlying these aspects of checking behavior, as discussed below.

The fact that checking recurrence (and number of places visited between checks) remained constant across injections may indicate that the time that the animal could spend outside the home base is tightly regulated, as if it were a controlled variable with behavior organized to keep the interval between checks at a relatively fixed set-point. For quinpirole rats,

this interval between checks is extremely short (about 25 seconds), and is consistent with the low number of locales visited between successive checks. The fact that these effects were present from the very first injection and remained constant throughout suggests that the changes in checking behavior that appeared after several quinpirole injections reflect another process, a process no doubt constrained in its development by the time limit that the rat could remain outside the home base (and similarly by the restriction on the number of places visited between successive checks). This second process, by increasing the frequency of checks and reducing the duration of visits in the home base, is probably what makes checking behavior more intense and gives it a compulsive appearance in the quinpirole sensitized rat. It is noteworthy that the intensification of checking behavior was concurrent with increases in locomotor activity across quinpirole injections. However, while an increase in locomotor activity is necessary for the intensification of checking behavior, locomotor hyperactivity alone cannot account for the increase in checking, as shown for instance by two measures of checking behavior that are relatively independent of the amount of activity, namely, the relative frequency (Fig 3b) and the relative recurrence (Fig 3d) of checking.

The compulsive appearance of checking behavior, as indexed by the affected measures reaching near maximum sensitization level, was full-blown already by quinpirole injections 5 to 7. Thus, compulsive checking may not require the 10 quinpirole injections used in previous studies [17,19,23]; 7 quinpirole injections may be sufficient. However, the present data shows a trend for the variance of the measures to be somewhat smaller at end of treatment (compared to injections 5-7), suggesting that the phenomenon may be more robust with the higher number of quinpirole injections.

**Dynamics of compulsive checking**

The present study reveals that checking behavior is organized into bouts; that is, there are clusters of checking activity separated by relatively long periods without such checking. A most striking feature of the comparison between the quinpirole and saline-treated rats is the absence of relatively long inter-bout intervals in the quinpirole animals. One plausible interpretation for long inter-bout intervals is that they represent periods of satiety. For instance, in considering what constitutes a "meal," it had been suggested that long intervals between periods of eating indicate the presence of post-ingestion satiety [24]. Using similar logic, the absence of relatively long inter-bout intervals in quinpirole rats, suggests that rats engaged in compulsive checking do not experience the same level of satiety as do saline controls. The present data does not permit the conclusion that quinpirole rats experience no satiety at all from their checking but only that it is less extensive than in controls. Nevertheless, the findings in the quinpirole model of compulsive checking are consistent with the theory that OCD reflects a dysfunction of a satiety signal that normally accompanies the performance of security-related behaviors such as checking [21,27,28].

In addition to the change in the timing between bouts, the number of bouts increased across quinpirole injections. Furthermore, there was an increase of checking within a bout, as evident from the rate of checking and the number of checks in a bout (see Figure 6). The present study does not address the question as to whether these changes reflect the existence of an altered within-bout satiety or some other processes.

In summary, the present study revealed that compulsive checking emerged from the operation of at least two underlying processes: a regulated process to keep the time outside the home base within a short and narrow range, and a process of sensitization that intensified the performance of checking behavior. The regulated process of time outside home base may

involve also the number of places visited between checks or the latter may be a separated process in itself – the present study cannot distinguish between these possibilities. The operation of these processes to yield compulsive checking appears to reach near maximum levels after about 5-7 quinpirole injections, although the variance of the measures of checking behavior appears to decrease with further treatment. The development of compulsive checking is represented also by changes in the temporal organization of checking as shown by the presence of checking bouts. Interestingly, quinpirole-treated rats show a paucity of long inter-bout intervals, suggesting a diminished sense of satiety. Finally, it should be noted that the measures of checking behavior in the current study were obtained using a method developed for the analysis of locomotion [4] and a custom-developed algorithm to compute checking behavior from digitized video tracking data. Considering the close correspondence between common results from the present and previous studies, this provides validation for the newly developed methodology, and supports its use in future studies.

**Figure legends**

**Figure 1**. Development of locomotor sensitization to repeated injections of quinpirole (0.5 mg/kg, every 3-4 days). Left y-axis represents total distance that rats moved during the 55 min session while the right y-axis shows the equivalent distance per min. Values are mean±SEM. The smooth line fitted to the quinpirole-treated rats (QNP) represents the hyperbolic function with parameters presented in Table 1; the function did not fit the saline-treated rats (Sal).

**Figure 2**. Changes in spatial distribution of locomotion in the open field during the course of 10 quinpirole injections as indexed by 2 standard deviational ellipse (*left*) and the path stereotypy index (*right*). The smooth line fitted to the quinpirole-treated rats (QNP) represents the hyperbolic function with parameters presented in Table 1; the function did not fit the saline-treated rats (Sal).

**Figure 3**. Development of compulsive checking across 10 quinpirole injections, as indexed by (**a.**) absolute and (**b.**) relative frequency of visits to home base, (**c.**) absolute and (**d.**) relative return time to home base, (**e.**) number of locales visited before returning to home base, and (**f.**) duration of visit to home base. The smooth lines fitted to measurements describing quinpirole-treated rats represent the hyperbolic functions with parameters presented in Table 1; solid lines indicate that these functions did not fit the data. Legend: QNP = quinpirole-treated rats; Sal = saline-treated rats.

**Figure 4**. Illustration of the division of locomotor activity into bouts of checking. The top and bottom rows show the first 25 min of the behavior of a quinpirole- and saline-treated rat, respectively. Each vertical line within the rectangular frame represents an episode of progression that occurred at the indicated time. The clustering of episodes of progression is used

to define the bouts of activity (shown by the upper red horizontal bar) using the criterion described in the Methods. These bouts of activity, together with the criterion related to the recurrence of visits to the home base (see Methods), define the checking bouts shown by the lower blue horizontal bar. Visits to home base (checks) are shown above the frame by black rectangles with their width proportional to the length of stay in the home base. Only 25 minutes of the session are shown to permit an adequate display resolution.

**Figure 5**. Temporal organization of compulsive checking across 10 quinpirole injections. (**a.**) Characteristics of inter-bout intervals as indexed by the relative frequency of time to the next checking bout in quinpirole (*left*) and saline-treated rats (*right*) pooled across all injections. (**b.**) Properties of checking bouts across injections as indexed by the number of bouts in a session (*left* panel), the total time engaged in checking bouts (*middle* panel), and the mean time to next checking bout (*right* panel). Legend: QNP = quinpirole-treated rats; Sal = saline-treated rats.

**Figure 6**. Changes across quinpirole injections in the organization of checks as indexed by the frequency (*left*) and the rate of checks (*right*) within a checking bout. The smooth line fitted to the quinpirole-treated rats represents the hyperbolic function with parameters presented in Table 1; solid lines indicate that this function did not fit the data. Legend: QNP = quinpirole-treated rats; Sal = saline-treated rats.

Table 1: Estimate and SE of parameters for the curves in Figures 1 to 6

| Fig # | Variable | Parameter[1] | | | | $r^2$ |
|---|---|---|---|---|---|---|
| | | $I_{50}$ | $R_{max}$ | $n$ | $R_{min}$ | |
| 1 | Average distance | 4.08±0.26 | 6.54±0.36 | 3.40±0.65 | 0.4 | 0.993 |
| 2 | 2 SDE | 3.67±0.29 | 3.52±0.12 | 2.38±0.42 | 1.73 | 0.996 |
| 2 | Path stereotypy | 3.49±0.16 | 4.72±0.07 | 4.61±0.61 | 2.83 | 0.993 |
| 3a | Checking frequency | 3.52±0.11 | 128.5±2.5 | 4.70±0.62 | 24.2 | 0.997 |
| 3b | Relative checking frequency | *2.59±2.49* | 5.79±0.11 | *8.81±58.9* | 3.44 | 0.977 |
| 6 | Checking rate | 3.99±0.64 | 0.14±0.02 | *3.72±1.94* | 0.03 | 0.971 |

[1] Equation (see Methods) fitted to the data for the indicated variables and shown in Figures 1 to 6. $I_{50}$ is the number of drug injections required to reach the half-maximal response, $R_{max}$ is the maximal response, $n$ is a parameter describing the sigmoidicity of the curve, $R_{min}$ is the lowest response that served as a fixed parameter in the equation, and $r^2$ indicates the square of the correlation coefficient between raw and fitted data. Standard error (SE) refers to the standard error of the estimate of the parameter; the estimate of each parameter is statistically significant except for the values indicated in italic font.

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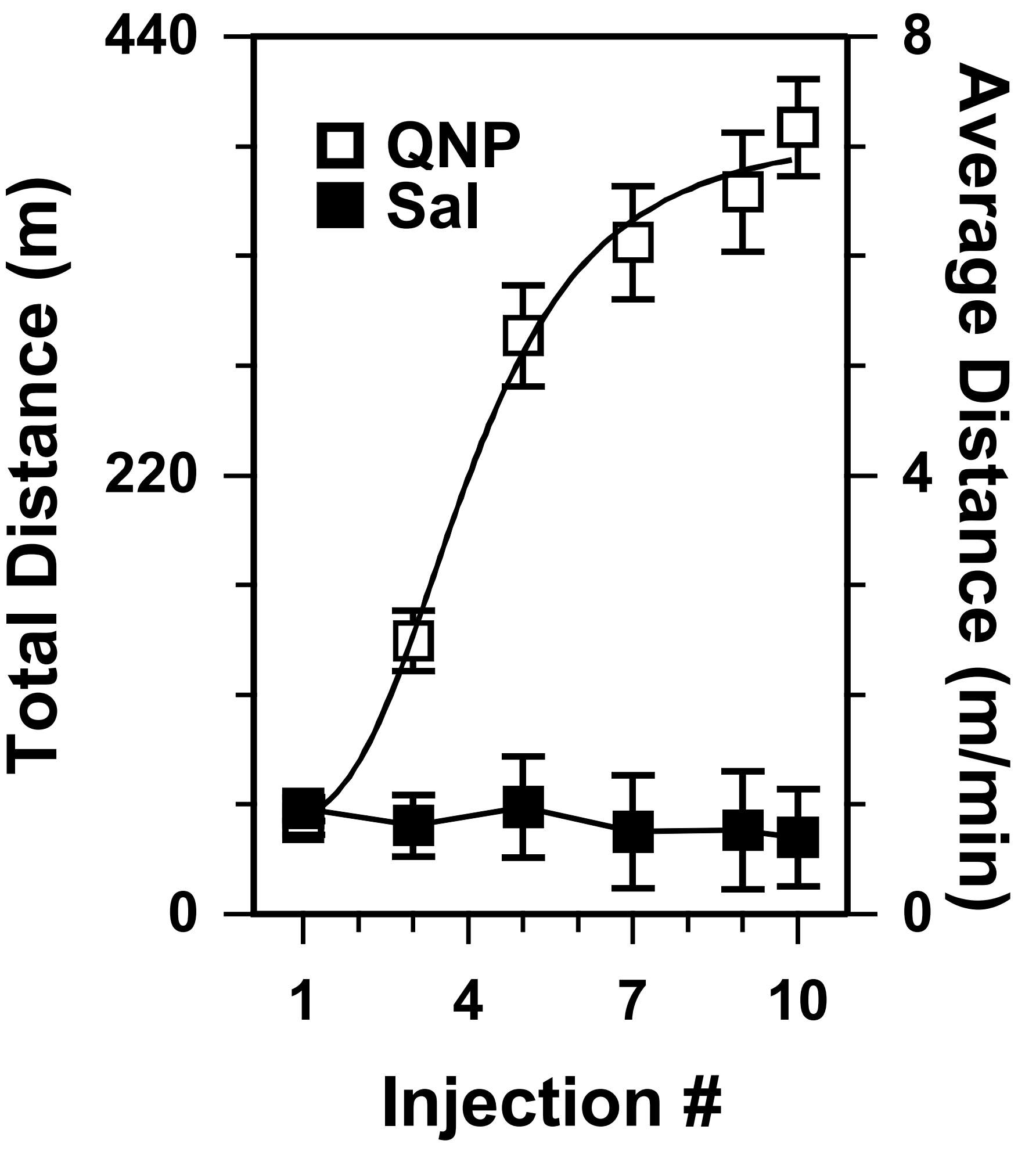
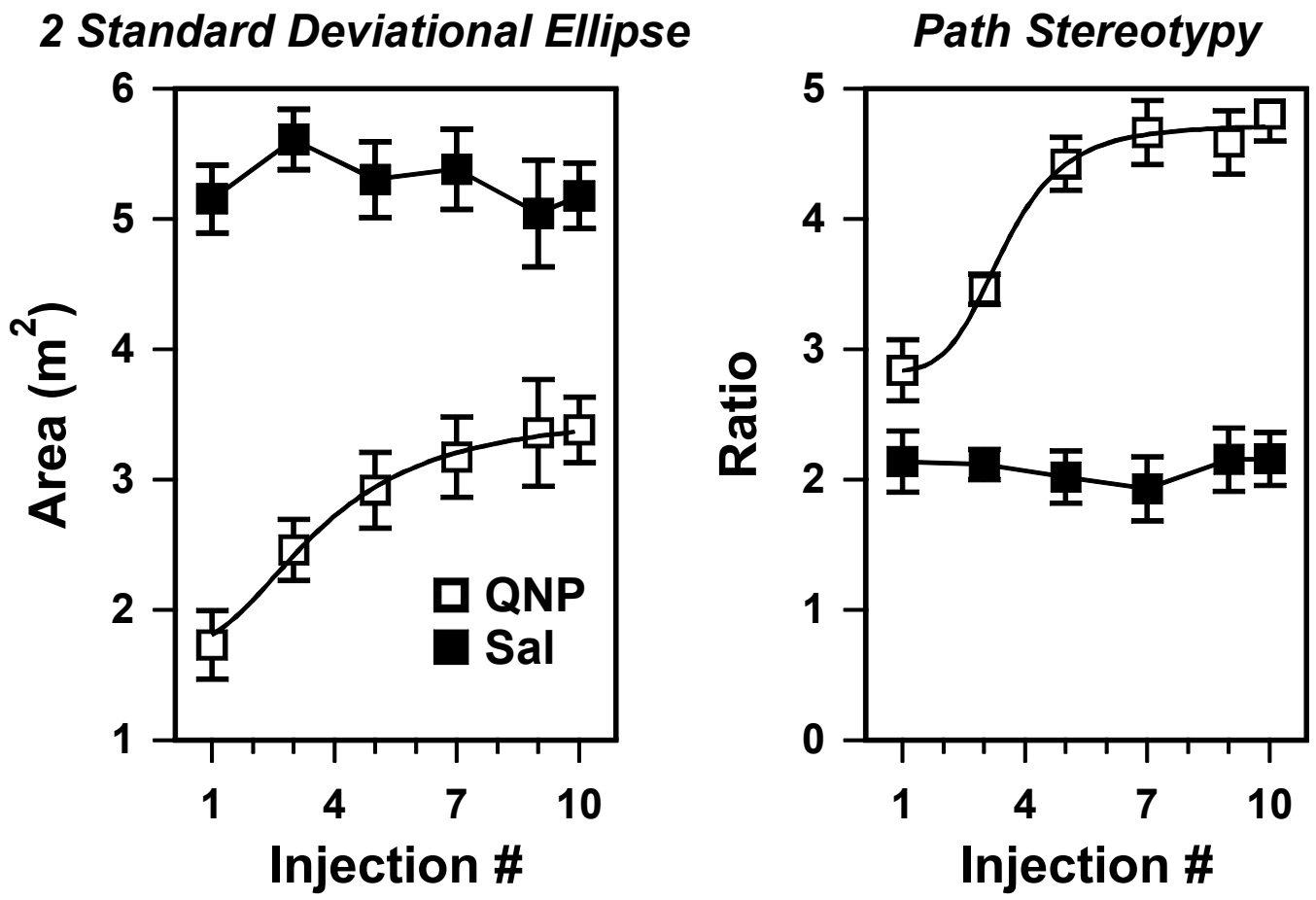
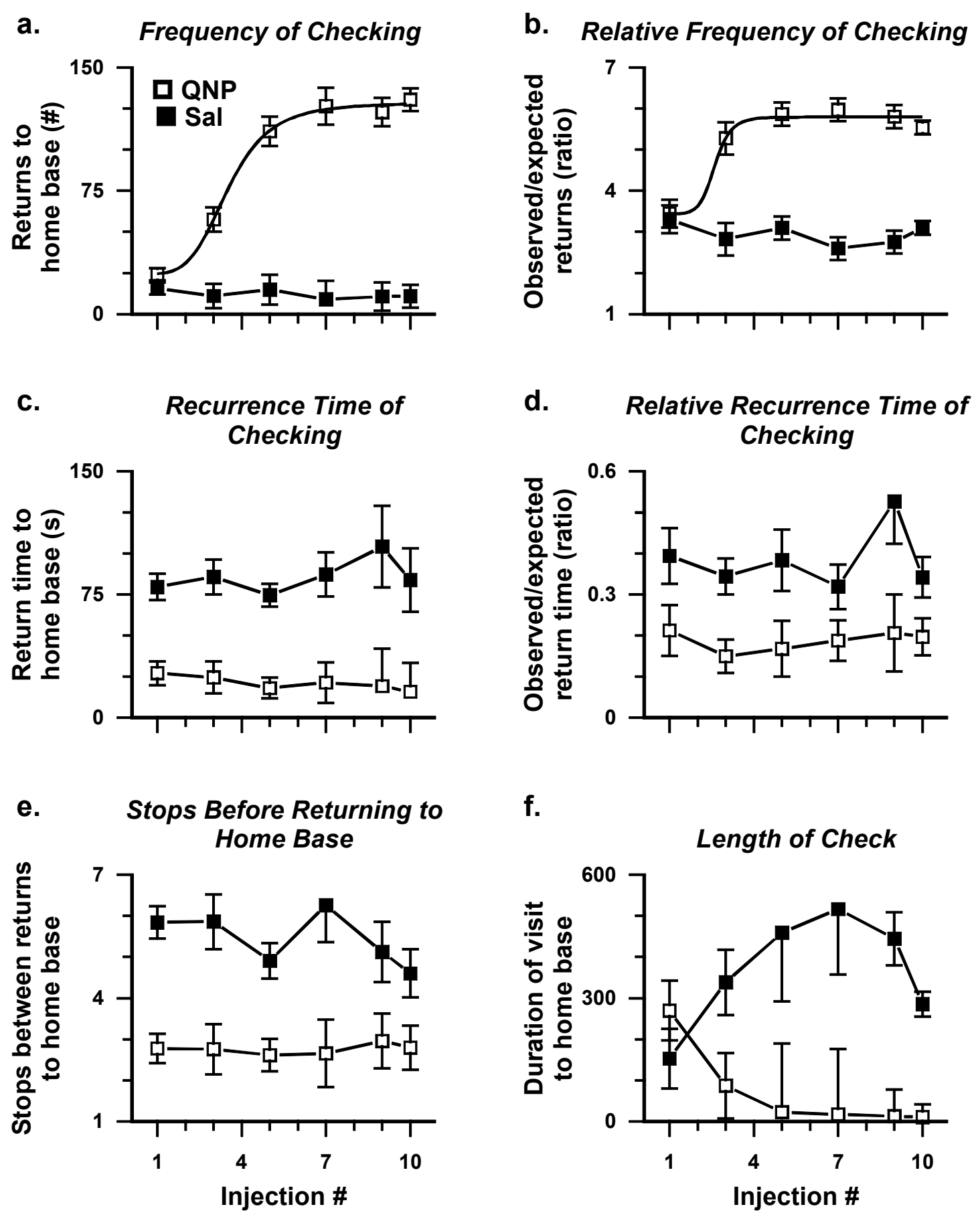
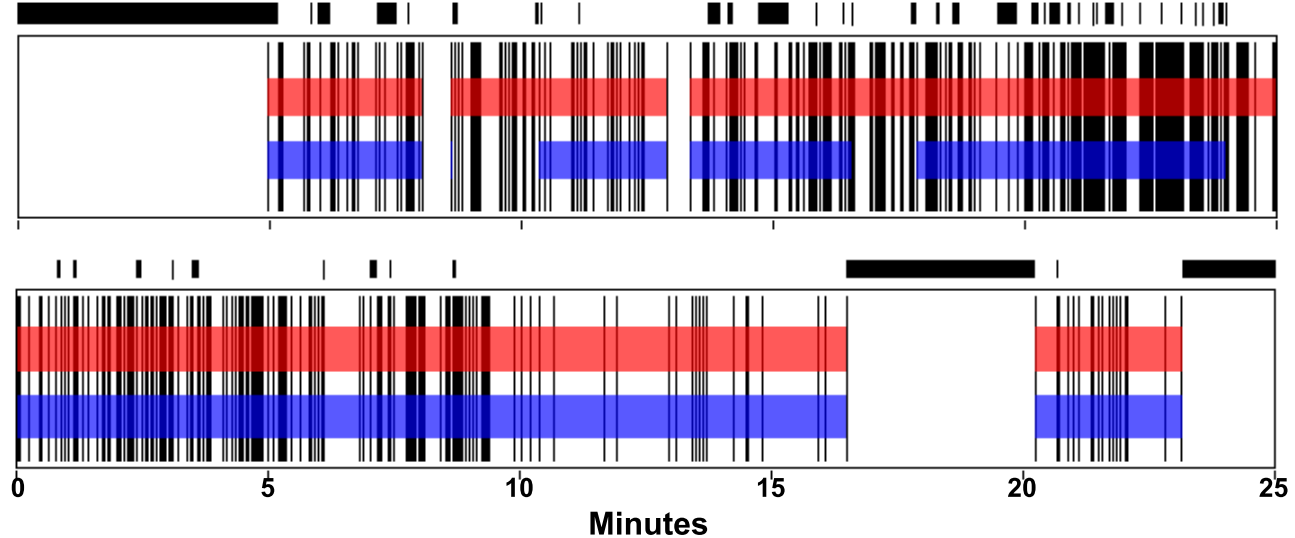
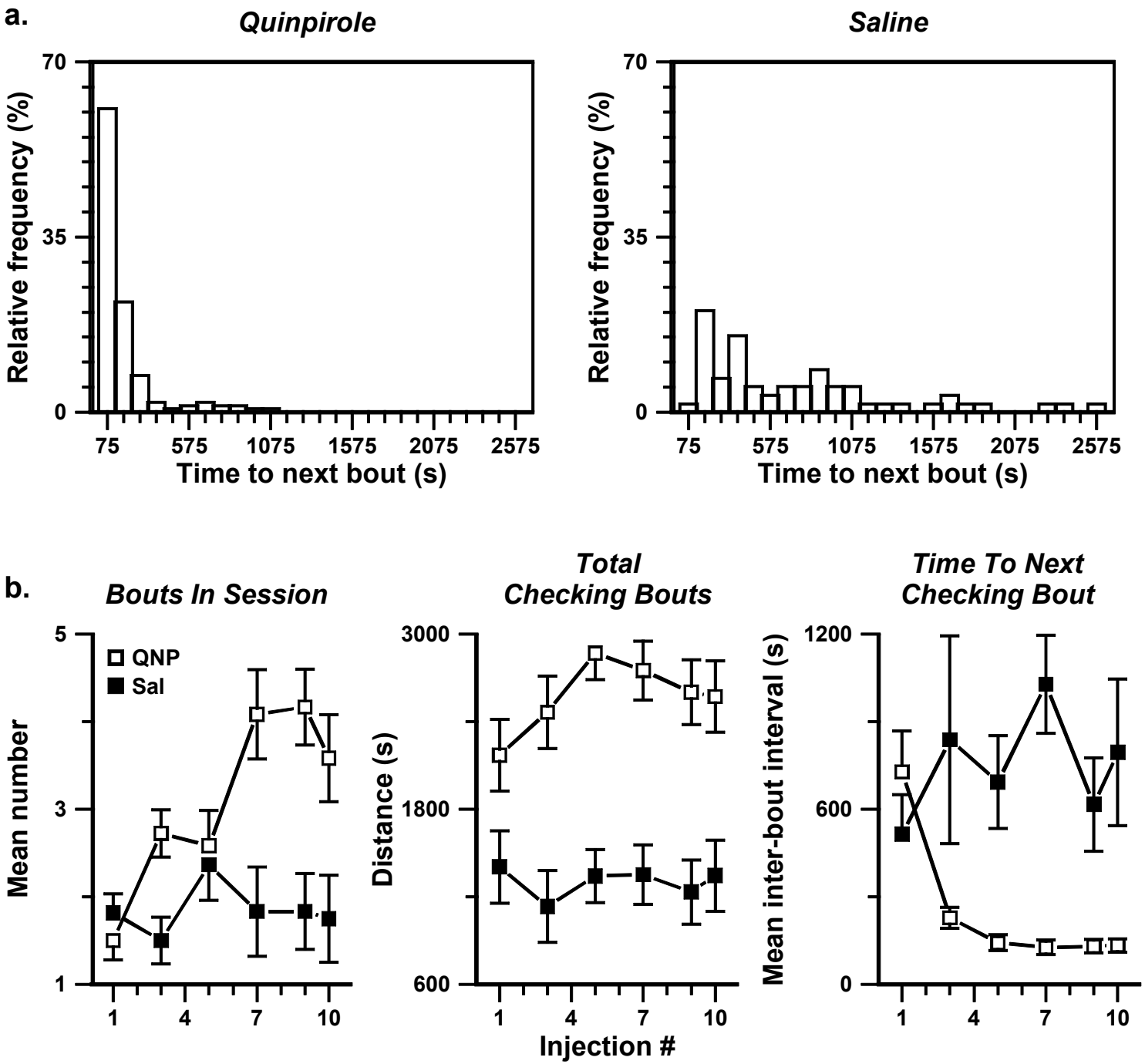
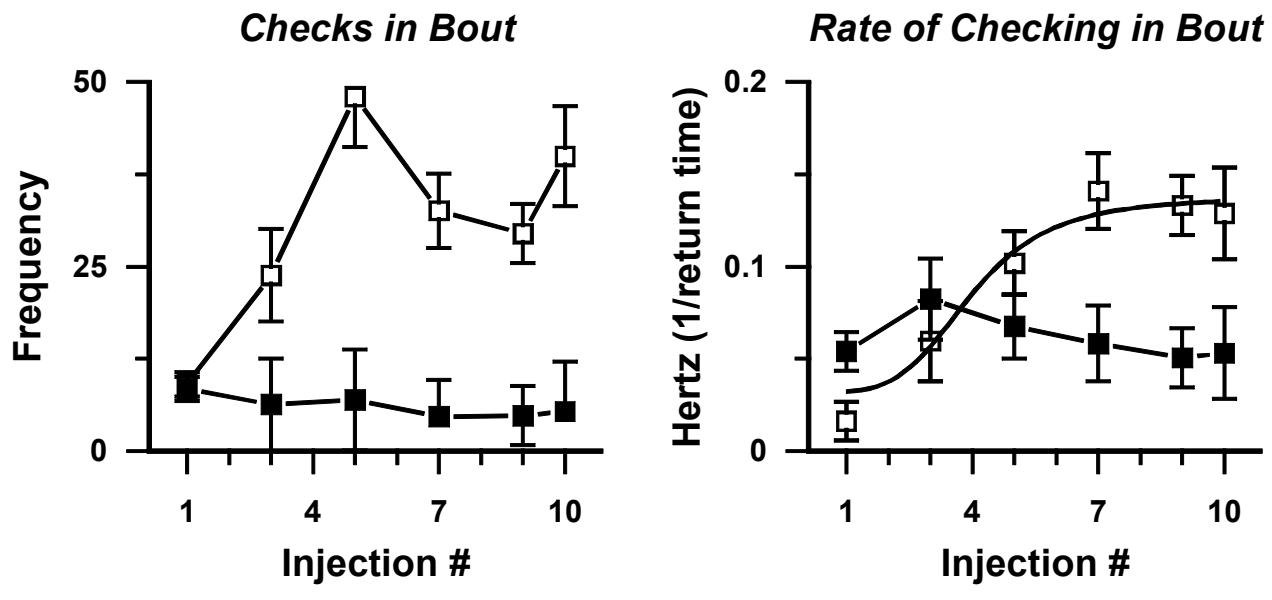

440
220
0
8
4
0
QNP
Sal
Total Distance (m)
Average Distance (m/min)
1
4
7
10
Injection #


2 Standard Deviational Ellipse
Area (m2)
6
5
4
3
2
1
QNP
Sal
1
4
7
10
Injection #
Path Stereotypy
Ratio
5
4
3
2
1
0
1
4
7
10
Injection #


a.
Frequency of Checking
Returns to home base (#)
150
75
0
QNP
Sal
b.
Relative Frequency of Checking
Observed/expected returns (ratio)
7
4
1
c.
Recurrence Time of Checking
Return time to home base (s)
150
75
0
d.
Relative Recurrence Time of Checking
Observed/expected return time (ratio)
0.6
0.3
0
e.
Stops Before Returning to Home Base
Stops between returns to home base
7
4
1
1
4
7
10
Injection #
f.
Length of Check
Duration of visit to home base
600
300
0
1
4
7
10
Injection #


0
5
10
15
20
25
Minutes


a.
Quinpirole
Saline
Relative frequency (%)
70
35
0
75
575
1075
1575
2075
2575
Time to next bout (s)
b.
Bouts In Session
Total
Checking Bouts
Time To Next
Checking Bout
QNP
Sal
Mean number
5
3
1
Distance (s)
3000
1800
600
Mean inter-bout interval (s)
1200
600
0
1
4
7
10
Injection #


Checks in Bout
Frequency
50
25
0
1
4
7
10
Injection #
Rate of Checking in Bout
Hertz (1/return time)
0.2
0.1
0
1
4
7
10
Injection #