

Research article

Compulsive checking behavior of quinpirole-sensitized rats as an animal model of Obsessive-Compulsive Disorder(OCD): form and control

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Abstract

Background: A previous report showed that the open field behavior of rats sensitized to the dopamine agonist quinpirole satisfies 5 performance criteria for compulsive checking behavior. In an effort to extend the parallel between the drug-induced phenomenon and human obsessive-compulsive disorder (OCD), the present study investigated whether the checking behavior of quinpirole rats is subject to interruption, which is an attribute characteristic of OCD compulsions. For this purpose, the rat's home-cage was placed into the open field at the beginning or the middle of a 2-hr test.

Results: Introduction of the home-cage reduced checking behavior, as rats stayed inside the cage. After 40 min, checking resurfaced, as quinpirole rats exited the home-cage often. An unfamiliar cage had no such effects on quinpirole rats or saline controls.

Conclusions: Checking behavior induced by quinpirole is not irrepressible but can be suspended. Results strengthen the quinpirole preparation as an animal model of OCD compulsive checking.

Background

Obsessive-compulsive disorder (OCD) is a psychiatric illness, more prevalent than schizophrenia or panic disorder [1,2]. The most frequent symptom of OCD is compulsive checking, shown by 63% of the patients [3,4]. Compulsive checking interferes with normal everyday functioning because of the many hours of time spent in the performance of checking rituals, a preoccupation that in extreme cases may even prevent the OCD sufferer from leaving home [5, p. 86]. Like normal behavior, OCD checking involves the performance of actions supposedly related to security, orderliness or accuracy, but is charac-

terized by the repeated and excessive re-doing of such rituals. These repetitions do not reflect a problem with memory recall [6–9] but rather an impediment in achieving a sense of task completion [10–15].

In a recent publication [16] we propose that behavior induced by chronic treatment with the D₂/D₃ dopamine agonist, quinpirole, may constitute an animal model of OCD checking. This proposal is based on three lines of evidence. First, the behavior of quinpirole-treated rats *looks like* OCD checking in that it meets formal ethological criteria of OCD compulsive checking identified by

the investigators: a) a preoccupation with and an exaggerated hesitancy to leave the item(s) of interest; b) a ritual-like motor activity pattern; and, c) dependence of checking behavior on environmental context. Second, the behavior of quinpirole-treated rats is directed at a likely stimulus for checking activity - the home base, and is thus an exaggerated form of normal checking in the rat, similar to the human condition where OCD compulsive checking is an exaggerated form of normal checking regarding one's well-being and security [11]. Finally, the checking behavior of quinpirole rats is partially attenuated by clomipramine, a drug used in the treatment of OCD.

In the present report, we investigate whether the checking behavior of quinpirole rats is subject to interruption, which is another attribute characteristic of OCD compulsions. Despite the urge to perform them, OCD patients may resist engagement in rituals for varying amounts of time depending on situational circumstances. In fact, one of the most effective psychotherapies for OCD [17] - exposure and ritual prevention (ERP) therapy - relies on this property. Patients are persuaded by the therapist to expose themselves daily to the ritual-provoking cues and to stay in contact with them without ritualizing for at least one hour or until any discomfort slowly subsides [17]. This form of therapy has a success rate that may be higher and longer-lasting than anti-compulsive medication, and produces brain changes in OCD patients similar to those found with drug therapy (reviewed in [17]). Here, we asked whether like OCD patients, quinpirole rats can desist from compulsive checking in the presence of checking-evoking cues.

As a potential non-trivial manipulation that could interrupt the incessant checking activity of quinpirole rats, we placed a cage in the open field environment and examined the effect of two factors on checking behavior: familiarity with the cage introduced into the open field, and the time at which the cage was introduced into the open field. With regard to the first factor, the cage was either the rat's home-cage (very familiar) or one that the rat has never seen before (completely unfamiliar). With regard to the time factor, the cage was introduced into the open field either at the start of the open field test (i.e., immediately after injection of quinpirole) or 60 min after start of the test (i.e., after the rat has been engaged in checking behavior for an hour). These factors were aimed to constitute a gradient making the suppression of quinpirole-induced checking more or less difficult, akin to the variable success that OCD patients have in resisting obsessions. Thus, it was expected that the familiar cage introduced at the start of testing would yield the maximum suppression and the unfamiliar cage intro-

duced 60 min after drug injection would yield the least suppression of checking activity.

Results

Induction of Compulsive Checking

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 - are said to be present if the subject meets three performance criteria [16]: the subject returns to one or two spots in its territory excessively often, excessively rapidly, and visits excessively few other places before returning to the spot of interest. In a large open field, one of these spots is the rat's home base [16] as defined by Eilam and Golani [19]. Consequently, in the present study, the presence of compulsive checking was examined with reference to the home base. As found previously [16], Figure 1 shows that 10 injections of quinpirole induced compulsive checking of home base, according to the above 3 criteria. In particular:

(1) As shown in Figure 1A, quinpirole-treated rats revisited their home base almost 15 times more often than did saline-treated animals (141.6 ± 13.5 returns under quinpirole vs. 9.7 ± 1.6 returns under saline; $t(22) = 9.7, p < .001$). Moreover, even after adjusting for the total number of visits, returns to home base were excessive in quinpirole rats because the *rate* of returning to the home base was significantly higher compared to the rate of visits to other locales in the open field, and significantly greater than the rate of home base return in saline controls (Figure 1B). Specifically, quinpirole-treated rats made 406.7 ± 25.1 visits to 19.7 ± 0.9 different locales in the open field, and thus on the basis of a uniform frequency distribution their expected rate of return to any locale in the open field was 21.1 ± 1.5 returns per locale. However, the observed rate of revisits to the home base was almost 7-fold higher than would be expected. This number was also significantly higher than the corresponding ratio of observed-to-expected visits to home base in saline controls (6.8 ± 0.5 under quinpirole vs. 2.2 ± 0.1 under saline, $t(22) = 9.3, p < .001$; Figure 1B).

(2) As shown in Figure 1C, the mean return time to the home base was 10-fold shorter in the quinpirole group than in the saline-treated rats (15.6 ± 2.4 s vs. 158.7 ± 20.4 s, $t(22) = 7.0, p < .001$). Moreover, return time to home base remained excessively rapid in quinpirole rats even when compared to their overall mean return time to places of visit in the open field (15.6 ± 2.4 s vs. 406.3 ± 35.8 s, $t(11) = 10.9, p < .001$), or when compared to saline controls using a normalized measure of return time, namely, home base return time normalized to overall return time ($4.5 \pm 1.2\%$ of overall return time under quinpirole vs. $40.2 \pm 6.9\%$ under saline, $t(22) = 5.1, p < .001$).

Checking of Home Base

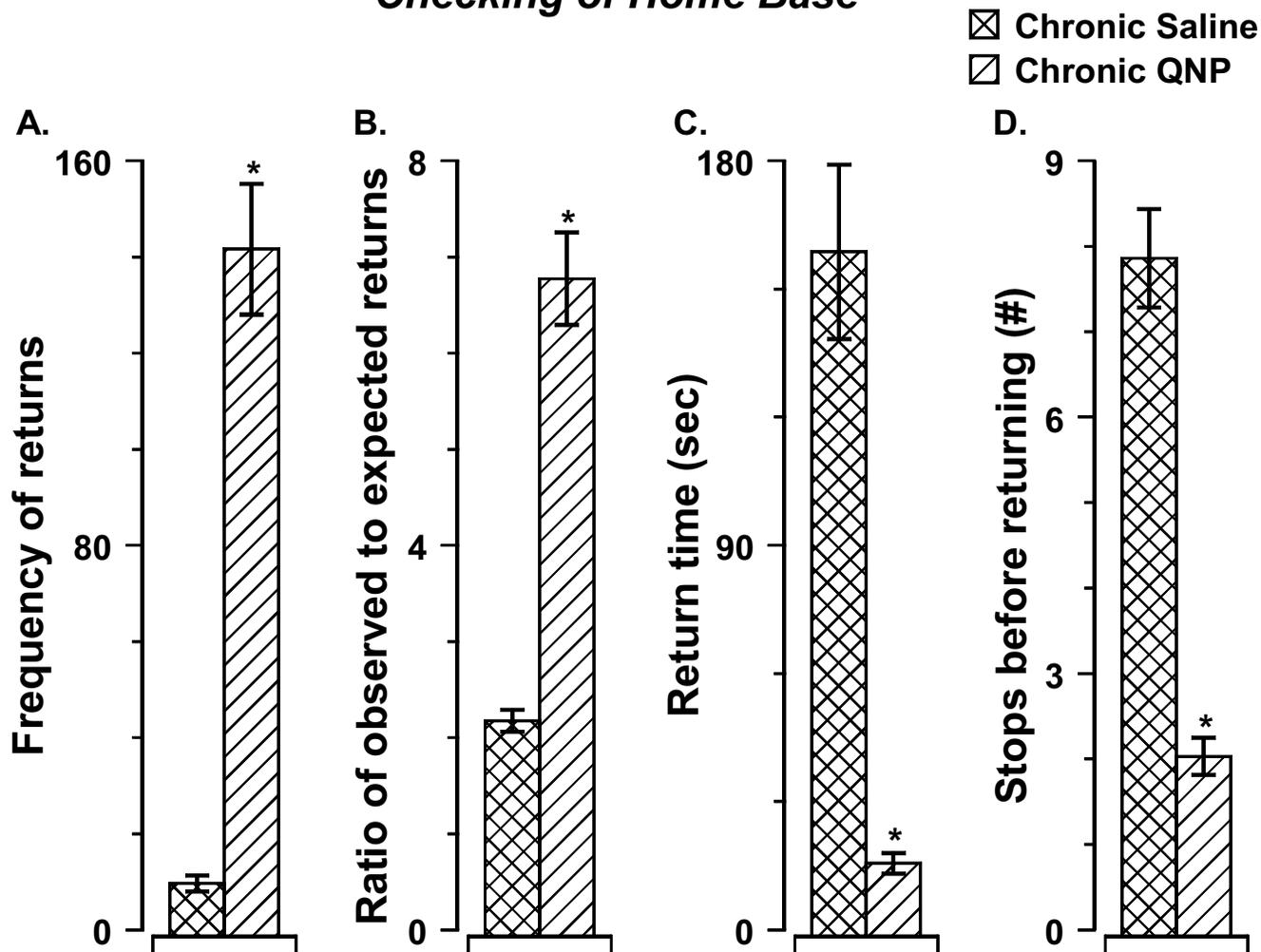


Figure 1
 Induction of compulsive checking as identified by formal performance criteria. Performance measures are in reference to the home base established by the rat on the tenth open field test shown here, and recognized as the locale with the longest total duration of stops. Quinpirole-treated animals (*hatched bars*) met compulsive checking criteria because compared to saline-treated rats (*crosshatched bars*), they showed: **(A)** more frequent returns to the home base, **(B)** a higher than an expected rate of returning to the home base, **(C)** more rapid returns to the home base, and **(D)** fewer visits to other places on trips from the home base. * $p < .05$, t test. Values are mean and SEM.

(3) Finally, as shown in Figure 1D, quinpirole-treated rats visited only a couple of places before returning to their home base, in contrast to saline controls which visited 4 times as many locales before re-entering home (2.0 ± 0.2 places under quinpirole *vs.* 7.9 ± 0.6 places under saline, $t(22) = 9.5$, $p < .001$).

Two additional criteria were proposed as required to identify in the rat compulsive checking behavior: the presence of a characteristic set of acts performed at the spot of interest, and a change in the pattern of checking behavior in response to a re-arrangement of the test en-

vironment (for a rationale for these criteria, see [16]). Although motor acts were not scored in the present study, indirect evidence does suggest that quinpirole-treated rats met the criterion of ritual-like motor activity. Specifically, quinpirole rats spent significantly less time at the home base during each visit than did saline controls (9.7 ± 1.1 s per home visit under quinpirole *vs.* 308.2 ± 68.2 s under saline, $t(22) = 4.4$, $p < .001$), a finding associated previously with the differential display of ritual-like acts in quinpirole versus saline rats [16]. Moreover, informal examinations of the videotape records were consistent with presence of rituals in quinpirole rats as observed

previously [16]. The final criterion, dependence of checking behavior on environmental context, was not examined explicitly in Phase 1 because it was deemed to be addressed in the Test Phase by virtue of introducing into the open field the unfamiliar and familiar cages.

Home Cage Arrests Locomotion

Because checking behavior involves locomotion to the item(s) of concern, a reduction in the distance of travel provides an indirect index of an attenuation in checking. Figure 2 shows the distance traveled by saline-treated control rats (*left column*) and by rats treated with quinpirole (*right column*) during tests when a novel or home-cage was introduced into the open field in the middle of the two-hour session (*top row*) or immediately at start of testing (*bottom row*). Inspection of the figure suggests the following. In control rats, both the novel and the home cage produced a small and transient increase in

distance traveled when the cage was placed in the open field in the middle of the session; there was little effect when the cages were present from the start of testing. However, in quinpirole rats, the effects produced by the two types of cages were strikingly different. The presence of a home-cage, regardless of the time it was placed into the open field, resulted in a virtual stop of locomotor behavior for about 40 minutes but a novel cage had no effect on distance traveled. Furthermore, although locomotor arrest waned after 40 minutes, the amount of travel did not recover to its usual levels during the test period. This pattern of effects is consistent with the prediction that checking behavior would cease, but only for a limited period of time, in the presence of an option to do something else. The observed differential impact of novel and home cages on locomotor behavior was supported by the statistical analysis below.

Table 1: Summary of statistical analyses for 4 dependent measures. Each dependent variable was analyzed in a Cage Familiarity (CAGE) by Time of Cage Introduction (INTRO) by Hour of Testing (HOUR) by Drug Treatment (DRUG) ANOVA with repeated measures on the first 3 factors.

| Source | df | Distance Traveled | | | Duration of Staying in Cage | | | Exits from Cage | | | Visits to Home Base from Phase I | | |
|----------------------------------|----|-------------------|-------|-------|-----------------------------|-------|-------|-----------------|------|-------|----------------------------------|------|-------|
| | | Mean Square | F | Sig. | Mean Square | F | Sig. | Mean Square | F | Sig. | Mean Square | F | Sig. |
| <i>Within-Subjects Contrasts</i> | | | | | | | | | | | | | |
| INTRO | 1 | 2224908867 | 22.9 | 0.000 | 16232863 | 79.8 | 0.000 | 3317 | 8.9 | 0.007 | 19320 | 24.6 | 0.000 |
| INTRO * DRUG | 1 | 1839965205 | 19.0 | 0.000 | 588913 | 2.9 | 0.103 | 3468 | 9.3 | 0.006 | 16725 | 21.3 | 0.000 |
| Error(INTRO) | 22 | 97033892 | | | 203487 | | | 373 | | | 784 | | |
| CAGE | 1 | 17701171788 | 375.4 | 0.000 | 169590106 | 419.9 | 0.000 | 4720 | 8.1 | 0.009 | 141484 | 33.0 | 0.000 |
| CAGE * DRUG | 1 | 17751213019 | 376.4 | 0.000 | 6113519 | 15.1 | 0.001 | 2228 | 3.8 | 0.063 | 137281 | 32.0 | 0.000 |
| Error(CAGE) | 22 | 47154899 | | | 403928 | | | 581 | | | 4289 | | |
| HOUR | 1 | 237500968 | 2.7 | 0.115 | 23543456 | 100.6 | 0.000 | 5355 | 12.4 | 0.002 | 1151 | 2.2 | 0.153 |
| HOUR * DRUG | 1 | 21492295 | 0.2 | 0.627 | 531418 | 2.3 | 0.146 | 7203 | 16.7 | 0.000 | 7 | 0.0 | 0.911 |
| Error(HOUR) | 22 | 88224156 | | | 234028 | | | 431 | | | 526 | | |
| INTRO * CAGE | 1 | 931631085 | 15.2 | 0.001 | 13760369 | 64.5 | 0.000 | 893 | 4.0 | 0.059 | 7033 | 5.4 | 0.029 |
| INTRO * CAGE * DRUG | 1 | 735495405 | 12.0 | 0.002 | 306872 | 1.4 | 0.243 | 721 | 3.2 | 0.087 | 7057 | 5.5 | 0.029 |
| Error(INTRO * CAGE) | 22 | 61156552 | | | 213365 | | | 225 | | | 1293 | | |
| INTRO * HOUR | 1 | 2609009790 | 29.3 | 0.000 | 21625057 | 225.4 | 0.000 | 30 | 0.3 | 0.610 | 29800 | 31.4 | 0.000 |
| INTRO * HOUR * DRUG | 1 | 4087487232 | 45.9 | 0.000 | 1798563 | 18.7 | 0.000 | 609 | 5.4 | 0.029 | 31468 | 33.1 | 0.000 |
| Error(INTRO * HOUR) | 22 | 89134994 | | | 95927 | | | 112 | | | 950 | | |
| CAGE * HOUR | 1 | 3303732675 | 57.1 | 0.000 | 23390748 | 104.8 | 0.000 | 2961 | 12.4 | 0.002 | 33867 | 25.1 | 0.000 |
| CAGE * HOUR * DRUG | 1 | 3331266987 | 57.6 | 0.000 | 327649 | 1.5 | 0.238 | 2523 | 10.5 | 0.004 | 33602 | 24.9 | 0.000 |
| Error(CAGE * HOUR) | 22 | 57815111 | | | 223114 | | | 240 | | | 1348 | | |
| INTRO * CAGE * HOUR | 1 | 4645326525 | 153.7 | 0.000 | 19868514 | 195.9 | 0.000 | 363 | 3.0 | 0.099 | 17710 | 40.9 | 0.000 |
| INTRO * CAGE * HOUR * DRUG | 1 | 4897187026 | 162.1 | 0.000 | 1727200 | 17.0 | 0.000 | 1764 | 14.4 | 0.001 | 17749 | 41.0 | 0.000 |
| Error(INTRO * CAGE * HOUR) | 22 | 30215914 | | | 101397 | | | 123 | | | 433 | | |
| <i>Between-Subjects Effects</i> | | | | | | | | | | | | | |
| DRUG | 1 | 73038969284 | 146.9 | 0.000 | 7882396 | 20.3 | 0.000 | 13635 | 17.2 | 0.000 | 509438 | 61.9 | 0.000 |
| Error | 22 | 497327329 | | | 387476 | | | 791 | | | 8236 | | |

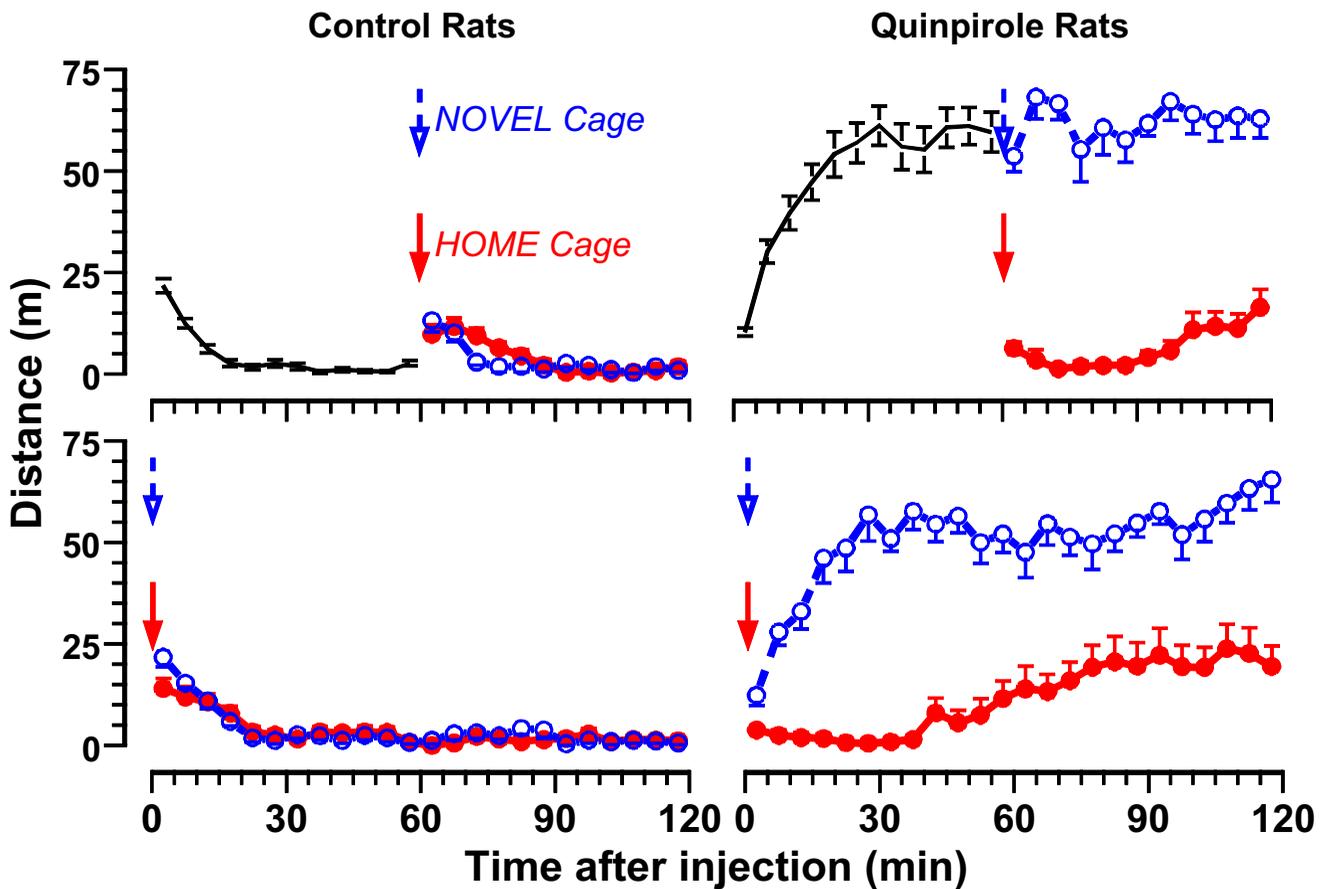


Figure 2
 The effect of cage familiarity on locomotor behavior in the open field. Arrows indicate the time point at which either a familiar container (the rat's home-cage) or an unfamiliar one (a novel cage) was introduced into the open field. *Solid* and *open circles* indicate distance traveled in the presence of a familiar and unfamiliar cage, respectively. Lines without symbols indicate the distance of travel before a cage was introduced into the open field and represent the mean of tests before placement of familiar and unfamiliar cages. *Left column* shows saline-treated rats and *right column* the quinpirole-treated group. Values are mean and SEM.

To simplify statistical analysis, the data were collapsed into two one hour intervals for a 4-way analysis of variance (ANOVA) with 3 repeated measures factors: Cage Familiarity (home-cage *vs.* novel cage). Time of Cage Introduction (at start of open field test *vs.* after 60 minutes of open field test) and Hour of Testing (hour 1 of open field test *vs.* hour 2 of open field test). The 4th factor was the between-subjects factor, Drug Treatment (chronic saline *vs.* chronic quinpirole). The results of this analysis are shown in Table 1 and confirm the summarized inspection of Figure 2. Specifically, the differential impact of cage familiarity in quinpirole-treated but not saline-treated rats is suggested by a significant Cage Familiarity by Drug Treatment interaction ($p < .001$; Table 1); inspection of the marginal means (and the associated 95% confidence intervals) showed that in quinpirole rats the distance of travel for the home-cage condition was signif-

icantly smaller than for the unfamiliar cage condition (244.3 ± 20.1 m with home-cage present *vs.* 628.7 ± 26.9 m with novel cage present) and no such difference between these conditions existed in saline controls (46.6 ± 20.1 m *vs.* 46.3 ± 26.9 m). With respect to the observation that the immediate effect on locomotor behavior was independent of the time at which the home-cage was introduced into the open field, this is supported by similar distances of travel in the immediate hour after placement of the home-cage at either 0 minutes or 60 minutes after start of open field test (46.0 ± 11.5 m *vs.* 77.3 ± 15.3 m, $p > .05$). With regard to the incomplete recovery of locomotor distance, this is supported by the findings of a significant four-way interaction (Table 1) and that in the second hour of testing under quinpirole, distance traveled in the presence of the home-cage (placed into the open field at start of the test) was significantly small-

er than in the presence of a similarly placed novel cage (229.5 ± 39.5 m vs. 663.9 ± 32.7 m).

Finally, an additional comparison suggests that locomotor activity under quinpirole increased with the length of exposure to the home-cage. In particular, when the home-cage was introduced into the open field at the 60 minute time point, locomotor distance in hour 2 was 77.3 ± 15.3 m. In contrast, when the home-cage was present from beginning of the test, locomotor distance in hour 2 was significantly more, 229.5 ± 39.5 m. It should be noted that this result is not a drug time-course effect because the two measures are from the same time period, 60-120 min after quinpirole injection.

Staying in Home Cage

In addition to reducing locomotor behavior, the home-cage (but not the novel cage) attracted rats into it. Figure 3 shows the duration of staying in the two types of cages by saline controls and quinpirole-treated rats. As can be seen, both saline and quinpirole rats spent a large portion of the test period inside the home-cage but not the novel cage (1931.4 ± 89.6 s in the home-cage vs. 51.5 ± 14.5 s in the novel cage; for Cage Familiarity, $F(1,22) = 419.8$, $p < .001$). However, the duration of staying in the home-cage was significantly longer in the quinpirole rats (2312.5 ± 126.7 s) than in the saline controls (1550.0 ± 126.7 s; for Drug Treatment, $F(1,22) = 20.3$, $p < .001$; for Drug Treatment \times Cage Familiarity, $F(1,22) = 15.1$, $p = .001$).

The 4-way interaction for duration of staying in the cage was also significant (for Cage Familiarity by Time of Cage Introduction by Hour of Testing by Drug Treatment, $F(1,22) = 17.0$, $p < .001$; Figure 3). This interaction effect seemed related to a between-groups difference. Specifically, during hour 2 (60-120 min intervals in Fig 3), quinpirole rats, compared to saline controls, stayed in the home-cage significantly longer in one of the Time of Cage Introduction conditions (cage introduced at 60 min: 3300.6 ± 242.6 s under quinpirole vs. 2158.2 ± 242.6 s under saline, $p < .05$) but not in the other one (cage introduced at 0 min: 2910.5 ± 258.2 s under quinpirole vs. 2153.1 ± 258.2 s under saline, $p > .05$).

Resumption of Checking Behavior

As was shown in Figure 2, in the presence of the home-cage, quinpirole rats began to move through the open field after a period of arrest. Two kinds of measures indicate that this rise in the distance of travel reflects a resumption of their usual checking behavior. One measure is the frequency of exits from the home-cage (Figure 4) and the other one is the frequency of visits to the spot of checking behavior in Phase 1 (Figure 5). Together, they suggest that when quinpirole rats began to venture from

the home-cage, almost every trip included their previous spot of interest, consistent with performance of checking.

Exits from cage.

Although saline-treated rats spent a large portion of the test period inside the home-cage (Figure 3), inspection of Figure 4 (*left column*) shows that they rarely left it. In contrast, quinpirole rats (Figure 4, *right column*) went out from the home-cage and returned to it often, especially in hour 2 (47.4 ± 7.5 exits from home-cage under quinpirole in hour 2 vs. 4.3 ± 7.5 exits from home-cage under saline in hour 2, $p < .05$; see Table 1 for significant main effect of Drug Treatment, and the triple interaction of Drug Treatment by Cage Familiarity by Hour of Testing).

It is also noteworthy that as for locomotor distance, longer exposure to the home-cage under quinpirole led to a higher number of exits from it (exits from the home-cage in hour 2: cage introduced at 60 min = 66.5 ± 11.7 vs. cage introduced at 0 min = 28.3 ± 4.6 , $p < .05$).

Even though quinpirole rats spent very little time at the location of the novel cage (Figure 3), they did come to it sporadically (Figure 4), though this number of visits did not reach statistical significance in the comparison between quinpirole and saline rats (11.7 ± 3.3 stops at novel cage under quinpirole vs. 1.7 ± 4.2 stops at novel cage under saline; for Drug Treatment by Cage Familiarity, $F(1,22) = 3.84$, $p = .063$).

Visits to previous home base.

Figure 5 shows the incidence of visits in each of the 4 conditions to one particular locale in the open field. This locale is the home base from Phase 1 and the then focus of checking behavior. Inspection of the figure shows readily that when a novel cage was introduced into the open field, checking behavior in quinpirole rats still continued to be directed to the same spot. However, as was suggested by the locomotor distance data (Figure 2), the incidence of visits to this spot declined precipitously when a novel cage was introduced into the open field. Importantly, when travel through the open field resumed, Figure 5 shows that the number of visits to that spot increased dramatically. Specifically, with the home-cage present from the start of testing, quinpirole rats visited the previous home base nearly 40 times during hour 2. This number was almost as large as the frequency of exits from the home-cage during hour 2 (39.0 ± 11.0 visits to previous home base vs. 66.6 ± 16.6 exits from home-cage, $t(11) = 2.17$, $p = .053$), suggesting that quinpirole rats traveled to this place of interest almost every time that they left the home-cage. The special attraction of the former home base is also evident from the obser-

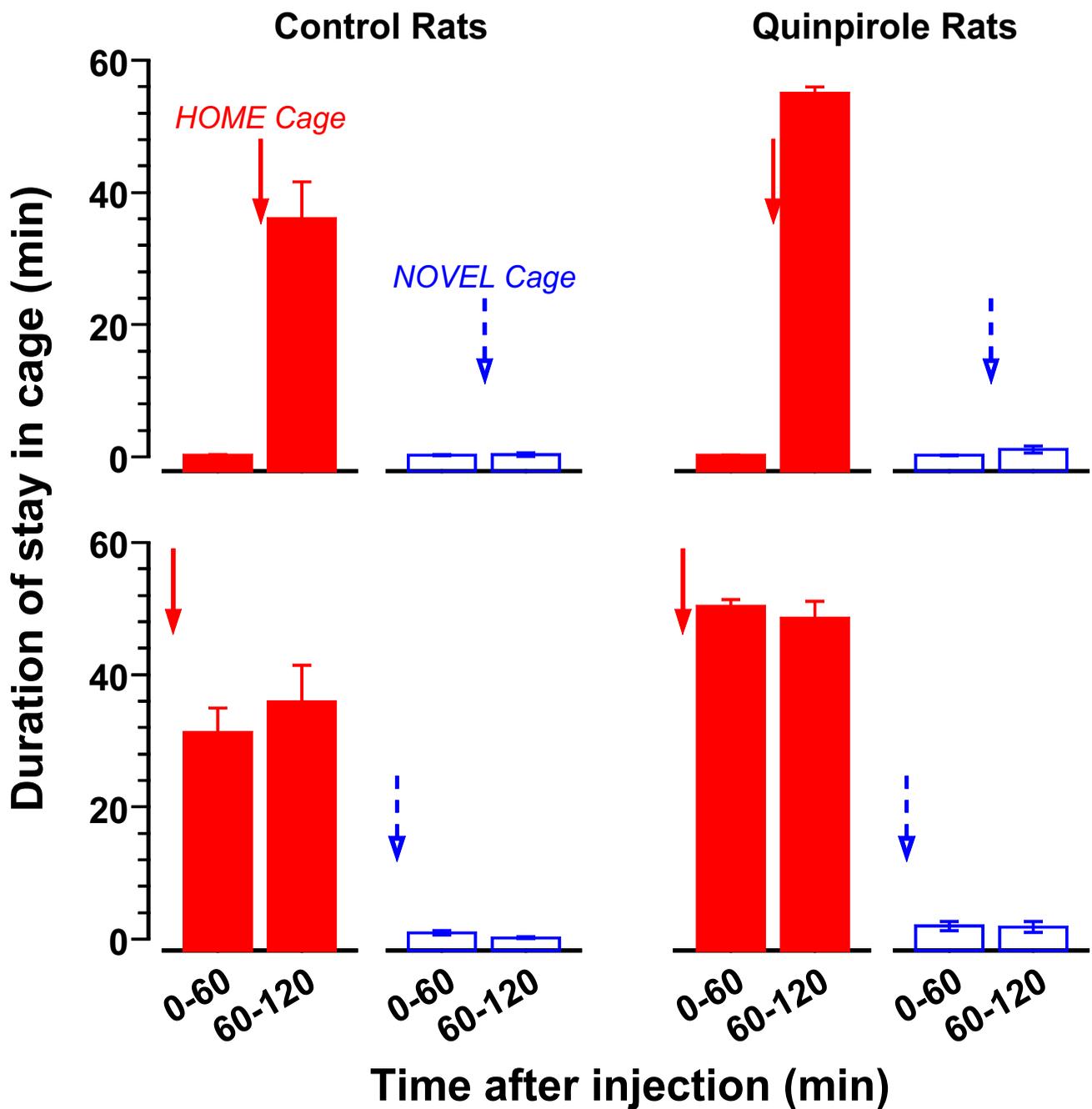


Figure 3
 The effect of cage familiarity on the duration of staying in the cage during a test of open field activity. Arrows indicate the time point at which the rat's home-cage or a novel cage was placed into the open field. *Solid* and *open* bars are tests with the home and the novel cage, respectively. *Control Rats* were treated chronically with saline and *Quinpirole Rats* were treated chronically with quinpirole. Values are mean and SEM.

vation that the frequency of visits to it was significantly higher than the mean number of stops to any other open field locale (excluding the place containing a cage): 39.0 ± 11.0 visits to previous home base *vs.* 12.2 ± 8.4 visits per locale, $t(11) = 2.8, p = .017$.

Finally, as found for other measures, longer exposure to the home-cage under quinpirole led to a higher incidence of checks to the spot of interest (visits to former home base in hour 2: cage introduced at 60 min = 39.0 ± 7.8 *vs.* cage introduced at 0 min = $13.0 \pm 2.9, p < .05$).

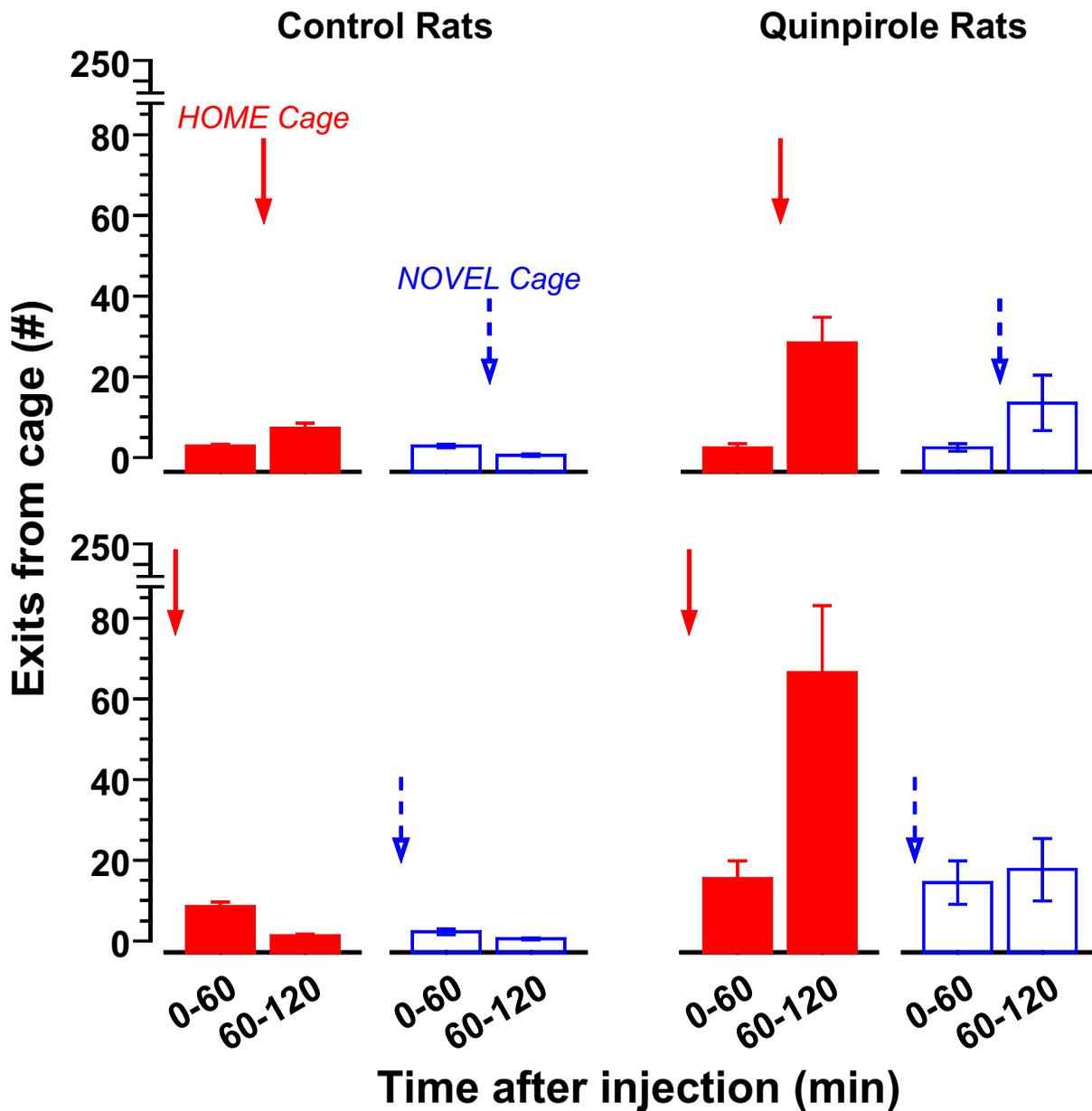


Figure 4
 The effect of cage familiarity on the frequency of exits from the cage. Arrows indicate the time point at which the rat's home-cage or a novel cage was placed into the open field. *Solid and open bars* are tests with the home and the novel cage, respectively. *Control Rats* were treated chronically with saline and *Quinpirole Rats* were treated chronically with quinpirole. Values are mean and SEM.

Discussion

The transformation of quinpirole-induced behavior produced by a home-cage in the open field was striking. Checking, and an incessant locomotion, disappeared, as the rat entered the home-cage and spent its time there. However, after about 40 minutes, checking resurfaced, as the rat began to exit the home-cage for brief periods of

time and to visit the previous spot of concern. A novel cage had no such effects on quinpirole-induced behavior. Below, we consider possible reasons for the effectiveness of the home-cage in arresting checking, discuss whether the obtained findings reveal the phenomenological experience of a compulsion in the rat, highlight the implications of the study for an animal model of OCD checking,

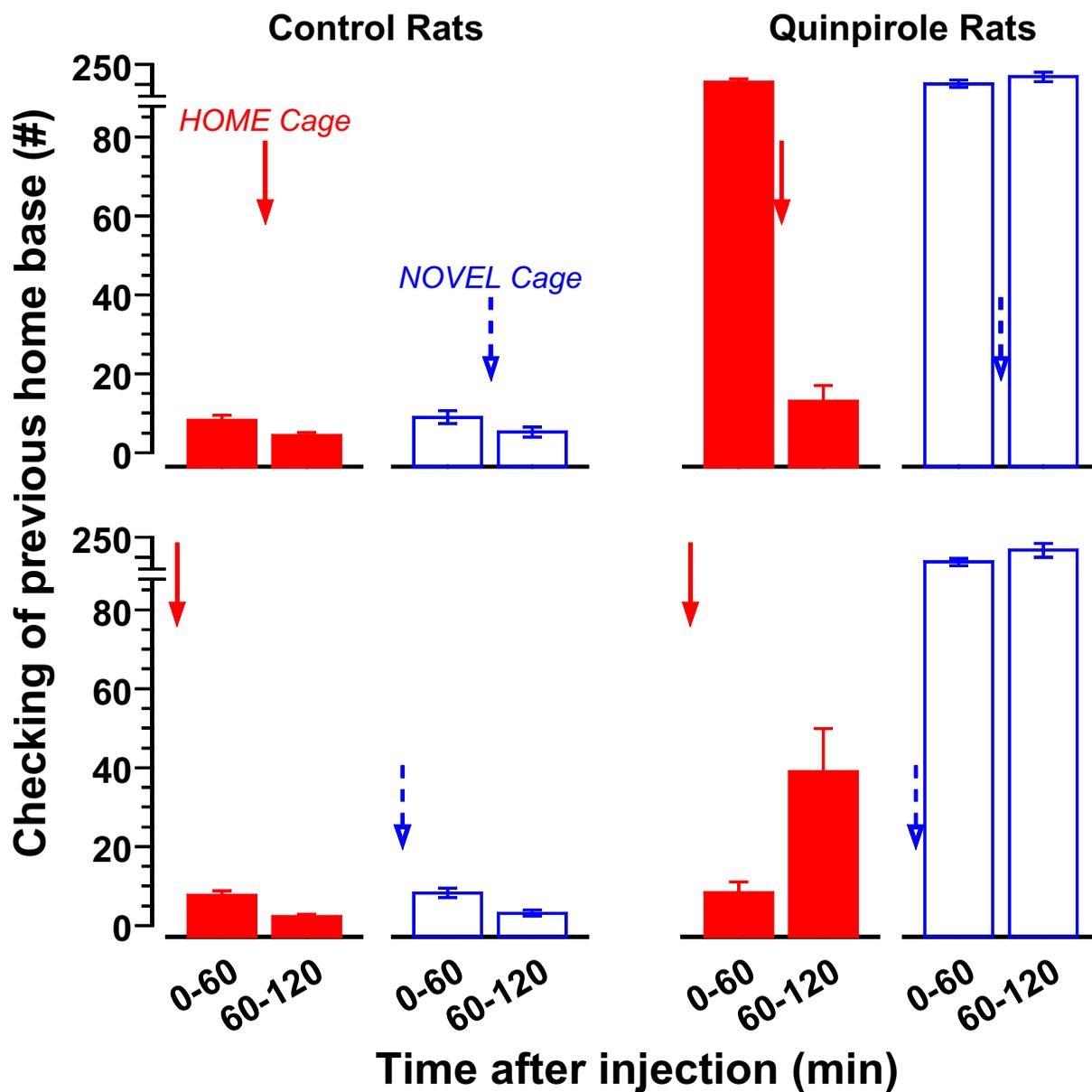


Figure 5
 The effect of cage familiarity on the number of visits to the site of the home-base from Phase I. Arrows indicate the time point at which the rat's home-cage or a novel cage was placed into the open field. *Solid* and *open bars* are tests with the home and the novel cage, respectively. *Control Rats* were treated chronically with saline and *Quinpirole Rats* were treated chronically with quinpirole. Values are mean and SEM.

and relate controllability of behavior to compulsive checking and stereotyped behavior induced by psychostimulant drugs.

'Safety' Cues, Gradient of Suppression and Reward

The home-cage, but not a novel cage, was effective in suppressing checking. Thus, some psychological attribute of the familiar container accounts for its effective-

ness. To the extent that OCD checking is an exaggerated form of normal checking regarding one's well-being and security [11], and a similar relationship exists between quinpirole-induced and normal checking in the rat, then it is reasonable to suppose that the suspension of quinpirole checking emanates from a sense of 'safety' provided by the familiar contextual cues of the home-cage. However, the effectiveness of such 'safety' cues was time-

limited, as quinpirole rats resumed their checking of the open field environment after spending 40 min in the home cage. This resumption could be the outcome of a habituation process to 'safety' cues of the home cage, occurring in the presence of continual drug-activated stimuli for checking. A similar dynamic process of a changing balance between 'safety' and 'checking' cues may account for the variable success that OCD patients have in resisting their compulsions [11].

While cage familiarity produced the expected suspension of checking, the time at which the cage was introduced into the open field did not show the predicted effect. Based on the notion that quinpirole-induced behavior may be related to the activation of dopamine reward circuits [24–26], we expected that an animal fully engaged in compulsive checking would find it more difficult to suspend this activity than an animal which has not yet started to check. However, regardless of the time at which the home cage was introduced into the open field, quinpirole rats entered it quickly and remained there for 40 min. Thus, both the suspension of checking behavior and the duration of this suspension, was independent of prior ongoing checking. This observation raises to question whether quinpirole-induced checking is indeed related to positive reward stimulation or whether, on the contrary, its repeated performance is propelled by factors with a negative valence. Moreover, it raises the question of whether the controlled variable in the rat's behavior is the duration of staying in the home cage or the length of time that the checking can be suspended. Unfortunately, the design of the present study is inadequate to answer these questions unambiguously. Nevertheless, we suggest that the latter alternatives are the more likely answers because they are consistent with our speculation that quinpirole rats may experience their checking activity as 'compulsive,' as discussed below.

Experience of Compulsion

As noted by Reed [11], the primary criterial attribute of OCD is the experience of compulsion. Yet, so few authors have tried to "elucidate or analyse compulsion itself. The normal ploy is simply to ascribe the adjective 'compulsive' to such nouns as 'ideas,' 'thoughts,' or 'impulses.' The *meaning* of 'compulsive' is never examined; it seems to be regarded as so self-evident as to be unworthy of study or exposition... It might well be enquired how it is possible to study a phenomenon without first examining the very factor that defines it" [11, p. 120, italics in original]. According to Reed, to be called 'compulsive' in a clinical sense, the subject must find that the urge to perform the behavior "is intrusive and ego-dystonic, that he feels it is absurd, and that he struggles unsuccessfully to resist it" [11, p. 11]. That is to say, the salient experiential features of 'compulsion', as defined by the first and the

last of the above three criteria, are a reluctance and an ultimately doomed resistance to engage in the behavior. From the above definitional criteria, it also follows that compulsions afford the subject with "no gratification or good cheer" as the subject fights "a losing battle with something which is not acceptable to him - a battle, moreover, which seems interminably protracted, exhausting, and thus, distressing" [11, p. 7]. In other words, the compulsive experience is not a pleasant one.

Although they do not prove it, the findings of the present study are consistent with the notion that the quinpirole rat experiences its checking activity as compulsive. The definitional criteria of compulsion predict that because the compulsive experience is distressing, subjects would at first avoid engagement in compulsive rituals if given an opportunity to do so. However, in the face of the compulsion-evoking situation, this avoidance would become unavailing, and, inevitably, the compulsive behavior would emerge. In other words, the expected behavioral pattern associated with phenomenological compulsion is but a temporary suppression of compulsive rituals. This is precisely the pattern found here for quinpirole-induced checking. Specifically, when provided with the opportunity to do something else, quinpirole rats did not engage in checking behavior but instead sought out and remained in their home-cage placed in an unattractive location of the open field. Ultimately, however, they did resume their checking activity. According to this schema, therefore, quinpirole-induced checking does seem *compulsive*.

The notion that rats experience compulsion under quinpirole is consistent with another finding. Quinpirole rats checked more, the longer they remained inside the home cage (Figure 4 and Figure 5). Such a result would be expected if staying in the home cage was indeed the rat's attempt of resistance to compulsions because the effectiveness of this strategy should decline as a function of home-cage time, based on an expected process of habituation to home-cage ritual-suppressive ('safety') cues.

While the obtained results are consistent with the hypothesis of a compulsive experience, the data are also open to alternative interpretations. For instance, rather than a presumed avoidance of checking under quinpirole, the observed pattern of results could merely reflect the choice between two relatively pleasant activities, namely, staying in the home cage and checking of the open field. Or, rather than using the home cage as a vehicle to refrain from checking, the quinpirole rat may be merely using it to escape the open space of the open field environment, a suggestion bolstered by the fact that not only quinpirole- but also saline-treated rats preferred the home cage. Clearly, to discount the alternative interpre-

tations, the current preference-like paradigm should be refined to require a certain amount of work to access the home cage, an amount that is beyond the interest of saline rats. Because quinpirole rats would need to exert extra effort for the opportunity to suspend their checking behavior, this would offer a more compelling test of whether checking behavior does, or does not, provide "good cheer."

It should be noted that the present findings do not address the remaining criterion for clinical compulsion, namely, the presence of insight into the "senselessness" of the compulsion. Consequently, for a full test of whether or not quinpirole rats experience their activity as "compulsive," future studies must address this criterion as well.

Animal Model of OCD

We noted previously [16] that compulsive checking may share mechanisms with drug-induced sensitization, as both phenomena are induced by quinpirole and exhibit similar features [23,27,28]. However, a blanket inference that all drugs that induce sensitization produce compulsive behavior seems unwarranted without a series of validation studies as being done for quinpirole [16; present study]. In fact, one must consider that the relevant factor for the genesis of compulsive checking may not be the mere induction of sensitization to quinpirole. Instead, the relevant factor may be repeated exposure to quinpirole in a specific environment, namely, an environment (such as a large open field) that evokes checking behavior readily. The latter possibility has merit because the psychological and physical characteristics of an environment affect not only the nature of the acute response to psychostimulant drugs [29–36] but also the amount and the type of behavior that is sensitized with chronic drug treatment [23,27,28][37–43].

Our focus on quinpirole-induced checking as a possible animal model of OCD, stemmed from serendipitous observations of an apparent surface similarity of the drug-induced behavior to that of the motor compulsions of patients with OCD [44–46]. While there exist different types of validity by which to evaluate animal models of psychiatric disorders [47–50], our process of validation of the quinpirole preparation does not fit neatly into any one of the described types. Specifically, our validation strategy involves the identification of the essential behavioral, psychological, and neurobiological properties of the human disorder and testing whether the same properties are present in the quinpirole preparation. In this context, we asked previously what characteristics define the spatiotemporal structure of OCD checking and examined whether the same features are found in the behavior of quinpirole-treated rats [16]. Moreover, we ex-

amined whether a pharmacological agent used in the treatment of OCD produces an amelioration of checking in the quinpirole preparation [16]. Similarly, in the present study, we investigated whether the expression of checking in the quinpirole preparation is subject to external inhibitory control as it is the case for compulsive checking in OCD. Other ongoing studies examine the presence of additional attributes of the human disorder.

Although we would view our strategy as striving for face validity, this term is used in a more restricted sense by Geyer and Markou [47]. These authors consider that "face validity refers to the superficial similarity in symptomatology between the model and the disorder," and that this type of validity is of little scientific use, being difficult to defend rigorously because of, invariably, "subjective arbitrary arguments." Clearly, such a description does not apply to the pursuit of validating the quinpirole preparation, as there is nothing arbitrary or subjective in testing for critical properties shared by OCD compulsions and quinpirole-induced checking, especially when those are defined and measured in a strictly objective manner. Of course, the task to identify which properties of OCD are the crucial ones, and how to define them operationally for measurement in the animal, is not a trivial one. However, its difficulties do not imply that the approach lacks rigor. One should note also that our strategy does not seek "superficial similarity" but, on the contrary, asks whether the disease-defining attributes of the human disorder are present in the animal preparation. Thus, our evaluation of the quinpirole preparation as to its face validity, extends well beyond the scope of such a validation as described by Geyer and Markou [47].

The usefulness of an animal model is particularly striking when findings from the model reveal an attribute of the human disorder hitherto unappreciated. While it is still premature for such studies using the quinpirole preparation, nevertheless an incidental observation from the model may prove revealing. Specifically, because quinpirole is a dopamine agonist, and to the extent that the drug does indeed induce compulsive checking behavior, then the model predicts an involvement of dopamine systems in OCD compulsive checking. Indeed, at a point in time when serotonin was thought to be the primary neurotransmitter system in OCD, our early observations with quinpirole were one of the few experimental findings that the authors employed to derive their then novel hypothesis that dopamine may play a role in OCD [51], a notion favored now for a particular subtype of OCD [52,53]. It follows, therefore, that the quinpirole preparation may turn out to be particularly useful for elucidating the role of dopamine circuits in OCD.

Stereotypy, Compulsions and Voluntary Control

The checking behavior of rats under quinpirole had been described as "flexible, yet recurrent" [16]. That is, even though the moment-to-moment flow of checking behavior under quinpirole is unpredictable, checking activity repeats itself on a larger time scale and hence the overall spatiotemporal structure of checking under quinpirole is highly predictable. The presence of recurrent behavior under quinpirole may give a reader the impression that the rat is engaged in a motor automatism uninfluenced by external stimuli or internal cues, akin to "stereotyped behavior" induced by psychostimulant drugs [36,54,55]. Such is not the case, however. Not only does the actual behavior appear as relatively spontaneous to an observer [16,22], but also it is closely coupled to environmental stimuli [16], and is even subject to interruption, as shown here. Nevertheless, we suggest below that the difference in the nature of quinpirole-induced compulsive checking behavior and psychostimulant-induced "stereotyped behavior" is one of degree rather than kind.

Stereotyped behavior induced by psychostimulant drugs is often conceptualized as consisting of movements that are repetitive, aimless and involuntary [54,55]. The view that the behavior is "involuntary" may imply that there are no controls over it, as is apparent from the early labels of the drug-induced behavior as "compulsion" [56], "compulsory" [57] or "forced" [36]. In fact, one method of scoring "stereotypy" evaluated whether prodding the animal would disrupt the drug-induced behavior [58]. However, it is now abundantly clear that psychostimulant-induced behavior is subject to modulation by environmental, psychological and experiential factors [36,38]. Importantly, recent studies showed that rats treated chronically with amphetamine can learn to suppress even sensitized stereotyped movements to obtain milk reward [55,59,60]. Thus, as pointed out by Wolgin [55], stereotyped behavior is not irrepressible, being subject to control by the organism as well as external stimuli. Therefore, the notion that stereotyped behavior is an uncontrollable motor automatism is not justified.

Because the stereotyped behavior induced by psychostimulant drugs is subject to control by external and internal stimuli, therefore, it is not a qualitatively different phenomenon than the quinpirole-induced compulsive checking. However, the two may differ in the degree of controllability, with quinpirole-induced checking being more open to control than the stereotyped behavior induced by other psychostimulant drugs. This suggestion stems from the observation that the variability in spontaneous behavior is greater under quinpirole than amphetamine [61,62], indicating a higher potential for flexibility under quinpirole than amphetamine (and related psychostimulants). Consequently, a wider range and inten-

sity of stimuli may be effective in influencing behavior under quinpirole than amphetamine. Alternatively, the domain of responses induced by quinpirole versus amphetamine-like drugs may be more open to modulation. Such difference in degree of controllability may be related to the specific mode of action of the various compounds and/or to the dosage of the drugs used.

Using the notion of controllability, stereotypy and compulsions can be viewed as sequential points on a continuum along a dimension of spontaneity [30,63]. Normal behavior is at one end of spontaneity as it represents behavior that is free to vary with changes in external and internal stimuli and is readily open to voluntary suspension. The other end, a loss in spontaneity, is represented by stereotyped behavior in that it reflects behavior with a narrow range of possible responses, few effective stimuli to modify it, and a limited capacity to suspend ongoing activity. Accordingly, compulsions fall to the right of stereotyped behavior in that there are relatively many stimuli that can modify compulsive behavior and the behavior can be suspended relatively more easily than stereotyped behavior. Thus, stereotypy and compulsive behavior may be differentiated by the degree of loss in spontaneity and in particular the extent to which the behavior can be suspended by the organism.

Conclusions

Like the compulsive behavior of OCD patients, so, too, the compulsive checking behavior induced by quinpirole is not irrepressible but can be suspended in the presence of appropriate stimuli. However, when checking-evoking cues remain, the suspension of checking behavior is not sustained and after a period of time rats resume their checking behavior, akin to the failed resistance that OCD patients show in refraining from performance of their compulsive rituals. These findings strengthen the quinpirole preparation as an animal model of OCD.

Materials and methods

Subjects and Drugs

Twenty-four experimentally naive Long-Evans male rats (Charles River, Canada) weighing 250 to 300 g at start of treatment were used. Rats were housed individually in translucent polyethylene cages (35 × 30 × 16 cm) in a temperature-controlled colony room with a 12-hr light-dark cycle, and with free access to food and water. Upon arrival from the supplier, they were permitted one week to acclimatize to the colony room, and were then handled by the experimenter for 5 days (2 to 5 min each day) before beginning the study. All treatments and testing were administered during the light hours.

Quinpirole hydrochloride (RBI, Natick, MA) was dissolved in physiological saline (0.5 mg/ml) and injected

subcutaneously under the nape of the neck at a dose of 0.5 mg/kg. Equivalent volumes of saline were used for non-drug injections. The 0.5 mg/kg dose of quinpirole was selected because it is representative of the sensitization effects induced by doses of the drug from 0.25 to 2.5 mg/kg [18] and because it was previously used to induce compulsive checking behavior [16].

Apparatus and Behavioral Analysis

Rats were tested in the apparatus used previously to assess compulsive checking behavior and is described in detail elsewhere [16]. Briefly, it was a large open field consisting of a mirrored glass table (160 × 160 and 60 cm high). Four small Plexiglas/glass boxes (approximately 8 × 8 × 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. For the tests in which an additional container was introduced into the open field, this was either a cage familiar to the rat or an unfamiliar one. The familiar container was the animal's home-cage with bedding that was at least a day old (providing the rat with familiar olfactory cues). The unfamiliar container was an opaque white plastic dish pan of similar dimensions as the familiar cage, but without bedding and novel to the rat. As rats were tested twice in the unfamiliar cage condition, a different unfamiliar cage was presented on each occasion. The open field and objects were wiped clean after each rat with a diluted solution of an ammonia glass cleaner (Windex); the unfamiliar cage was washed clean after each usage with dish detergent and water.

Behavior was videotaped continuously on a video-cassette recorder together with a computer-readable time code (Telcom Research, Burlington, Ontario, Canada). As noted previously [19], in an open field a rat can be either locomoting or not. Periods of no locomotion are referred to as *stops* or *visits*. A computer, interfaced with the video recorder, was used to score locomotor behavior during playback of the video records. Custom-made software provided several measures of distribution of activity, as described previously [16,20,21]. The following measures were selected for the present report: (a) distance traveled; (b) frequency of stops in each open field locale; (c) mean duration of return times to place, where return time is the interval from departure to the next arrival to a given locale; (d) mean stop bout duration, defined as the mean duration of stopping in a given place; (e) total duration of stops, defined as the total time of all visits to a given place; and, (f) sequence of visits, that is, the temporal order of places in which the rat stopped, and derived from this sequence, the number of stopping places in between returns to the home base. The home

base was identified as the locale with the highest total duration of stops [19].

Design and Procedure

Two groups of rats were tested in a repeated measure design: one of the groups was treated chronically with quinpirole (N = 12) and the other one was treated chronically with saline (N = 12). Rats were tested in a semi-random order in all 4 conditions, the restriction being that the two time conditions would be presented before switching to the other familiarity condition.

The experiment consisted of two phases. In Phase I, the experimental group received repeated injections of quinpirole to establish checking behavior, according to our standard protocol of twice weekly injections of quinpirole (0.5 mg/kg) for a total of 10 injections. The control group was treated similarly but injected with saline. Immediately after each injection, the rat was placed into the open field and videotaped for 55 min. The chosen number of quinpirole injections is sufficient to establish reliable checking rituals [16] as well as robust locomotor sensitization [18,22,23]. The 11th to 14th twice weekly injections of quinpirole (or saline) constituted the Test Phase, with either a familiar or an unfamiliar cage present in the open field. Behavior was videotaped for 120 min, with the cage being introduced immediately at the start of the session or after 60 min of open field activity. The cage was placed at one of three locations in the open field, rarely visited during last injection of Phase 1. The placement of the cages in the locale was such that a stop at the locale was identical to a stop inside the cage or on top of the wall of the cage.

The procedure for introducing the animal into the open field was the same throughout the study. Each animal was carried individually in its home-cage from the colony room to the experimental room. After removal from the home-cage, the animal was injected and placed in the middle of the open field facing away from the camera and curtain. For injections 11 to 14, the same preparatory procedure was used, with one minor difference when the familiar (home) cage was introduced immediately at the start of the open field test. Here, before injection, rats were transferred temporarily to a cage with fresh bedding while their home-cage was placed on the open field. At the end of each recording, the rat was carried back into the colony room in its home-cage.

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