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Meta-analysis

From an animal model to human patients: An example of a translational study on obsessive compulsive disorder (OCD)

David Eilam*

Department of Zoology, Tel-Aviv University, Ramat Aviv 69978, Israel

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ABSTRACT

The application of similar analyses enables a direct projection from translational research in animals to human studies. Following is an example of how the methodology of a specific animal model of obsessive-compulsive disorder (OCD) was applied to study human patients. Specifically, the quinpirole rat model for OCD was based on analyzing the trajectories of travel among different locales, and scoring the set of acts performed at each locale. Applying this analytic approach in human patients unveiled various aspects of OCD, such as the repetition and addition of acts, incompleteness, and the link between behavior and specific locations. It is also illustrated how the same analytical approach could be applicable to studying other mental disorders. Finally, it is suggested that the development of OCD could be explained by the four-phase sequence of Repetition, Addition, Condensation, and Elimination, as outlined in the study of ontogeny and phylogeny and applied to normal development of behavior. In OCD, this sequence is curtailed, resulting in the abundant repetition and addition of acts.

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1. Prologue

Obsessive-compulsive disorder (OCD) was considered as a variant of insanity until 1850. It was then regarded as belonging to the class of neuroses, later still as a variant of newly formed psychosis, and finally as a proper neurosis. In the late 1880s, OCD achieved full clinical nosological definition (Berrios, 1989). Obsessions refer to recurring, persistent thoughts, impulses, or images that inappropriately intrude into awareness and cause marked distress or anxiety. Compulsions are the need to repeat physical behaviors such as checking or counting things, and they occur as a response to an obsession or in accordance with strictly applied rules (APA, 2000). Regarding the cause of OCD, Sigmund Freud theorized that it is brought on by a psychological trauma (Stein and Stone, 1997), and it was not until the early 1980s that Judith Rapoport posited the notion that OCD is a physiological disorder (Rapoport, 1989a,b). Once the notion that OCD has biological roots was established, the search for reminiscent animal behavior and animal models began. Indeed, studies of human compulsions frequently describe the profuse rate of performance of behavioral patterns using terms borrowed from ethology, such as 'displacement activity' and 'stereotypy' (Insel, 1988), or 'ritualized behavior' (Rapoport, 1990). In ethology, ritualized behavior is described as a behavior that has become divorced from its original function and

* Corresponding author.
E-mail address: eilam@post.tau.ac.il
URL: http://david-eilam.weebly.com/.

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now possesses a display function. This involves an increase in conspicuousness by means of simplification and exaggeration of form, rhythmical repetition, emphasis of particular components, and a constancy in vigor and rapidity with which the behaviors are performed (Immelmann and Beer, 1989). In terms of form, although these properties can be strictly applied to compulsive OCD rituals, in animal behavior ritualized behavior has a communicative function whereas in OCD patients compulsions are usually aimed at gaining a brief relief from the intrusive obsessions. Indeed, in one of the early discussions of animal models of OCD, Thomas Insel (1988) wrote: "*The available analysis of the phenomenology of compulsive rituals pales before elegant observations of analogous behaviors in fish and birds*". The next step was to try to induce compulsive-like behavior in animals and to examine whether they could serve as models for OCD.

2. Animal models: the designation of compulsive-like OCD behavior in animals

Animal models are usually assessed and classified in accordance with the criteria established by McKinney (1988), such as that of: (i) face validity, based on an analogy between the model and OCD the symptoms; (ii) predictive validity, when the model is sensitive to treatment modalities of OCD; and (iii) construct validity, in which there is a similarity in the neural system and mechanisms between the model and OCD. Various animal models for OCD were offered, each with different pros and cons (see Alonso et al., 2015; Manning, 2016; Monteiro and Feng, 2016; Szechtman et al., 2016). Of these models, the present survey focuses on the quinpirole-rat model. This was chosen mainly since it is based on tools that were derived from the study of human movement (a sort of reversed-translational approach). These tools were applied to the study of compulsive-like behavior in rats, and then successfully "translated" for the study of compulsive behavior in human patients. In other words, the present survey does not review the available animal models for OCD since, as noted above, this has been thoroughly discussed in recent studies. Rather, the focus here is on the quinpirole rat model, and its implementation in the study of OCD human patients.

Professor Ilan Golani, in the 1970s, first applied the Eshkol-Wachman Movement Notation (Eshkol and Wachman, 1958) to the study of animal behavior, and especially to the behavior of rats (Golani, 1992). Golani's methodology opened up new avenues for a detailed and objective study of rat behavior, first in terms of body movements and subsequently in terms of the paths traversed by rats under various drugs (Eilam and Golani, 1994; Szechtman et al., 1985, 1994). The comprehensive description and understanding of rat behavior obtained through Golani's approach was then utilized for a study of rat behavior under quinpirole, a D_2-D_3 dopamine-stimulating drug (Eilam et al., 1989), leading to the suggestion by Henry Szechtman and his colleagues that the behavior of rats under chronic administration of quinpirole presents a reasonable animal model for human OCD (Szechtman et al., 1998). Specifically, after several subcutaneous injections of 0.5 mg/kg quinpirole (two injections/week), the rats became sensitized, displaying profound activity with excessive and repeated traveling of the same paths and performance of similar acts in the same places (Szechtman et al., 1998). This repetitive behavior of quinpirole rats was described as follows: "*They locomote hurriedly from place to place, seemingly exploring the environment with unbounded curiosity. Yet, they never appear to habituate to the environment or to fatigue. Their level of activity may be as much as 16-fold higher, but yet, this hyperactivity is confined in space to only a restricted portion of the environment, seemingly reflecting a shrinkage of the explored space*" (Szechtman et al., 1994).Indeed, quinpirole rats displayed spatial regularities in their spatial behavior, as illustrated in Fig. 1A–G. While the incessant behavior of the quinpirole rats clearly demonstrates substantial face validity, the model was also shown to have robust construct validity but ambiguous predictive validity (for review see Stuchlik et al., 2016).

While the quinpirole rat model was further supported in numerous studies (e.g. Alkhatib et al., 2013; Tucci et al., 2013, 2014), it was also criticized (Alonso et al., 2015), suggesting that the rats' behavior could be considered as drug stereotypy, (de Haas et al., 2011, 2012). Indeed, after administering other psychoactive drugs, such as amphetamine, traveling along the same path and performing the same acts in the same places also prevailed (Eilam and Golani, 1990, 1994). However, the suggestion that quinpirole-induced behavior is merely drug stereotypy can be rejected by discriminating among what is repeated in this compulsive-like behavior. Specifically, a detailed analysis of the acts that quinpirole rats revealed that while they perform shorter sequences of acts, and fewer repetitions of each act, they perform excessively more repetitions of these sequences. Notably, rat movements comprise progression, clockwise and counterclockwise lateral movements, and up and down vertical movements. More acts appear in a more structured environment (contacting, climbing, and stepping down from objects)—and all these occur in both quinpirole-treated and saline-treated rats. Nevertheless, the recurrence of shorter sequences of acts with fewer repetitions confer upon the behavior a stereotyped form, despite the similarity in act repertoire (when repetitions are excluded) and answer the question of what is the repeated unit in stereotypy (Ben-Pazi et al., 2001; see Fig. 2). Moreover, a distinctive feature of quinpirole-induced behavior is that despite the numerous spatial regularities, quinpirole rats retain a certain amount of flexibility. Specifically, they change the sequence of acts performed in each location, they change certain sections of their trips, and skip or add stops at various places. Indeed, as shown in Fig. 1, while the spatial regularities are apparent, there is a certain flexibility (Fig. 1A,C,E,G). This flexibility is in contrast with, for example, amphetamine stereotypy, which constitutes a sort of motor automatism with periodic repetitions of the same sequence of acts. This is not like the behavior of the quinpirole rats, which seem to show a general plan of action within which they have a certain flexibility. In light of the definition of OCD compulsions as "*purposeful behavioral ritual, perceived as unnecessary, and performed in response to an obsession*. . ." where obsession constitutes recurrent, persistent ideas or thoughts (APA, 2000), the repeated performance in the framework of a general plan is reminiscent of compulsive rituals in response to intrusive ideas or thoughts (Eilam, 2006, 2015). While there are other animal models of OCD (see for review Alonso et al., 2015; Szechtman et al., 2016), the quinpirole rat model was easy to directly applied in human patients by virtue of its analytic approach. In other words, it was possible to copy into human studies the method used for scoring quinpirole rats' stopping places, the paths connecting them, and their behavior at these places.

3. Compulsive rituals in OCD patients

Diagnosis and longitudinal monitoring of OCD patients traditionally employ rating scales, patient introspection, and patient self-reporting. Consequently, very few clinical descriptions have provided a detailed account of who does what, when, and how often (Boyer and Lienard, 2006). For example, in an April 2006 interview to the *Sunday Mirror*, David Beckham, a renowned soccer player and former Captain of England's national team, and a successful male-model, revealed his obsessive-compulsive disorder. Under the title "I want to stop but I can't", which is so typical to OCD patients, Beckham admitted that he cannot control his need to constantly