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QUINPIROLE INDUCES COMPULSIVE CHECKING BEHAVIOR IN RATS: A POTENTIAL ANIMAL MODEL OF OBSESSIVE-COMPULSIVE DISORDER (OCD)

Henry Szechtman
Dept of Psychiatry and Behavioural Neurosciences, McMaster University
William Sulis
Dept of Psychiatry and Behavioural Neurosciences, McMaster University
and
David Eilam
Dept of Zoology, Tel-Aviv University

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Correspondence:
Dr H. Szechtman
Dept Psychiatry and Behavioural Neurosciences
McMaster University
1200 Main St West
Hamilton, Ontario
CANADA L8N 3Z5
tel: (905) 525-9140 ext. 22201
FAX: (905) 522-8804
email: szechtma@fhs.mcmaster.ca

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Abstract

Rats treated chronically with the dopamine agonist quinpirole (0.5 mg/kg, twice weekly x 10) met 5 criteria for performance of compulsive checking. Specifically, in a large open field with single small objects in 4 of 25 locales, quinpirole rats revisited two places/objects excessively often and rapidly, compared to other locations in the environment or saline controls. They performed a ritual-like set of behavioral acts at these two places/objects and stopped in relatively few locales before returning to the preferred places/objects. Finally, they shifted their behavior to a new location when the object was moved there. Clomipramine (10 mg/kg, daily) postponed, but did not prevent the development of the quinpirole effect. Quinpirole-induced compulsive checking may be an exaggeration of normal checking of home site in rats. Results suggest an animal model of Obsessive-Compulsive Disorder and a role for dopamine in this disorder.

Key words: compulsive checking; home base; animal model; Obsessive-Compulsive Disorder; dopamine; D2 agonist; quinpirole; clomipramine; sensitization; stopping behavior; locomotion; motor rituals; exploration

Obsessive-Compulsive Disorder (OCD) is a psychiatric affliction with a prevalence rate of 1 to 3%, almost twice that of schizophrenia (Karno, Golding, Sorenson, & Burnam, 1988; Weissman, Bland, Canino, Greenwald, Hwu, Lee, Newman, Oakley-Browne, Rubio-Stipec, Wickramaratne, & et al, 1994). The most common form of OCD is compulsive checking (Henderson, Jr. & Pollard, 1988; Rasmussen & Eisen, 1992). This generally involves the performance of routines related to security, orderliness, and accuracy (Reed, 1985, p. 35), but without resolution. As noted by one patient, "I have to go and check, but then I'm not convinced about the checking. So I have to go and check that I checked properly... " (Reed, 1985, p. 153). Checking rituals may be performed for hours, and in extreme cases such preoccupation may prevent the subject from leaving his home (Neziroglu & Yaryura-Tobias, 1991, p. 86). OCD is an economic and emotional hardship not only for the afflicted individuals, but also for those who must live and work with them (Hollander, Kwon, Stein, Broatch, Rowland, & Himelein, 1996). Although the pathogenesis of OCD is unknown, effective pharmacotherapy is often provided by serotonin reuptake blockers, raising the serotonin hypothesis of OCD (DeVeaugh-Geiss, 1991). However, many patients do not respond to such medication (Greist, Jefferson, Kobak, Katzelnick, & Serlin, 1995), and for many others effective treatment includes the co-administration of dopamine antagonists (McDougle, Goodman, Leckman, Lee, Heninger, & Price, 1994). The latter implicates the involvement of dopamine systems in OCD (Goodman, McDougle, Price, Riddle, Pauls, & Leckman, 1990), a suggestion strengthened by recent findings of a higher risk for OCD in males possessing the low activity allele, rather than the high activity allele of the catechol-O-methyltransferase gene (Karayiorgou, Altemus, Galke, Goldman, Murphy, Ott, & Gogos, 1997).

Several behavioral preparations in animals are sensitive to current anti-OCD medication, and for this reason these behavioral paradigms had been proposed as animal models for the screening of potential anti-OCD drugs (Rapoport, Ryland, & Kriete, 1992; Winslow & Insel, 1991; Woods, Smith, Szewczak, Dunn, Cornfeldt, & Corbett, 1993; Yadin, Friedman, & Bridger, 1991). It has been also suggested that some OCD symptoms resemble species-typical animal behaviors (Holland, 1974; Winslow & Insel, 1991). However, no study has formally shown a correspondence between the form of an animal behavior and the form of compulsive behavior in OCD patients, and in this respect, an animal model of OCD with face validity (Willner, 1984) has not been identified. Here we provide evidence for such a model. We first propose 5 performance criteria for compulsive checking and then show that the behavior of rats treated chronically with the D2/D3 dopamine agonist quinpirole has these characteristics. We also show that the quinpirole-induced compulsive checking behavior is partially attenuated by the serotonin reuptake blocker, clomipramine.

METHODS AND MATERIALS

Subjects. Fifty 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 polyethylene cages (35 x 30 x 16 cm) in a temperature-controlled colony room with a 12:12 h light cycle, and with free access to food and water. Rats were handled by the experimenter for 5 days (2 min each day) prior to the beginning of treatment. All treatments and testing were administered during the light hours.

Drugs. Quinpirole hydrochloride (RBI, Natick, MA) was dissolved in physiological saline (0.5 mg/ml) and injected subcutaneously under the nape of the neck. Clomipramine

hydrochloride (RBI, Natick, MA) was also dissolved in saline (10 mg/ml) and injected intraperitoneally. Equivalent volumes of saline were used for control injections.

Apparatus and Behavioral Analysis. Rats were tested in a large open-field that consisted of a glass table (160 x 160 and 60 cm high) without walls as described in detail by (Eilam & Golani, 1989), and which was placed at least 70 cm from walls of an air-conditioned experimental room illuminated by fluorescent ceiling lights. A mirror below the glass surface provided a bottom view of the rat's limbs and trunk. The open-field platform was partitioned into a grid of 25 rectangular places (locales) but no actual lines were marked on the glass surface. Instead, only a sign for each place was drawn on the glass surface, with 40 cm (twice the length of rat's body, excluding tail) between two adjacent markings (see Fig. 1). A rat's position in the open field was assessed with reference to these markings, the rat being at a particular locale if its body was within a 20 cm square block adjoining the sign. Four small Plexiglas/glass boxes 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 (see Fig. 1). Three of the objects consisted of clear plastic cubes (8 x 8 x 8 cm) secured to the open field with transparent packing tape; one of the cubes was covered with black electrician's tape. All of these cubes had one side open which allowed the rat to put its head and front paws inside the box. The fourth object was a rectangular glass container (10.5 x 8.5 x 7 cm) with the top side open, but covered with a wire mesh. The open field was wiped clean with Windex after each rat was videotaped.

Behavior was videotaped continuously on a video-cassette recorder together with a computer-readable time code (Telcom Research, Burlington, Ontario, Canada). As noted previously (Eilam & Golani, 1989), in an open field a rat can be either locomoting or not.

Periods of no locomotion are referred to as *stops* or *visits*. A stop begins whenever forward stepping is interrupted by a closing step. In making a closing step, the stepping fore- or hindleg lands alongside the corresponding leg; during forward locomotion it lands ahead of the other leg, shifting the animal's weight forward. During *stops*, rats perform various acts including rearing, large lateral movements, grooming and crouching. Therefore, we scored separately locomotor behavior and behavior during stops, as follows.

Locomotor behavior. A computer interfaced with the video recorder was used to score locomotor behavior during playback of the video records, with a resolution of 1/30 of a second, and custom-made software provided several measures of distribution of activity, as described previously (Eilam, Clements, & Szechtman, 1991; Eilam, Talangbayan, Canaran, & Szechtman, 1992). The following measures were selected for the present report: (a) frequency of stops in each open field locale; (b) mean duration of return times to place, where return time is the time interval between 2 successive visits to a given locale; (c) mean stop bout duration, defined as the mean duration of stopping in a given place; (d) total duration of stops, defined as the total time of all visits to a given place; and (e) 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 two most visited locales.

Behavior during stops. The sequence of movements which rats performed during stopping in specific places was scored using tools adopted from the Eshkol-Wachman (EW) Movement Notation (Golani, 1992). On the basis of such EW scores of motor rituals in specific places (for an example, see Fig 3), the following behavioral acts at a given location were quantified from the video records. (a) Vertical movements, where a vertical movement was

defined by a change in the orientation (position) of the head or trunk in the vertical plane. Such movements included rearing and head dips over the edge of the open field. Both the number of vertical movements and the compass horizontal direction of the trunk during each vertical movement, were scored. (b) Lateral movements, where a lateral movement was defined by a change in orientation of the trunk in the horizontal plane, either clockwise or counterclockwise. The number of lateral movements, the direction of turning, and the compass horizontal direction which the trunk reached at the end of the movement, were scored. In scoring vertical and lateral movements, the duration and amplitude of movements were not considered, only the initiations of the movements were counted. Lateral movements of less than 22.5° and minimal vertical movements were ignored. For a rationale of this scoring method, see (Eilam & Golani, 1988). (c) Frequency of contacts with an object, where a contact was scored if the rat inserted its head into the Plexiglas cube; sniffed the object; placed its forelegs on top of the cube; or climbed on top of the object. (d) The distribution of compass directions by which the rat arrived to a given place and of the compass directions by which it left the place. (e) The incidence of grooming and crouching.

Unless noted otherwise, all behaviors were scored from 30 to 55 min after injections of quinpirole and from 0 to 55 min after injections of saline. Saline rats were scored for the entire observation period because they were substantially less active than the drug-treated rats, and usually showed little activity in the 30 to 55 min interval when drug rats were most active.

Mathematical analyses for the presence of a predictable organization in the sequencing of visits was performed using software packages (Hailman & Hailman, 1993; Sprott & Rowlands, 1995), and the following indices were computed: the Limpel-Ziv complexity measure (Kaspar &

Schuster, 1987), the autocorrelation function tau (Gardiner, 1985), and zeroth order Markov entropy (Grimmett & Stirzaker, 1992). The Lempel-Ziv complexity and Markov entropy provide measures of organization and structure in discrete data sets. Low values (<0.5) indicate the presence of structure in the data and are typical of data sets possessing periodicity. High values (>.75) indicate a relative absence of structure, and are typical of randomly generated data sets. The autocorrelation function tau provides a measure of temporal correlations within a time series, where values <1.0 suggest an absence of long range correlational structure and values >5.0 suggest its presence as seen, for instance, in periodic time series. It should be noted that there is a distinction between periodicity, in which a pattern repeats exactly at regular intervals, and recurrence, in which a pattern merely recurs but not necessarily at regular intervals (Devaney, 1986, p. 48)

Procedure. Two studies were performed. In the first study, 14 rats were injected twice a week with quinpirole (0.5 mg/kg) and 14 control rats were similarly treated with saline. After each injection, rats were placed individually into the open field and videotaped for 55 min. The videotapes of the tenth injection were used to obtain the reported measures of the rats' activity. The particular drug dosage and injection regimen were chosen 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 effects of chronic treatment reach a plateau after 8-10 drug injections administered 2 to 8 days apart (Eilam & Szechtman, 1989; Szechtman, Dai, Mustafa, Einat, & Sullivan, 1994; Szechtman, Talangbayan, Canaran, Dai, & Eilam, 1994) and reach near saturation at a dose of about 0.2 mg/kg (Szumlinski, Allan, Talangbayan, & Szechtman, 1997). An additional test from the 14th quinpirole injection is also reported. On this test, the spatial

arrangement of the four objects in the open field was rotated 180 degrees, such that the objects were now located at two other corners and at two other places near the center of the open field (see Fig 1).

In the second study, one group of rats (N=12) was injected daily with clomipramine (10 mg/kg) and twice a week with quinpirole (0.5 mg/kg) for a total of 10 quinpirole injections. A second group of rats (N=10) received an equal number of injections except that they received saline instead of clomipramine. Following each injection of quinpirole, rats were immediately placed for 55 min into the large open field with objects in it, and videotaped. Analyses of activity from 30 to 55 min after the first, fifth and tenth quinpirole injections are presented. The dose and route of administration of clomipramine was chosen on the basis of previous positive findings (Ichikawa & Meltzer, 1995; Woods et al., 1993). The design of the study focused on the development of quinpirole-induced checking behavior to maximize the possibility of identifying a positive effect of clomipramine on quinpirole-induced activity.

RESULTS

Criteria for compulsive checking behavior

To establish whether the behavior in animals resembles the behavior of OCD patients, it is necessary to compare animal behavior to the performance attributes of obsessive-compulsive symptoms. Here we focus on one particular OCD symptom, compulsive checking. In the human, compulsive checking is identified using one of several rating instruments, such as Leyton Obsessional Card Inventory, Maudsley Obsessive-Compulsive Inventory, Comprehensive Psychopathological Rating Scale, NIMH Global Obsessive Compulsive Rating Scale, Yale-Brown Obsessive Compulsive Rating Scale, and DSM IV (Jenike, Baer, & Minichiello, 1990).

However, those instruments take as their data the subject's introspection and self reporting, and thus cannot be applied in the same manner to identify compulsive checking in animals. Nevertheless, it is noteworthy that the instruments, and the Yale-Brown Obsessive-Compulsive Rating Scale in particular (Jenike et al., 1990), probe for compulsive behavior by asking the subject to estimate real-world measures such as the duration of time engaged in the performance of rituals, the frequency of performance, the duration of ritual-free intervals, and the extent to which performance of rituals interferes with normal daily function. A rating of "extreme" is given if the subject engages in the compulsive behavior for more than 8 hr/day and a rating of "mild" if this is less than 1 hr/day. These items are meant to assess the presence of the two most salient features of compulsive behavior, namely, a preoccupation with its performance and a reluctance/resistence to engage in it (Reed, 1985, p. 10). Implicit in the ratings is also the notion that performance of compulsive behavior has a "ritual" quality to it.

In light of the above, we reasoned that compulsive checking would present itself to an observer as a behavior with the following spatio-temporal structure:

(1) in the subject's territory, there would be one or two places/objects to which the subject returns excessively more often than to other places/objects in the environment;

(2) the time to return to these preferred places/objects would be excessively shorter than to other places/objects;

(3) excessively few places would be visited in between returns to the preferred places/objects;

(4) a characteristic set of acts would be performed at the preferred place/object, which would differ from the acts performed at other locations/objects; and,

(5) activity would be altered when the environmental properties of the places/objects are changed.

The first 3 performance attributes should reflect a preoccupation with and a reluctance to leave the checked place/object, and are related to the measures on the Yale-Brown Obsessive-Compulsive Rating Scale. The notion that OCD performance is ritual-like, would be encompassed in the fourth property of the spatio-temporal structure of compulsive checking. The fifth criterion, though not usually probed on the rating scales is included because, as will be considered in the Discussion, it addresses the property of coupling between OCD rituals and environmental stimuli/context. In the following sections, behavioral findings are examined as to whether or not they meet the above criteria for the spatio-temporal structure of compulsive checking. The last section presents the results of pretreatment with clomipramine on the identified measures of checking behavior.

Excessive number of returns to place/object

As found previously (Szechtman et al., 1994b), rats administered the tenth injection of quinpirole in a large open field were active throughout the test period (data not shown). Of relevance here, they returned to two specific locations in the environment several times more frequently than to any other place (Fig. 2, left). The incidence of visits (stops) at each of these locations was 101.5±8.2 (site #5) and 89.4±11.3 (site #14), which is about 5 fold higher than expected on the basis of a uniform frequency distribution of stops to places of visit in the open field. This number of greater than would be expected visits, was significantly higher than the corresponding ratio of observed to expected visits in the saline rats (for site #5, 5.27±0.25 *vs* 3.41±0.15, $p<0.001$; for site #14, 4.35±0.29 *vs* 1.72±0.17, $p<0.001$; t-tests). As is evident from

Fig. 2, an object was present at each of these preferred sites. It should be noted that the differences between quinpirole and saline rats were similarly significant when the data were analyzed with respect to the two highest rank frequency of stops, regardless of the physical location of the visited places.

Excessive rapid return time to place/object

Also shown in Fig 2 is the distribution of return times to each visited place. Return time is the duration of time that the rat stayed away from a given locale and is given by the absolute value of the difference between the time of departure from the place and the time of next arrival to the place. As is evident, the periods of time that rats under quinpirole stayed away from the two preferred places was 1/20th of that shown by saline rats (for site #5, 11.0±0.7 s under quinpirole *vs* 225.9±26.6 s under saline, $p<.001$; and, for site #14, 19.0±3.9 s *vs* 371.2±110.3 s, $p=.003$, t-tests).

Few visits to other places

Between successive returns to a preferred location/object, quinpirole rats typically stopped at only one additional place compared to about 4 stopping places in saline rats (0.8±0.1 *vs* 3.7±0.4 stopping places, $p<0.001$, t-test).

Motor rituals

From the study group of 28 subjects, the videorecords of 5 quinpirole and 5 saline rats were selected and the animals' movements were analyzed for the presence of motor rituals, where a motor ritual constitutes some set of behavioral acts which are performed according to an idiosyncratic rule. It was evident that at a key location that was common to all rats (site #14 in Fig. 1), both quinpirole and saline rats performed a few typical acts. These included contact with

an object (an open Plexiglas box) present at this corner location, and movements in the vertical and lateral domains (Golani, 1992). Saline-treated rats performed these acts with much variability: they made contact with the box by climbing onto it, by leaning on it with the forelegs, placing their head into it, or by merely touching it with the snout; they made a variety of vertical movements such as head dips beyond the edge of the open field, head raises above the horizontal, elevations of the forequarters above the open field surface, or rears on their hindlegs; finally, they made lateral turns both clockwise and counterclockwise to face different directions in the environment. These acts were repeated often, seemingly in a random sequence.

Quinpirole rats were different, however. They had fewer types of acts, performed them with less variability, and repeated each one less often during a visit to the key location. The diminution in types of acts was evident by the absence of grooming and crouching in quinpirole rats, acts which all of the saline rats performed, spending 114±34 s in grooming, and 291±86 s in crouching. The decrease in variability was most conspicuous in the performance of lateral movements, as quinpirole rats turned to one direction predominantly whereas saline rats turned to face many compass directions. The directional turn bias was significantly higher for the difference between turn frequency to two most preferred compass directions (7.0±0.9 turns in quinpirole *vs* 2.6±0.8 turns in saline rats, $p<.004$, t-test), even though turn frequency was 9 fold higher in saline than quinpirole-treated rats (12.3±5.3 *v*s 1.4±0.1 turns per visit, $p=.05$, t-test). Finally, quinpirole rats repeated a behavioral act typically less than twice compared with 5 to 12 repetitions by saline controls (contact with object: 1.2±0.1 *vs* 5.8±2.5 repeats, $p = .10$; vertical movement: 1.3±0.1 *vs* 8.6±3.3 repeats, $p=.03$; lateral movement: 1.4±0.1 *vs* 12.3±5.3, $p=.05$, t-tests). However, despite fewer repetitions, quinpirole rats performed every act on virtually every

visit to the key location (one type of act was skipped on only 8 of 299 visits). Not surprisingly, given fewer movement repetitions, the mean duration of visits was much shorter in quinpirole than saline rats (3.4±0.5 *vs* 421+197.8 s; p = .016, Mann Whitney U Test).

Quinpirole rats were also more confined in the compass direction of arrival to and departure from the key location. Seventy-eight percent of all arrivals were from one compass direction in quinpirole rats *vs* 56% of the arrivals in saline controls (p = .003), and the proportions of departures in one compass direction were similarly different (89% *vs* 71%, p=.006). Remarkably, in 77% of all departures, quinpirole rats turned clockwise to the preferred compass direction and left the locale, while in saline rats this incidence was only 48% (p=.009, Fisher's exact probability tests).

Put together, the described differences between quinpirole and saline-treated rats substantiate an observer's impression of a ritual-like quality to the motor behavior of quinpirole rats. Specifically, the following motor ritual could be discerned. Quinpirole rats would arrive to the key location from a preferred compass direction; touch the object; make a vertical movement; turn laterally - usually clockwise - to a preferred compass direction and leave the key location to another place. These acts would be virtually never skipped and would be repeated only once or twice during a stop. It is probably this limited and invariant number of behavioral acts at the key location, together with brief but frequent and relatively rapid returns to the place, which gave an observer the impression of compulsive performance of a motor ritual (Fig 3, left). Behavior of saline rats, despite similar elements, did not appear to have a ritualistic quality to it as every act was repeated unpredictably often, and returns to the key location were relatively few (Fig 3, right).

A different kind of motor ritual was present at the other key place, which was located towards the center of the open field and on which there was a glass container covered at the top with a wire mesh (site #5 in Fig 1). Twenty visits to this location were scored for each rat, or the entire observation period in the case of saline animals which had fewer than 20 visits. Quinpirole rats made contact with the object on only 50% of the 100 visits scored at this location, whereas saline rats touched the object virtually every time (60 out of 64 visits to this place). As was the case at site #14, so too at locale #5, quinpirole rats had a preference for a particular compass direction of arrival to the locale, which was stronger than the preference shown by saline rats ($p = 0.0015$, Fisher's exact probability test). Moreover, quinpirole rats had a typical orientation with which they approached the object, because almost always (in 98 of 100 instances) they approached it with a side of their body whereas saline rats sometimes approached it snout on (in 27 of 54 instances) and sometimes with a side of the body. In 4 of the quinpirole rats the approach to the object was typically directed to a particular corner of the object; the other rat approached the object from any side of it but always by keeping the box on the right side of its body; saline rats arrived to the box from all directions. Finally, quinpirole rats repeatedly walked over the glass container, which the saline rats never did.

Context specificity

To examine the contextual specificity of quinpirole-induced motor activity, we compared the rat's behavior in a key location (site #14 in Fig 2) with the behavior in a non-preferred location (also a corner of the open field but on which there was no object present, site #18). We also moved the object from the key location to the non-preferred site, and examined whether a motor ritual developed there. As shown in Table 1, when an object was placed at the non-

preferred site, the frequency of visits to this locale increased, return time declined, the time spent at that location increased, and the incidence of rearing increased. Removal of the object from the key location had also some effect on behavior: the mean duration of staying at the locale declined, as well as the frequency of rearing and the preference to use one compass direction for leaving the locale (Table 1). Thus, the new location to which the object was moved acquired some of the characteristics associated with the spatio-temporal structure of checking behavior and the old place from which the object was removed, lost a few of those features, suggesting that activity under quinpirole was influenced by environmental factors.

At first glance, the above suggestion may seem contradictory to the results of the previous section showing a ritual-like quality to the motor activity under quinpirole. However, although ritual-like, the moment-to-moment flow of behavior under quinpirole appeared unpredictable (see Fig 4 for a time series of stops in a representative quinpirole rat). This impression was substantiated by mathematical analyses in which no predictable organization in the sequencing of visits could be identified, using for the analyses the entire sample of 14 quinpirole and 14 saline rats. Specifically, the Limpel-Ziv complexity measure of the time series of stop positions indicated an absence of periodicity in both the quinpirole and saline rats, though the paths appeared relatively more structured under quinpirole than saline (0.95±0.16 *vs* 1.20±0.01, $p < .001$, t-test). An absence of periodicity under quinpirole was reflected also by the correlation time from the autocorrelation function (0.557±0.007 *vs* 0.711±0.132, $p < .001$, t-test). Zeroth order Markov entropies, which reflect the unconditional predictability of the rat's present location, demonstrated that for both groups the predictability was low but relatively higher for quinpirole (0.709±0.005) than saline (0.888±0.003). Thus, formal analysis suggests that

quinpirole animals moved from place to place in a somewhat more structured manner than the saline controls. However, their spatial pattern of locomotion was not rigid and periodic. Instead, it appeared flexible, yet recurrent. In all, absence of periodicity in the behavior of quinpirole rats is consistent with the interpretation that the rats' activity can be modulated by environmental events.

Effects of clomipramine

Since clomipramine had been found effective in the treatment of OCD compulsions (The Clomipramine Collaborative Study Group, 1991), we examined whether this serotonin reuptake blocker would attenuate development of the checking activity induced by quinpirole, measured by the first two criteria for the spatio-temporal structure of compulsive checking. Compared to rats treated with saline-quinpirole, clomipramine pretreated rats made fewer revisits to their preferred site and did not return to it as rapidly (Fig 5), suggesting that clomipramine attenuated the development of at least these aspects of presumed checking activity. However, this effect of clomipramine was not persistent as group differences declined by the tenth exposure to quinpirole for two of the three variables measured (Fig 5).

DISCUSSION

The prevalent viewpoint holds that behavior induced in animals by dopamine stimulants is a model of schizophrenia (Segal & Schuckit, 1983). However, chronic treatment with the dopamine agonist quinpirole did not induce in rats an expected psychotic-like behavioral profile (Szechtman et al., 1994b). Instead, it was noted that quinpirole-induced behavior was ritual-like with a surface similarity to the motor compulsions of patients with OCD (Eilam, Canaran, & Szechtman, 1989; Eilam & Szechtman, 1995; Einat & Szechtman, 1995). The present report is a

follow-up on those serendipitous observations, and uses a set of formal criteria to evaluate the similarity between the drug-induced behavior and a specific OCD symptom, compulsive checking. Below we address: a) adequacy and attainment of proposed criteria; b) relationship of drug-induced to normal checking; and, c) implications of the quinpirole model.

The form of compulsive checking

Psychiatry has generally focused upon understanding the *content* of obsessive-compulsive behavior, but it had been noted that to unravel the mechanisms of OCD, one should focus instead upon the *form* of the symptoms (Reed, 1985). Such a focus is particularly relevant for an animal model because the spatio-temporal structure of compulsive behavior can be measured in the same domain across species. Unfortunately, a suitable quantitative description of human compulsive checking is not available. Nevertheless, based on items rated on the Yale-Brown Obsessive-Compulsive Rating Scale, we surmised that performance of compulsive checking would be distinguished by an exaggerated hesitancy to leave the item(s) of interest and that this would be indexed by measures of return to the checked item. On this basis, we proposed that both the frequency of returns and the speed of returning (return time) to the item(s) of interest, would be exaggerated in compulsive checking. Along the same line, we also expected reduced attention to other features of the environment between episodes of checking. As results showed, behavior under quinpirole did have all three of these features, in that there were excessively many, and relatively rapid, revisits to two places/objects in the subject's environment, and relatively few stops in other places, compared to the performance of saline controls. In this respect, quinpirole-induced activity meets the first 3 criteria for compulsive checking. However, without similar data in the human, one cannot be certain that the attributes

measured here are also characteristic of human compulsive checking. Clearly, such a study is warranted.

The other two criteria proposed here for compulsive checking - ritual-like motor activity and environmental dependence - have been identified in human OCD. With regard to rituals, OCD symptoms often consist of idiosyncratic motor routines, as illustrated in the following diary record of a patient with checking compulsions who describes switching on the TV thus: *Before I start to turn it on, I have to wash and dry my hands. Then I go and touch the corner curtain followed by touching the side of the TV two times. Then I have to go back and wash my hands. When I am finished with that I will look behind the lamp 2 times, go back and wash my hands, come back, move the lamp to the left and look behind it, move the lamp two times to the right and look behind it, go back, wash my hands, and then look in back of the TV on the left 4 times, washing my hands in between each one. Then I look in back of the TV on the right 8 times, wash my hands, and put the TV on channel 6. Then I turn the knob from channel 6 to 7, 4 times, and from channel 6 to channel 8, 4 times. Then finally I turn it on. The whole thing probably takes around half an hour*. (Rasmussen & Eisen, 1991, p. 28). As shown here, quinpirole rats had distinct motor routines which they performed at each of the preferred places. These routines formed the behavioral elements of almost every visit to the place/object of interest, consistent with an observer's impression of a ritual-like performance. In this respect, therefore, quinpirole-induced activity meets also the fourth criterion for the performance of compulsive checking.

With regard to the criterion of environmental modulation of compulsive checking, this is seen, for instance, in reports that OCD behavior is performed usually in the person's home and not outside of it. A striking example of such context-specificity is provided by the patient who

often slept at park benches to avoid going home, because at home he would be compelled to perform his rituals (Rapoport, 1989, p. 132). However, removing the object(s) being checked does not eliminate the compulsive checking in OCD patients. Rather, checking becomes attached to a different object/location (Marks, 1987). As shown here, moving the object of interest to a new location, induced a change in measures of quinpirole activity consistent with a shift in checking from the old to the new locale. However, not all features of rat's activity at the old locale shifted to the new location of the object. This is probably because a checking ritual requires repeated practice for its establishment and this was the first test for the rats with the new arrangement of objects. It appears, therefore, that quinpirole-induced activity meets also the final criterion for the performance of compulsive checking.

Experience of compulsion

Although the behavior of rats under quinpirole may *look like* the behavior of OCD checkers, mere observation of behavior is insufficient to infer the presence of "compulsions". As stated by Reed (1985; p. 11): "However repetitious a piece of behaviour, however stereotyped, however bizarre, its definition as 'compulsive' relies totally upon the form of the associated experience". Specifically, to be called "compulsive", 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". Clearly, it remains to be shown whether the rat engaged in "compulsive checking behavior" under quinpirole, experiences its activity as "compulsive", defined by the above criteria. While the task is challenging, without appropriate tests of the associated experience, the rat's behavior under quinpirole remains open to alternate interpretations.

Motivational basis of compulsive checking behavior

It can be argued that compulsive checking in OCD is an exaggerated form of normal checking regarding one's well-being and security (Reed, 1985). For the following two reasons, quinpirole-induced activity may represent a similar exaggeration of normal checking in the rat. First, many species engage in territorial patrols and display typical rituals along the territorial boundary lines (Nolet & Rosell, 1994; Serruya & Eilam, 1996), suggesting that checking routines are part of normal life in animals. Second, checking implies that the subject attributes a special significance to the specific environmental stimulus, context, or event, and, indeed, it is known from other studies (Eilam & Golani, 1989; Eilam & Golani, 1990; Eilam & Golani, 1994; Golani, Benjamini, & Eilam, 1993) that the preferred places/objects do posses a unique significance to the rat. In particular, normal rats establish one or two key locations, termed home base(s), and organize their behavior in relation to them. The crucial variable that identifies a location as the rat's home base is the cumulative time of stopping, the highest one or two durations defining a home base (Eilam & Golani, 1989). In every case, the cumulative stopping times for the quinpirole rats were the longest at the two preferred locations. It turns out, therefore, that the presumed spatio-temporal structure of checking was directed under quinpirole towards the home base, a probable target of normal checking. Interestingly, consistent with the notion of the home base as a place of security, normal rats often return to the home base to engage in grooming and crouching (Eilam & Golani, 1989), behaviors often suggestive of emotional relief (Fentress, 1968; vanErp, Kruk, Meelis, & Willekens-Bramer, 1994). However, quinpirole rats never displayed grooming and crouching. Conceivably, compulsive checking under quinpirole may be related to an apparent absence of emotional relief from visits to home

base, similar to the reported lack of satisfaction from checking suffered by OCD checkers (Pitman, 1989; Reed, 1985).

Insights from quinpirole model

The fact that chronic treatment with a dopamine agonist was effective in inducing compulsive checking behavior in the rat, strengthens the hypothesis that dopamine systems play a role in OCD (Goodman et al., 1990). Furthermore, consistent with the observation that OCD checkers may be different from OCD washers (Jenike et al., 1990, p. 227), the model suggests that the role of dopamine may be greater in the former patients because no grooming was observed under quinpirole. Interestingly, recent findings show that separately from its binding to D2 receptors, quinpirole is also a ligand at a novel MAOI-sensitive site linked to D2-like receptors (Levant, Moehlenkamp, Morgan, Leonard, & Cheng, 1996). Conceivably, quinpirole may induce checking by binding to this site, consistent with the observation that an MAO inhibitor, clorgyline, blocks the locomotor effects of quinpirole (Allison, Ivanova, & Greenshaw, 1995; Culver & Szechtman, 1997). If so, MAO inhibitors which had been used clinically for OCD (Jain, Swinson, & Thomas, 1970; Jenike, 1982; Jenike, Baer, Minichiello, Rauch, & Buttolph, 1997; Liebowitz, Hollander, Schneier, Campeas, Welkowitz, Hatterer, & Fallon, 1990) may exert their effects by acting on the same site.

The finding that clomipramine attenuated measures of quinpirole-induced checking, may be related to a dopamine blocking activity of clomipramine (Austin, Lydiard, Ballenger, Cohen, Laraia, Zealberg, Fossey, & Ellinwood, 1991), and/or indicate a dopamine-serotonin interaction in OCD (Austin et al., 1991; Wise & Rapoport, 1989). However, the observed effect of clomipramine was transient. Clinically, clomipramine treatment is effective in only 50% of

OCD patients and the rate of relapse is high (Leonard, Swedo, Lenane, Rettew, Hamburger, Bartko, & Rapoport, 1993). Possibly, the quinpirole preparation is a model for the type of OCD that is less responsive to clomipramine.

A striking feature of the current model is environmental modulation of the quinpirole-induced compulsive checking. Perhaps this should not be surprising, given that by its nature checking implies an awareness and interaction with the environment. However, it does raise the novel suggestion that compulsive checking may share common mechanisms with drug-induced sensitization, since context-dependent and context independent locomotor sensitization to quinpirole had been observed in similar paradigms (Einat, Einat, Allan, Talangbayan, Tzafnat, & Szechtman, 1996; Szechtman, Talangbayan, & Eilam, 1993).

In summary, the similarity between the forms of activity under quinpirole and compulsive checking in OCD, the possible presence of a motivational basis for each, and an effect of clomipramine on both behaviors, suggest that the quinpirole preparation provides an animal model of OCD with strong face validity. Furthermore, because quinpirole is a dopamine agonist, the model indicates that dopamine may play a role in OCD, at least in compulsive checking.

Figure Captions

Fig 1. Schematic of open field locales and arrangement of objects. The open field platform (160 x 160 cm) was partitioned into 25 locales, numbered 1 to 25 as indicated in the figure. The distance between horizontally and vertically adjacent numerals was 40 cm. The 3 Plexiglas cubes (8 x 8 x 8 cm) were located as shown, with the open side of the cube indicated by the dotted line. Two of the cubes were clear and one was black as represented by the grey shading. The object at location #5 was a glass jar covered with a wire mesh. Dimensions of the open field and of the objects are drawn to scale. The actual numerals were not visible, but, instead, a unique black symbol was marked on the glass platform to identify each location; the dimension of each symbol was approximately 3 x 3 cm. On the test when the location of objects was rotated 180 degrees, objects were moved from site #10 to #18, from #14 to #22, from #5 to #9, and from #8 to #4. Numerals correspond to locale (site) numbers in text and figures.

Fig 2. Distribution of frequency of stops and return times to each locale in the open field for rats injected with quinpirole (left) and saline (right). For each of the 25 locales the maximum number of data points is 14 (the number of rats). Underlined numerals along the X-axis indicate locales containing an object. Gray shading highlight sites #5 and #14, the identified key locations to which quinpirole rats returned most frequently and rapidly.

Fig 3. Motor acts performed at the key location (site #14) by an exemplary rat injected with quinpirole (left) and by a rat injected with saline (right). Five consecutive visits to the place are shown, demarcated by horizontal lines. Symbols represent movement types: the first and last symbol in each visit indicate, respectively, the compass direction of

arrival to the place and the compass direction of departure from the place (in units of 45 degrees); contacts with the box are shown by ⊥, ⊤, ⊣, and indicate, respectively, snout contact with the box, forelegs on top of the box, and poking of the head into the box-opening; vertical movements are indicated by↑ and ↓, with the adjoining letter identifying the body part performing the vertical (h = head, t = torso, P = pelvis) and the combinations representing head dips below the horizontal, head raises, partial rears and rearing on hindlegs; clockwise and counterclockwise lateral movements are shown respectively by ∩ and ∪, and the numeral inside the symbol indicates the compass direction to which the lateral movement was made in units of 45 degrees, where 0 is north (top of the open field). A bold symbol identifies the first occurrence of a movement type. The left to right order of symbols indicates the order in which acts were performed. The presentation of the behavioral sketch is adapted from the Eshkol-Wachman Movement Notation score (Golani, 1992).

Fig 4. The sequence of visits to places in the open field by one representative rat injected with quinpirole. The first 170 stops are shown. Underlined numerals along the Y-axis indicate locales containing an object. While there is a high recurrence of visits to a few places, there is no evidence for a periodic structure in the sequence of visits.

Fig 5. The effect of pretreatment with clomipramine on the development of checking behavior induced by quinpirole. Measures of checking behavior are the frequency of returns to the preferred site (left column), the ratio of observed to expected visits assuming a uniform frequency distribution of stops (middle column), and the mean return time to the preferred site, following the first, fifth, and tenth injections of quinpirole. Preferred site

was identified as the site with the highest cumulative time of stopping. Values are mean±SEM. * $p < 0.05$ compared to rats treated with quinpirole plus saline (Sal-QNP), t-test. CMI-QNP indicates the quinpirole plus clomipramine group.

Table 1. Characterization of the context-dependency of quinpirole-induced motor activity. On the first test, the arrangement of objects was as usual: an object at the key location and no object at the non-preferred place (shaded columns). On the second test, the spatial arrangement of objects in the open field was rotated such that an object was no longer present at the key location but one was at the non-preferred site (clear columns). Values are mean±SEM as appropriate. Statistical comparisons were performed for the measure with and without the object at each site (Wilcoxon Signed Ranks Tests, and Fisher's exact probability test). The preferred compass directions of departure were clockwise and counterclockwise at Sites #14 and #18, respectively.

Measure	Key Location (Site #14)			Non-preferred Location (Site #18)		
	Object present	Object absent	p	Object absent	Object present	p
Frequency of stops	60.4±16.6	66.2±13.1	ns	13.4±2.7	73.6±14.7	0.009
Return time to place (s)	30.2±8.8	24.9±6.9	ns	123.0±26.0	19.1±3.6	0.012
Stop bout	3.4±0.5	1.9±0.2	0.011	2.5±0.3	3.2±0.5	ns
Total duration of stops (s)	193.1±55.4	121.5±22.9	ns	33.7±7.6	218.8±34.5	0.005
Frequency of rearing	35.6±15.3	1.0±0.5	0.043	0.4±0.4	20.6±2.0	0.042
Compass direction of departure preference	259/291 (89%)	250/337 (74%)	0.001	37/62 (60%)	196/372 (53%)	ns

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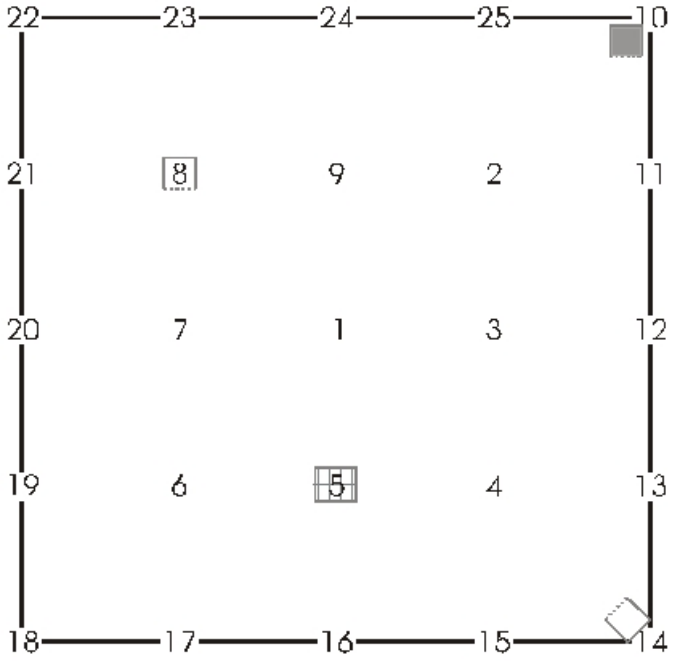
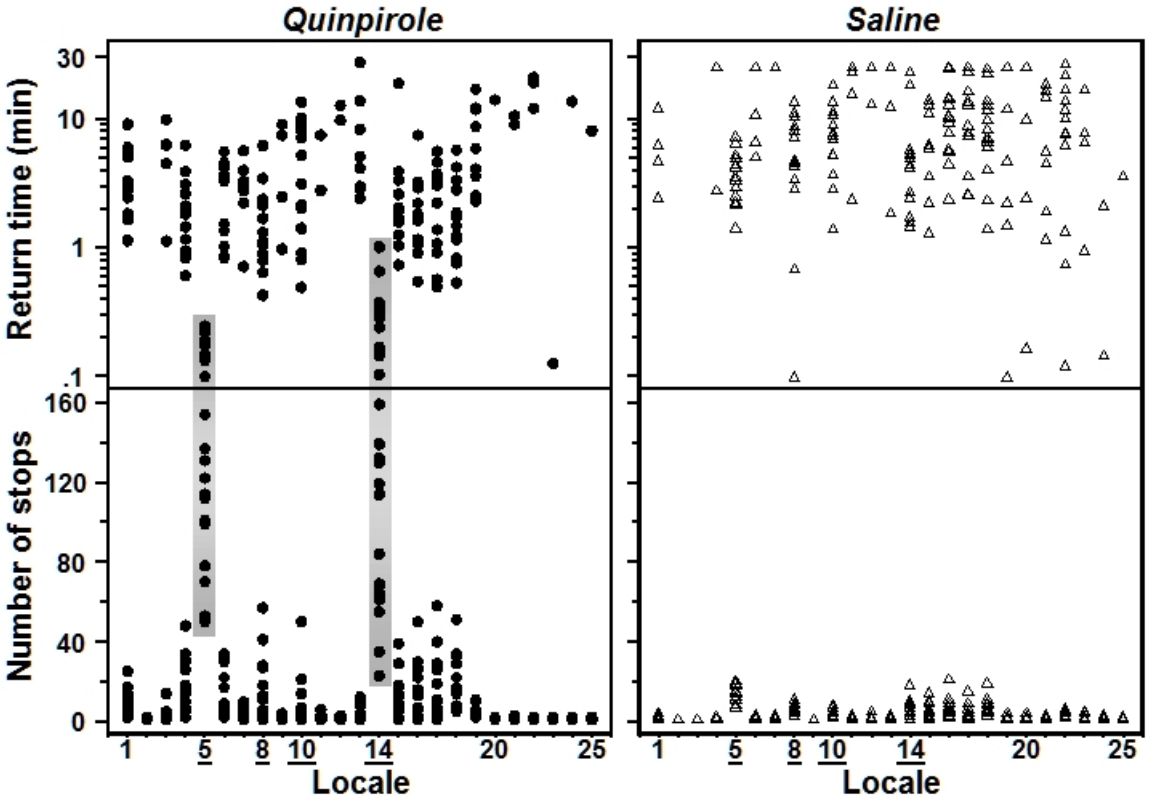


Fig 1. Szechtman



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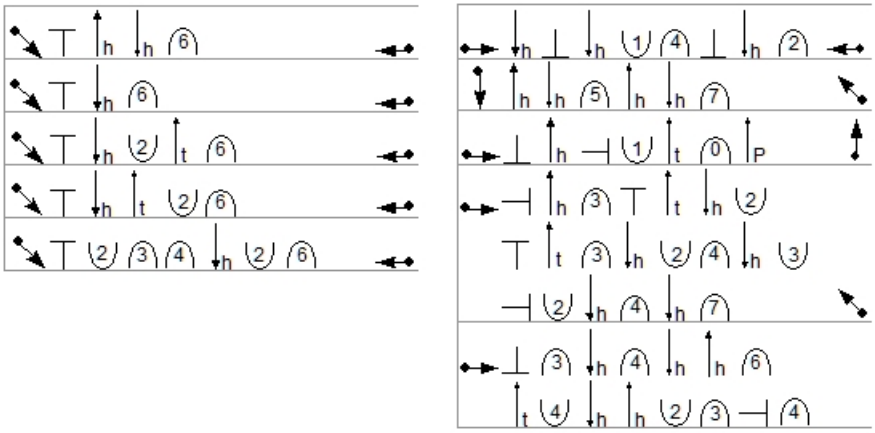

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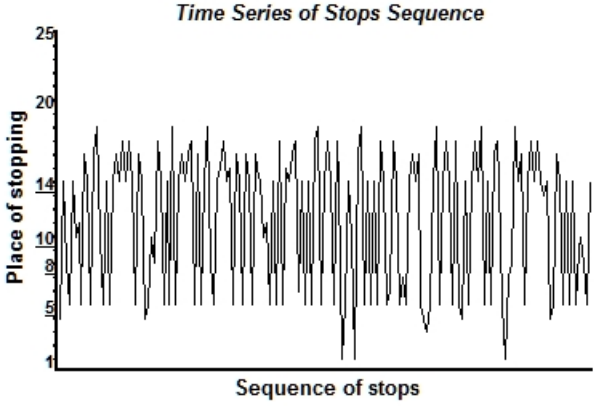

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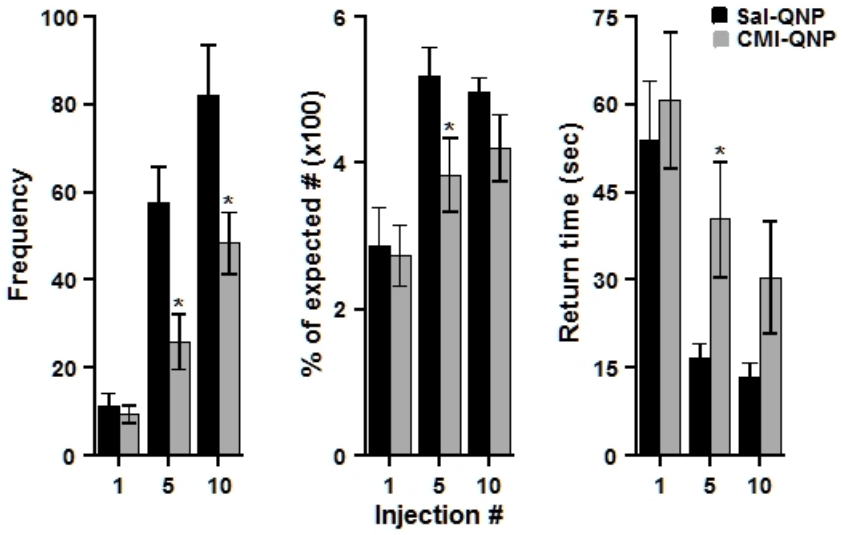

Fig 5. Szechtman