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# OBSESSIVE-COMPULSIVE DISORDER: INSIGHTS FROM ANIMAL MODELS

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Highlights

- Utility of animal models in research on OCD is considered and insights gained reviewed
- Optogenetic studies in mice demonstrate that hyperactivity in CBGTC circuits can result in compulsive behavior

- Parallel use of several animal models indicates DBS targets may depend on specific OCD endophenotypes
- Mechanisms of compulsive behavior are revealed by considering spontaneous behavior in deer mice, animal models of enhanced SIP, and compulsive checking induced by quinpirole
- Methods of analysis in animal models provide tools for translational research and clinical tests in OCD patients

Abstract

Research with animal models of obsessive-compulsive disorder (OCD) shows the following: (1) Optogenetic studies in mice provide evidence for a plausible cause-effect relation between increased activity in cortico-basal ganglia-thalamo-cortical (CBGTC) circuits and OCD by demonstrating the induction of compulsive behavior with the experimental manipulation of the CBGTC circuit. (2) Parallel use of several animal models is a fruitful paradigm to examine the mechanisms of treatment effects of deep brain stimulation in distinct OCD endophenotypes. (3) Features of spontaneous behavior in deer mice constitute a rich platform to investigate the neurobiology of OCD, social ramifications of a compulsive phenotype, and test novel drugs. (4) Studies in animal models for psychiatric disorders comorbid with OCD suggest comorbidity may involve shared neural circuits controlling expression of compulsive behavior. (5) Analysis of compulsive behavior into its constitutive components provides evidence from an animal model for a motivational perspective on OCD. (6) Methods of behavioral analysis in an animal model translate to dissection of compulsive rituals in OCD patients, leading to diagnostic tests.

Abbreviations: 5-HT, serotonin; ACC, anterior cingulate cortex; AAV, adenovirus-associated vector; DBS, deep brain stimulation; BLA, basolateral amygdala; BNST, bed nucleus of the stria terminalis; cAMP, cyclic adenosine-monophosphate ; CBGTC, cortico-basal ganglia-thalamo-cortical; ChR2, channelrhodopsin; DA, dopamine; DPAT, 8-hydroxy-2-(di-n-propylamino) tetralin hydrochloride; EP, entopeduncular nucleus; EWMN, Eshkol-Wachman Movement Notation; EYFP, enhanced yellow fluorescent protein; fMRI, functional magnetic resonance imaging; FT, fixed time; GABA, γ-amino butyric acid; GSH, glutathione ; GP, globus pallidus; GPi, internal segment of the globus pallidus; H, high stereotypic (deer mice); LGP, lateral globus pallidus; mPFC, medial prefrontal cortex; N, non-stereotypic (deer mice); NAc, nucleus accumbens; NB, nest-building; NMDA, N-methyl-D-aspartate; OC, obsessive-compulsive; OCD, obsessive-compulsive disorder; OFC, orbitofrontal cortex; PDE, phosphodiesterase; PFC, prefrontal cortex; QNP, quinpirole; SA, signal attenuation; Schizo-OCD, comorbid schizophrenia and obsessive-compulsive disorder; SERT, serotonin transporter; SIP, schedule-induced

polydipsia; SSRI, serotonin-selective reuptake inhibitor; STN, subthalamic nucleus; VI, variable interval; VMS, ventromedial striatum; Keywords, Compulsive checking behavior; quinpirole; security motivation system; animal model; nucleus accumbens core; obsessive-compulsive disorder; orbitofrontal cortex; striatum; basal ganglia; deer mouse; endophenotypes

## 1. Introduction

Animal models of psychiatric disorders simulate signs or symptoms of a psychiatric disorder to provide a preparation for testing specific etiological theories and underlying mechanisms of the disorder as well as for conducting preclinical drug evaluations (Eilam and Szechtman, 2005a; Jones *et al.*, 2011; Lazar *et al.*, 2011; McKinney, 1988; Szechtman and Eilam, 2005; Willner, 1984). The use of animal models in psychiatry has had a stormy history in part because of the need to work out their proper place in the context of psychiatry as a scientific discipline (Szechtman and Eilam, 2005). One challenge often levelled at animal models is scepticism that the model fully replicates the clinical condition or bears relevance for the mechanisms of the human condition. Attempts at dealing with this challenge led to influential formulations of criteria to evaluate animal models in psychiatry (Abramson and Seligman, 1977; Belzung and Lemoine, 2011; Geyer and Markou, 1995; Hoffman, 2016b; McKinney and Bunney, 1969; Willner, 1984, 2005; Willner *et al.*, 1992). While the use of animal models in psychiatry is accepted as proper today, it is worthwhile to reiterate briefly what constitutes a "model."

A scholarly exposition regarding what a "model" is and the "tortuous" history of models in psychology was provided by Chapanis (1961). Of relevance to the present review using animal models of OCD, Chapanis (1961) pointed out that a model is "…only an analogy, a statement that in some ways the thing modeled behaves 'like this'" (p. 188). Indeed, "…the worst error committed in the name of models is to forget that at best a model represents only a part — and usually only a small part — of the thing being modeled" (Chapanis, 1961, p. 126). The same notion had been echoed by McKinney (1988), in *Models of Mental Disorders: A New Comparative Psychiatry*, who admonished against the quest for comprehensive animal models of psychiatric disorders because no model can be a miniature replica of the entire human condition. Unfortunately, even today this crucial point is not always remembered. Chapanis (1961) has argued that because of their inherently limited scope, models should be evaluated differently from

theories: “Models, in a word, are judged by criteria of usefulness; theories, by criteria of truthfulness” (p. 119). In other words, good models generate novel insights and new research. Of course, models designed to test particular theory regarding an aspect of the human disorder are evaluated by criteria of both usefulness and truthfulness.

This paper reviews several animal models of OCD symptoms and highlights the insights derived from research using those models. OCD is a severe and highly prevalent disorder (Koran, 2000; Murray and Lopez, 1996), with a lifetime prevalence of 1% to 2% (Crino *et al.*, 2005; Karno *et al.*, 1988; Rasmussen and Eisen, 1991). Symptoms consist of recurrent and persistent thoughts ("obsessions") and/or repetitive, relatively stereotyped behaviors ("compulsions") that the person feels compelled to think or perform but recognizes as irrational or excessive (Goodman *et al.*, 1990; Leckman *et al.*, 2010; Stein, 2002). The most common subjective clinical features are doubt and indecision; and the two most common compulsive behaviors are checking (repeated redoing of actions related to security, orderliness, or accuracy) and washing (generally of hands but sometimes also of clothes, etc.) (Henderson and Pollard, 1988; Rasmussen and Eisen, 1992; Reed, 1985). In the following sections, some aspects of the disorder that benefited from research using an animal model are considered.

When modelling OCD in animals, it is difficult to assess obsessions because their detection depends heavily on verbal or written communications. Compulsions, on the other hand, are manifested behaviourally and therefore observable in animal models. As a result, all of the animal models discussed in this review are putative models of compulsive behaviour involving repetitive actions and often focusing on the structure of those actions. Results provide convergent insights into brain circuits and neurotransmitters involved in the overt, behavioural component of OCD.

Importantly, the review does not provide an exhaustive summary of the growing area of research using animal models of OCD, as a number of such first-rate publications exists (Ahmari, 2015; Ahmari and Dougherty, 2015; Albelda and Joel, 2012a; Albelda and Joel, 2012b; Alonso *et al.*, 2015; Boulougouris *et al.*, 2009; Camilla d'Angelo *et al.*, 2014; Diniz *et al.*, 2012; Eilam and Szechtman, 2005b; Eilam *et al.*, 2012; Grados *et al.*, 2015; Gunaydin and Kreitzer, 2016; Hoffman, 2011; Hoffman, 2016a; Joel, 2006a; Korff and Harvey, 2006; Man *et al.*, 2004; Ting and Feng, 2011b; Wang *et al.*, 2009; Westenberg *et al.*, 2007). Instead, the current synthesis is unique by bringing together several independent investigators who highlight a piece of their research where animal models served as the source and exemplars of fruitful questions and areas of investigation into OCD.

The usual emphasis in translational research of psychiatric disorders is to consider clinical studies as primary, directing animal model research in the laboratory. However, there is another equally important and invaluable property of animal models in psychiatry—using animal models to generate novel findings and hypotheses about the disorder that should be examined in the clinic. The 5 sections which follow each highlights how studies using different animal models of obsessive-compulsive disorder (OCD) generated some novel insights into this disorder. In so doing, the review acknowledges the value of animal work in directing research on OCD and encourages pursuit of theory-driven behavioral neuroscience research on this disorder.

## 2. Insights into OCD from optogenetics in mice: using new technologies to build bridges between mice and humans

Treatment options for OCD are still limited. To develop new, more effective treatments, a better understanding of the underlying pathophysiology is required. Many current models center on the idea that disruption of CBGTC circuit activity may directly lead to obsessions and/or compulsions in OCD patients (Maia *et al.*, 2008; Rauch *et al.*, 1997; Rotge *et al.*, 2010; Saxena *et al.*, 2001). However, this inference is based on very strong correlative evidence from functional imaging studies in patients with OCD. Animal models provide an essential resource for testing whether indeed abnormal activity in CBGTC circuits leads to OCD symptoms, such as abnormal repetitive behaviors. In particular, mouse models can be combined with optogenetic and chemogenetic tools that permit precise control over activity in specified neural circuits, allowing the direct determination of the relationship between activity in a particular neural circuit and behavioral changes relevant to OCD. Here we highlight how use of optogenetic technology in mice made it possible to begin to simulate neuroimaging findings from OCD patients and directly determine if hyperactivity originating in a specific CBGTC circuit node leads to abnormal behaviors relevant to OCD.

### 2.1. CBGTC circuits in OCD

Several key areas of research suggest that dysregulation in CBGTC circuits may lead to OCD symptoms in humans. First, some of the earliest work supporting this theory arises from functional magnetic resonance imaging (fMRI) and positron emission tomography studies which examined metabolic activity in OCD patients, both at baseline and when OCD symptoms were provoked in the scanner (Mataix-Cols *et al.*, 2004; Rauch *et al.*, 1997; Rotge *et al.*, 2008). These studies showed hyperactivity in OFC, anterior cingulate cortex (ACC), caudate (particularly the head), and anterior thalamus, with OFC showing the most robust activation during symptom provocation. Recent studies emphasizing resting state connectivity using both seed-based and graph-theory based approaches

have demonstrated abnormal functional connectivity in OFC (Beucke *et al.*, 2013; Harrison *et al.*, 2013; Harrison *et al.*, 2009; Posner *et al.*, 2014), ACC (Anticevic *et al.*, 2014; Posner *et al.*, 2014), ventral (Anticevic *et al.*, 2014; Harrison *et al.*, 2013; Harrison *et al.*, 2009; Posner *et al.*, 2014) and dorsal striatum (Anticevic *et al.*, 2014; Harrison *et al.*, 2009), putamen (Anticevic *et al.*, 2014; Beucke *et al.*, 2013), and anterior thalamus (Anticevic *et al.*, 2014). Abe et al. (2015) found increased directional connectivity between OFC and ventral striatum using resting state fMRI and Granger causality analysis. Second, structural magnetic resonance imaging studies in OCD patients have generally demonstrated volume changes in key CBGTC circuit hubs, including OFC, ACC, and striatum (de Wit *et al.*, 2014; Pittenger *et al.*, 2011; Rodman *et al.*, 2012). Though two meta-analyses (Radua and Mataix-Cols, 2009; Rotge *et al.*, 2009) and a recent mega-analysis (de Wit *et al.*, 2014) highlight the fact that directionality of findings varies across structural imaging studies, particularly in the striatum, these discrepancies can likely be accounted for by factors including methodological differences (e.g., region of interest vs. whole-brain voxel-based morphometry) and heterogeneity of patient populations (e.g., age, comorbidity, medication status, symptom dimensions). Finally, a last category of studies has examined regional activity during cognitive activation in an attempt to unmask functional abnormalities that may not be present at baseline. Findings have included decreased OFC activation during Go/NoGo tasks (measuring inhibitory control) (Page *et al.*, 2009; Roth *et al.*, 2007), increased frontostriatal activation during the Simon task (measuring cognitive control and conflict resolution) (Marsh *et al.*, 2009), and decreased lateral OFC activation during reversal learning (Chamberlain *et al.*, 2008). Though it remains to be determined how these task-related alterations in activity are related to OCD symptoms, overall, these findings suggest that: 1) altered structure and function in CBGTC circuits is a key feature of OCD, and 2) these alterations may contribute to symptom generation.

2.2. Optogenetic activation within CBGTC circuits in mice produces increased grooming

Based on this convergence of evidence, Ahmari *et al.* (2013) used optogenetic technology to produce hyperactivity in the OFC-ventromedial striatum (VMS) pathway in mice and assessed OCD-related behaviors. Mice were first infected with a virus [adenovirus-associated vector (AAV)] encoding a light-activated excitatory ion channel, channelrhodopsin (ChR2), via injection of AAV-diO-ChR2-EYFP (Tsai *et al.*, 2009) in medial OFC of EMX-Cre mice (Gorski *et al.*, 2002). This manipulation led to specific expression of both ChR2 and an enhanced yellow fluorescent protein (EYFP) visualization tag in excitatory OFC projection neurons. They next used combined optogenetic stimulation of VMS terminals (473 nm light: 10 Hz, 10 msec, 10 mW) and *in vivo* electrophysiological recording at the same site to determine that these OFC-VMS

projections could be selectively and robustly activated. This system made it possible to test the primary hypothesis: OFC-VMS hyper-stimulation will lead to an acute increase in OCD-relevant behaviors; perseverative grooming was tested based on previous transgenic studies highlighting the potential relevance of this behavior to OCD (Bienvenu *et al.*, 2009; Ting and Feng, 2011a; Welch *et al.*, 2007; Zuchner *et al.*, 2009). Surprisingly, acute stimulation instead triggered increased locomotion, which immediately ceased when the light was turned off. However, repeated hyper-activation of the OFC-VMS projections via 5 min of daily ChR2-based stimulation over the course of 5-7 days led to a progressive increase in perseverative grooming that was observed both 1 hour and 24 hours after stimulation; the behavioral changes were therefore not directly time-locked to ChR2 activation. The increased perseverative grooming was correlated with an increase in the evoked firing rate at OFC-VMS synapses, suggesting that pathologic plasticity might be responsible for the generation of the observed behavioral changes. The increased grooming persisted for at least 2 weeks after complete cessation of stimulation (though levels decayed over time), demonstrating that repetitive grooming, once established, could persist without further direct circuit hyper-activation. This again suggested a link between circuit plasticity and the development of abnormal grooming behavior. Finally, both the behavioral and plasticity changes were reversed by treatment with chronic, but not acute, high-dose of the 5-HT-selective reuptake inhibitor (SSRI) fluoxetine, a regimen that is effective in reducing symptoms in a subset of OCD patients.

### 2.3. Insights from the results of optogenetic studies in mice: Potential involvement of plasticity mechanisms

Optogenetic approaches in mice provide several insights that may help us understand pathologic changes underlying the development of maladaptive repetitive behaviors in OCD patients. First, Ahmari et al. (2013) demonstrated for the first time that hyper-activation of circuits linked to OCD in humans can lead, over time, to the development of abnormal repetitive grooming behavior in wild-type, healthy mice. Potential relevance of this phenotype to OCD in humans is supplied by the observation of pathologic grooming behavior in transgenic OCD mouse models that have been linked back to human OCD through genetic studies (Bienvenu *et al.*, 2009; Ting and Feng, 2011a; Zuchner *et al.*, 2009). Second, chronic, but not acute, treatment with high-dose fluoxetine, which parallels the time course and drug levels used in human OCD patients, leads to reversal of both the abnormal repetitive grooming behavior and the associated putative plasticity changes. Although many OCD patients have only a partial response to fluoxetine, these findings may provide insight into pathophysiologic processes in the subset of OCD patients who do have robust pharmacologic responses, and potentially

lead to clues regarding how to improve treatment response to SSRIs in this disorder. Overall, being able to use advanced neuroscience techniques to directly test causality is one of the unique advantages of rodent model systems over human studies.

This series of experiments also offered surprising insights into the potential involvement of plasticity mechanisms in the development of abnormal repetitive behaviors relevant to OCD. Ahmari et al. (2013) initially predicted that hyper-activation of OFC-VMS circuits would directly lead to abnormal grooming behavior, but contrary to this expectation, repeated abnormal stimulation was required for pathologic behaviors to evolve. Surprisingly, only 5 min of stimulation a day was necessary, although repetition of this relatively small but disruptive intervention was required for behavioral change. It remains to be seen whether similarly brief but repeated alterations in neural activity could also lead to the development of pathologic plasticity and symptoms in humans. The findings from this study could provide a rationale for investigating whether evidence for similar mechanisms exists in OCD patients.

Also surprising was the fact that abnormal activity was not directly time-locked to the evolution of abnormal repetitive grooming. Although it is clear that ChR2-mediated stimulation of OFC-VMS circuits was required for the development of abnormal behavior since matched controls did not display the phenotype, the behavioral changes were observed at time points removed from the acute stimulation paradigm. As discussed above, this is highly suggestive that the evolution of abnormal repetitive behaviors is linked to plasticity originating at OFC-VMS synapses. However, even though it is known that the OFC-VMS node displays electrophysiological changes that parallel the observed behavioral changes, it is possible that the actual causative event(s) may be localized at a downstream node of the CBGTC network (such as the ventral pallidum or anterior thalamus). Alternatively, the key source of dysfunction may lie in the interaction between plasticity at OFC-VMS synapses and activity alterations within the extended connected neural network, either within or outside of CBGTC circuits. Ongoing experiments in rodents are investigating these questions by combining precise *in vivo* neural manipulations with sophisticated observational approaches, such as multi-site electrophysiology and *in vivo* imaging. Further studies will be able to directly assess the effects of optogenetic stimulation at a single site on activity in the entire extended neural network, and identify the key network of nodes responsible for the observed behavioral changes.

### 2.4. Summary and conclusions

In summary, experiments in animals can be an extremely useful complement to human studies for the investigation of neural mechanisms underlying development of

pathology relevant to neuropsychiatric illness. To this point, it is very important to recognize that optogenetic stimulation of OFC-VMS projections, as described above, does *not* yield an OCD model. Simply put, through these experiments an optogenetic mouse model of OCD was not created. Rather, the strength of this approach lies in the ability to directly test hypotheses regarding whether circuit dysfunction observed via neuroimaging methods in the psychiatric illness under study can either directly or indirectly lead to OCD-like behaviors and/or changes in neural substrates. Results highlight this fact by demonstrating that repeated OFC-VMS stimulation leads to perseverative grooming behavior, as discussed here, but does not lead to alterations in either anxiety-related behaviors or prepulse inhibition, two phenotypic changes that might be expected in an 'OCD mouse model' (Ahmari *et al.*, 2013). In fact, this approach could be used as a template for dissecting circuit components underlying specific symptoms within a particular disorder, as seen in examination of the diverse features of anxiety by Kim *et al.* (2013). Thus, animal models can be highly informative, since they provide a valuable tool for: 1) determining how activity disruptions in specific circuits can lead to OCD-like behaviors; and, 2) uncovering the basic molecular and cellular mechanisms underlying translation of abnormal CBGTC circuit activity into abnormal repetitive behaviors. It is important to simultaneously recognize the limitations of animal models and to frame interpretations of the data accordingly.

## 3. Insights into OCD from animal models of enhanced schedule-induced polydipsia

### 3.1. The SIP paradigm

Schedule-induced polydipsia (SIP) is a ritualized act that neither serves an obvious physiological need nor the overall goal of obtaining food, and can lead to functional impairments associated with excessive fluid intake. SIP therefore has several features of the compulsions observed in OCD and related illnesses. As suggested by Moreno and Flores (2012), consideration of the variables affecting SIP and the neurocircuitry underlying this maladaptive behavior may provide novel insights into OCD.

John Falk first reported SIP in 1961. He trained food-restricted rats to lever press on a variable interval (VI) 1-min schedule in daily 190-min sessions. According to this schedule, food (a 45 mg food pellet) availability is programmed at variable times during the session; in Falk's study, the time from one pellet to the next varied from 3 s to 2 min but averaged 1 min. Food delivery depends on a lever press. Thus, the animals have to lever press for food but cannot predict when a lever press will produce food although average food availability is at a frequency of one pellet per min. As originally described by Skinner (1938), the rats in Falk's study lever pressed at a fairly constant rate throughout the session; for example, one rat pressed at a rate averaging about one

response every 5 s throughout the entire session (Falk, 1961). The novel feature in Falk's study was the mounting of a water-filled drinking tube outfitted with a drinkometer that monitored licks inside the lever-pressing chamber. He observed that shortly after each pellet delivery, the rats frequently drank. This drinking behavior often lasted so long that pellets made available at short intervals were not earned as rapidly as possible. Most interestingly, drinking was excessive and far beyond physiological need. Rats drank on average more than three times their normal daily fluid intake during the 190-min lever-pressing session. Control rats that received the same number of pellets all at once in a dish and were observed to eat those pellets did not show excessive drinking.

SIP has been observed in several species including humans and with different reinforcers. Instead of SIP, schedule-induced aggression, escape, wheel-running, gnawing and pica (eating of non-food objects, e.g., wooden shavings) has been observed when appropriate stimuli are available to the animal (Falk, 1971). These behaviors including SIP have been termed "adjunctive" because they are added to feeding but not essential to it. The generation of SIP depends on the level of food restriction, SIP being less intense or absent in less food-restricted animals. It is not necessary to require an operant response of the animal in order to observe SIP; Falk (1969) showed that presenting response-independent food pellets at the same inter-pellet intervals that were used in the VI 1-min schedule described above led to the same level of SIP as that observed when a response was required. Fixed-time (FT) schedules of response-independent food presentations produce optimal SIP when the inter-pellet interval is 60 s (see Moreno and Flores, 2012).

3.2. SIP as a compulsive behavior

If SIP is a good animal model of compulsive symptoms of OCD and related disorders, pharmacological agents that are effective in treating OCD would be expected to reduce SIP. In general they do. Thus, SIP is reduced by DA receptor antagonist drugs including typical (e.g., haloperidol) and atypical antipsychotics (e.g., clozapine) and by serotoninergic drugs including chronic SSRIs (e.g., fluoxetine, chlomipramine), a 5-$HT_{1A}$ antagonist and 5-$HT_{2C}$ agonists (reviewed by Moreno and Flores, 2012). As discussed in Section 2, CBGTC circuits have been implicated in OCD (Chamberlain *et al.*, 2008; Menzies *et al.*, 2008). Brain structures implicated in SIP include the prefrontal cortex (PFC), hippocampus and NAc. Lesions placed in these structures reduce the development of SIP. Hypothalamic-pituitary axis changes are also implicated in OCD and SIP. Reduced levels of plasma corticosterone and increased levels of prolactin are observed in animals showing SIP and blockade of corticosterone synthesis reduces SIP

(reviewed by Moreno and Flores, 2012). Results may reveal some overlap of the neural mechanisms of OCD and SIP. The SIP model appears to have face validity as a compulsive behavior and possibly construct validity based on the involvement of prefrontal cortical and striatal structures in OCD and SIP. However, the homology of frontocortical regions in humans and rats remains a topic of discussion.

Compulsive drinking characterized by fluid consumption that exceeds homeostatic need has been observed in OCD and is comorbid in a subpopulation (about 20%) of patients with other disorders, the largest proportion being those with chronic schizophrenia (de Leon *et al.*, 1994). A number of animal models of schizophrenia symptoms have been introduced in recent years (reviewed by Jones *et al.*, 2011) raising the question of whether these models will show greater polydipsia than control animals. Results of empirical studies with three of these models suggest that they do.

3.2.1. Animal models of polydipsia

Before discussing polydipsia in animal models of enhanced SIP, it should be noted that increased drinking has been observed in other animal models of OCD. Rowland et al. (1981) used an amphetamine-sensitization procedure with rats and assessed their water intake each day in the 5 hours following injection. They observed increased, apparently non-regulatory drinking over days. Similar effects have been observed with the DA D2/D3 receptor agonist quinpirole (QNP) (Amato *et al.*, 2007; Amato *et al.*, 2008; Fraioli *et al.*, 1997). Excessive drinking was blocked by haloperidol or clomipramine, agents used to treat OCD (Amato *et al.*, 2008). In this model, polydipsia is only seen in non-water-restricted animals; water-restricted animals instead show decreased drinking following repeated injections of amphetamine or QNP (Milella *et al.*, 2008; Stolerman and D'Mello G, 1978). A further twist on this paradigm is the observation that QNP increases what has been termed “contrafreeloading”; mildly water-restricted rats given simultaneous access to a lever that can be pressed for water reward and a water bottle from which water can be freely drunk were observed with daily injections of QNP to progressively lever press more for water and to drink less from the water bottle (Amato *et al.*, 2007; Cioli *et al.*, 2000; De Carolis *et al.*, 2011; Schepisi *et al.*, 2013). This apparently compulsive-like, non-regulatory behavior was reversed by clomipramine (De Carolis *et al.*, 2011). An examination of the relationship of non-regulatory drinking and lever-pressing in these models to polydipsia in the SIP model awaits further study.

3.3. Animal models of enhanced SIP

Sub-chronic treatment with an NMDA receptor-blocking drug (Jentsch *et al.*, 1997) leads to enhanced SIP. Sub-chronic NMDA receptor blockade is produced by twice-daily

injections of an NMDA receptor blocker such as phencyclidine or MK-801, often for a period of 7 days. Sub-chronically treated animals showed an enhanced response to amphetamine when tested a week after the end of injections (Jentsch *et al.*, 1998) and changes in markers for γ-amino butyric acid (GABA) neurotransmission (Schroeder *et al.*, 2000) respectively mimicking elevated DA function (Abi-Dargham *et al.*, 2000) and possibly decreased GABA function seen in schizophrenia (Costa *et al.*, 2004). Hawken and colleagues (2011) used this model to compare treated and control animals in the SIP paradigm. Results showed significantly elevated SIP in rats that had been sub-chronically treated with the NMDA receptor blocker MK-801 (see Figure 1). This observation extends the face validity of the sub-chronic NMDA receptor-blockade model to include increased susceptibility to compulsive behaviors such as polydipsia.

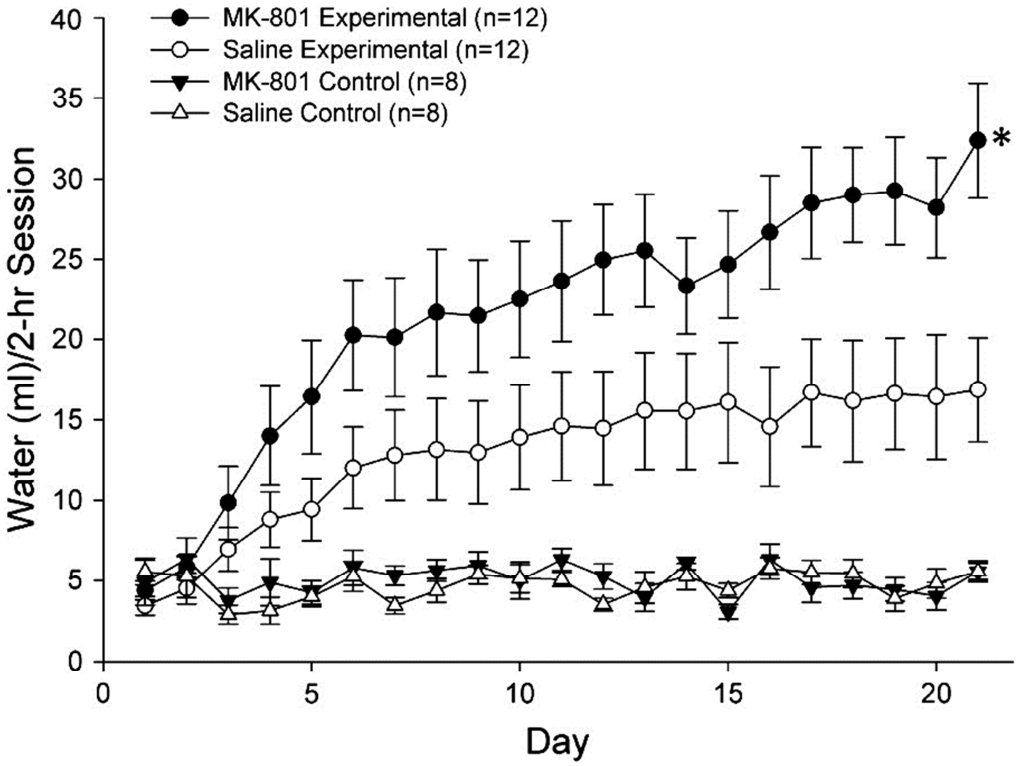



**Figure 1**

Figure 1: MK-801 significantly increased daily mean (±SEM) water drinking across days in the schedule-induced polydipsia (SIP) paradigm. Experimental groups received saline (1.0 ml/kg) or the NMDA receptor blocker MK-801 (0.5 mg/kg) twice daily for 7 days followed by a 4-day washout prior to the beginning of testing. Control groups received the same drug treatments but instead of receiving one food pellet each minute according to the fixed time schedule during daily 2-hr sessions, they received 120 pellets in a dish placed next to the feeder cup in the test chamber. Only the experimental

groups showed SIP and the MK-801 group drank more. *Analysis of variance revealed a significant 3-way interaction [group (MK-801 and saline) x condition (experimental and control) x day], $F(1,36) = 5.88$, $p = 0.02$. MK-801 Experimental and Saline Experimental groups did not differ significantly on day 1, $t(22) = 0.98$, $p = .34$, but by day 21 the MK-801 Experimental group was drinking more, $t(22) = 3.30$, $p = .004$. (From Hawken *et al.*, 2011).

Another model that showed enhanced SIP is post-weaning social isolation. Rats are housed singly in clear Plexiglas cages in a colony room where they can see, hear and smell conspecifics but they do not have physical contact with them from the age of weaning (postnatal day 21) until the end of testing with testing beginning after at least 5 weeks of social isolation. Post-weaning socially isolated animals show impaired sensorimotor gating, social withdrawal, impaired cognitive flexibility and increased activity in a novel environment (Powell and Miyakawa, 2006; Simpson *et al.*, 2010), mimicking some of the positive, negative and cognitive symptoms of schizophrenia. Changes in markers for GABA function are also seen in the social isolation model and in schizophrenia (Hickey *et al.*, 2012). Social isolation rearing in rats presents with increased oxidative stress as well as immune-inflammatory dysregulation (Moller *et al.*, 2011; Moller *et al.*, 2013), both of which are evident in schizophrenia, and these changes can be reversed with clozapine or N-acetylcysteine, an antioxidant (Moller *et al.*, 2013). This links with oxidative stress in OCD, as well as the response of OCD to N-acetylcysteine (see Section 4). Moreover, disordered redox is also noted in the deer mouse model of OCD (Section 4). Animals socially isolated for an equivalent period in adulthood do not show these behavioral changes (Geyer and Moghaddam, 2002). When post-weaning socially isolated rats were tested for SIP, significantly more drinking was seen compared to age-matched group-housed rats (Hawken *et al.*, 2013). Results show that behaviors observed in the social isolation model extend to increased susceptibility to a compulsive action.

Amphetamine-sensitized rats show increased drinking in the SIP paradigm. This model involves daily injections of amphetamine, e.g., 1.5 mg/kg per day for 5 consecutive days, followed by a washout period, e.g., 28 days. These animals show a chronic state of elevated dopaminergic function (Lodge and Grace, 2012) and neurocognitive deficits that model some of those seen in schizophrenia (Castner *et al.*, 2004). Hawken and Beninger (2014) showed that amphetamine-sensitized rats tested in the SIP paradigm involving intermittent presentations of food pellets as described above drank significantly more than saline-treated controls or controls fed all of the pellets in a dish.

The amphetamine-sensitized rats were given one additional test day following 23 days of SIP testing. On this day, all animals were given all of their food pellets in a dish instead of intermittently throughout the session. The amphetamine-sensitized group drank significantly more than the saline group. This result suggests that compulsive drinking had become conditioned to cues associated with SIP and may be related to the finding of Ahmari et al. (2013) that mice that had undergone repeated optogenetic activation of OFC-VMS projection neurons showed grooming even 24 hr after stimulation. These results with the amphetamine sensitization model are consistent with those from studies using the sub-chronic NMDA receptor blockade or post-weaning social isolation models in showing increased susceptibility to compulsive behavior.

3.4. Striatal vs. hippocampal phenotypes

Rats show phenotypic differences in their susceptibility to SIP. Such phenotypic heterogeneity has also been noted in the deer mouse model described in Section 4 (Korff *et al.*, 2008) and may reflect differences in brain circuitry that may be linked specifically to SIP susceptibility and more generally to susceptibility to compulsive behavior and OCD.

Behavioral tasks can be used to identify individual differences in rats and to relate those differences to particular brain circuits. A simple choice task has been used in rats to identify response strategies that are thought to reflect differential reliance on striatal versus hippocampal circuitry. Food-restricted rats were trained in a Y-maze discrimination task where rats always started in one arm and found food in a goal arm that never varied (see Figure 2, *Training*). On periodic probe trials, they were started in the third arm that was neither the usual start box nor the goal box (Figure 2, *Testing*). Rats that chose the goal arm were identified as relying more on their hippocampus and rats that chose the former start arm were identified as relying more on their striatum (Figure 2, Two choices); one of the functions of the hippocampus is learning the position of things in space (place learning) and one of the functions of the striatum is learning stimulus-response associations (habit learning). Rats that chose the goal arm are putatively relying on hippocampal learning. Rats that chose the former start arm are putatively relying on the striatum, i.e., if they normally turned right in the start arm and then used the turn-right-at-the-choice-point (stimulus-response or habit) strategy in the probe test they would enter the former start arm (see Packard and McGaugh, 1996).

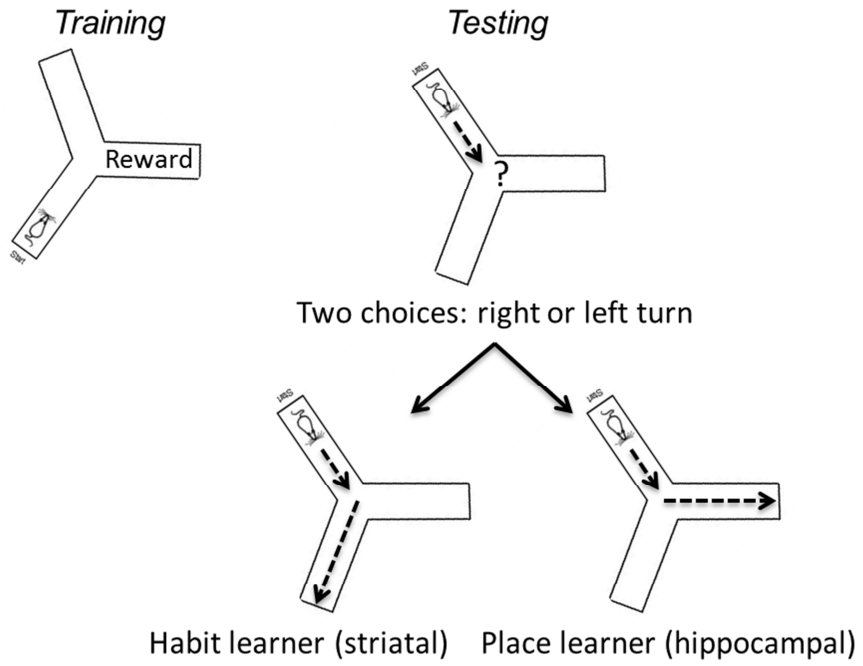



**Figure 2**

Figure 2: Y-maze test used to identify different response strategies in rat. During the training phase, food-restricted rats are started in the same arm on each trial and learn to choose the arm baited with a food pellet (Reward). On probe test trials, rats are started in the arm that was neither the usual start arm nor the arm where a food pellet was found. At the choice point, a right turn reflects a habit learning (striatal) strategy and a left turn reflects a place learning (hippocampal) strategy. No food reward is provided on probe trials.

Gregory *et al.* (2015) tested rats for response strategy using the Y-maze task and then tested them in the SIP paradigm. They found that significantly more rats that developed SIP were those with a habit strategy while more rats that failed to develop SIP had a place strategy. The amphetamine-sensitized and saline control rats from the study by Hawken and Beninger (2014) discussed above were also evaluated for response strategy in the Y-maze before being tested for SIP. Half of the saline control rats used a habit (response) strategy and half used a place strategy. On the other hand, significantly more of the amphetamine-sensitized rats used a habit strategy suggesting that amphetamine sensitization led to a shift towards a habit strategy (Figure 3). These results reveal that groups of rats that show a greater level of SIP are overrepresented by rats that use a habit strategy.

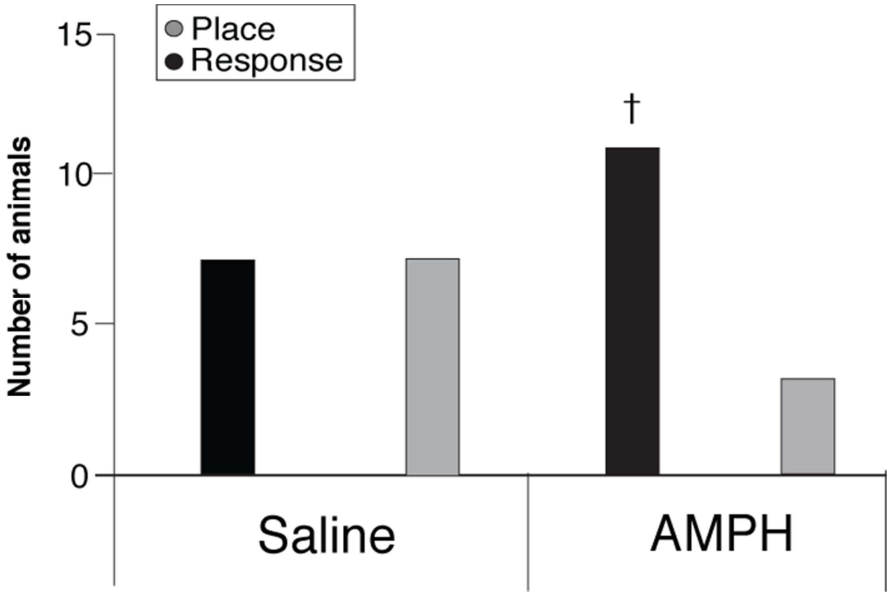



**Figure 3**

Figure 3: Number of animal that used response (habit) or place-learning strategies in groups pre-treated for 5 days with amphetamine (AMPH; 1.5 mg/kg) or saline. H = significantly greater proportion than expected by chance in binomial probability test. (From Gregory et al., 2015)

3.5. Brain structures associated with SIP

Gregory *et al.* (2015) tested additional rats for SIP and then sacrificed them 90 min after the final session. Their brains were processed for FosB/ΔFosB immunohistochemistry, a marker for neuronal activation. Results revealed greater activity in the mPFC and the OFC of the rats that showed SIP compared to those that did not. Pellón *et al.* (2011) similarly found greater c-Fos activity in the mPFC of high-drinking SIP rats. Frontocortical regions have been implicated in the formation of habits and compulsions (Chamberlain *et al.*, 2008; Menzies *et al.*, 2008). Differences in DA receptor binding also have been identified between high- and low-SIP rats. High-SIP rats show higher binding for D2 receptors and lower binding for D1 receptors than low-SIP rats in the NAc, mPFC, amygdala and ventral tegmental area (Pellon *et al.*, 2011). Results differentially implicate DA in high- versus low-SIP rats. Electrophysiological studies have identified differences in the firing of bed nucleus of the stria terminalis (BNST) neurons between SIP and non-SIP rats (Welkenhuysen *et al.*, 2013). Unpublished studies from the laboratory of Eric Dumont at Queen's (personal communication) have also identified differences in GABA-produced inhibitory postsynaptic currents in the oval nucleus of the

BNST of SIP versus non-SIP rats possibly implicating this area in the control of compulsive behavior.

The brain has multiple memory systems that may compete for the control of behavior (McDonald and White, 1993). For example, the hippocampus and striatum are respectively associated with declarative and non-declarative (e.g., habit) memory (Squire, 2004). When hippocampal function is compromised, as it appears to be in patients with psychogenic polydipsia (Goldman, 2009; Umbricht, 1994), striatal circuits may dominate in the control of behavior. The animal studies discussed above show that a significantly larger proportion of rats showing SIP use striatal response strategies in the Y-maze test. Amphetamine sensitization leads to a shift towards more animals with a striatal response strategy and more animals that show SIP. Results are consistent with reduced hippocampal function in polydipsia patients and greater control of behavior by striatal circuits. Imaging researchers have identified activity in CBGTC circuits in OCD (Chamberlain *et al.*, 2008; Menzies *et al.*, 2008) and Ahmari et al. (2013) showed that optogenetically induced over-activity in the OFC-VMS component of this circuit leads to compulsive behavior in mice (Section 2); the suggestion that animals showing SIP rely more heavily on striatal response strategies is consistent with these findings. The observation from FosB/ΔFosB studies of greater activity in the mPFC and OFC in animals showing high SIP supports a role for OFC-striatal circuits in compulsive behavior. Changes in striatal DA receptor subtypes further implicate this circuit.

### 3.6. Conclusions

Animal models can provide insights into the brain mechanisms of human disorders such as OCD. By investigating SIP, excessive, non-regulatory drinking that resembles compulsive behaviors observed in humans, in animal models it is possible to identify brain regions and circuits that may be involved. Future studies will be able to use these models to identify further details of the brain mechanisms underlying compulsive behavior and new and more effective therapeutics for treating OCD and related disorders.

## 4. Insights into OCD from the deer mouse: A platform for research in neurobiology, behaviour and drug discovery

### 4.1. Spontaneous stereotypy in the deer mouse

As a naturalistic animal model of OCD, deer mice exhibit two topographies of stereotypy, viz. pattern running and vertical stereotypies (backward somersaulting, repetitive jumping) (Hadley *et al.*, 2006; Korff *et al.*, 2008). The perseverative and seemingly goalless quality of such stereotypy, and that it develops spontaneously,

provides face validity for OCD (American Psychiatric Association, 2013). Heterogeneous distribution within a population of animals (see Figure 4) (Korff *et al.*, 2008) suggests a genetic association akin to OCD (Lochner *et al.*, 2015). While the prevalence of OCD is markedly lower than that of high stereotypic (H) animals in a deer mouse population (45%, Figure 4), what is important is that H stereotypy is naturally expressed in these animals and requires no pharmacological, gene knock-in or knock-out or other means of induction. It therefore implies a genetic basis to its development and possible conservation across generations. This provides a platform for gene association studies of relevance for modeling OCD genetics. In order to consolidate this trait for accurate behavioral and biological analysis, a new method of analysis replaces the HSB, LSB, NS classification described in Figure 4 with H and non-stereotypic (N) animals (see Wolmarans *et al.*, 2013) by considering severity of stereotypy *and* time spent executing such behaviors. This method of scoring increases the density of truly H animals, and excludes a non-specific "grey area" of stereotypy that presents with more N-related qualities, thereby reinforcing the potential value of H vs. N animals in genetic studies of OCD.

As in OCD (Fineberg and Craig, 2007), these behaviors are inhibited by chronic *but not* sub-chronic high dose SSRIs (Korff *et al.*, 2008; Wolmarans *et al.*, 2013), while also failing to respond to a noradrenaline reuptake inhibitor (NRI) (e.g., desipramine) (see Figure 5) (Korff *et al.*, 2008). Environmental enrichment partially suppresses the expression of stereotypy, also prompting delayed presentation (Hadley *et al.*, 2006; Powell *et al.*, 1999), indicating that confinement stress is more a triggering factor than an etiological determinant, and since compulsions can be distinguished from rigid motor patterns on the basis of thoughtfulness (Eilam *et al.*, 2006), deer mouse stereotypy can be regarded as flexible. Also deer mouse stereotypy appears to be associated with social deficits, is independent of anxiety and presents with symptom heterogeneity with regard to other forms of compulsive-like behavior that has value for studying the obsessive-compulsive interface of OCD (Section 4.3.; Wolmarans *et al.*, 2015; Wolmarans *et al.*, 2016a, b). As in OCD (Evans *et al.*, 2004; Husted *et al.*, 2006; Markarian *et al.*, 2010) and as emphasized in the earlier two models (Sections 2 and 3), high stereotypic (H) deer mice also present with frontal cortical pathology, e.g., disordered redox balance (Guldenpfennig *et al.*, 2011) and altered cyclic adenosine-monophosphate (cAMP)-phosphodiesterase (PDE) signaling (Korff *et al.*, 2009). Finally, the 5-HT transporter (SERT) is the primary target for SSRI's, while decreased SERT density in OCD (Atmaca *et al.*, 2011; Matsumoto *et al.*, 2010) is associated with increased symptom severity (Hesse *et al.*, 2005; Reimold *et al.*, 2007; Zitterl *et al.*, 2008). H deer mice demonstrate decreased striatal *but not* frontal cortical SERT density (Wolmarans *et al.*, 2013). Deer mouse stereotypy is therefore a useful preparation to extend our knowledge of the

phenomenology, genetics, and biological basis of OCD, and its response to treatment. Valuable insights into OCD have been obtained that would have been difficult to obtain from human studies.

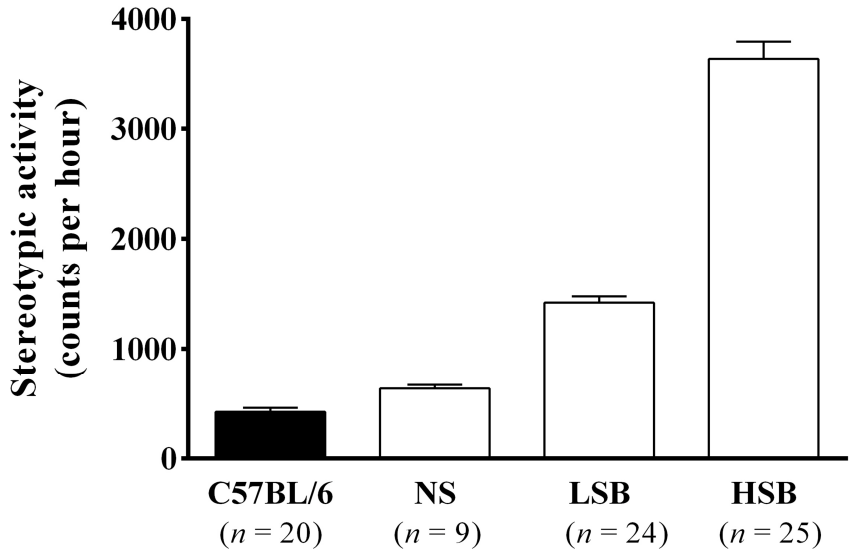



**Figure 4**

Figure 4: **The heterogeneous nature of deer mouse stereotypy**. Deer mouse stereotypy is heterogeneous within a given population of animals, with 45% of animals classified as having high stereotypic behavior (HSB, or H in the text), 41% as having low stereotypic behavior (LSB), and 16% as being non-stereotypic (NSB, or N in the text). In this graph, deer mice are compared to C57Bl/6 mice as control. (From Korff *et al.*, 2008).

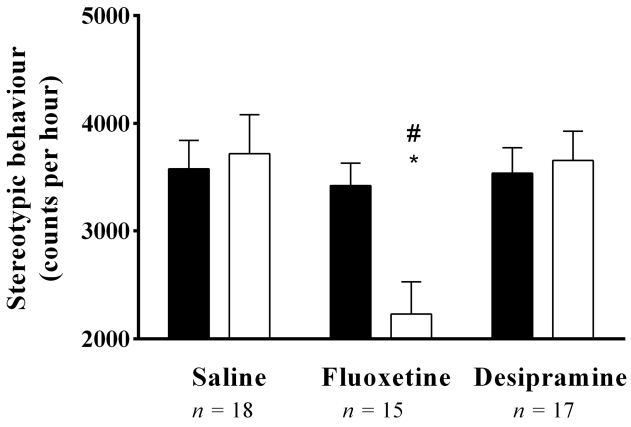



**Figure 5**

Figure 5: **Differential response of deer mouse stereotypy to chronic fluoxetine and desipramine treatment**. Effect of treatment with 20 mg/kg fluoxetine, 20 mg/kg desipramine and saline on stereotypic behaviour of deer mice. Baseline (untreated) stereotypic activity for each treatment group (solid bars) is provided for high stereotypic behavior (H) mice. Data represent the average of three behavioural assessment sessions for the baseline score and a once-off measurement for the treatment altered score (open bars), and expressed as the mean ± SEM. The number of animals (*n*) is shown below the indicated drug treatment. Locomotor effects following the various drug treatments were minimal (data not shown). *p<0.05 end-point vs baseline analysis for each treatment group (Student's t-test). #p<0.05 end-point analysis compared to post-saline treatment (Dunnett's test). (From Korff *et al.*, 2008).

4.2. Relating neurochemistry to treatment response

4.2.1. The question of serotonin involvement

The model has attempted to shed light on the selective response of OCD to SSRI treatment and not noradrenergic or dopaminergic agents. Striatal concentrations of 5-HT, DA and their associated metabolites do *not* differ as a function of stereotypy, nor is stereotypy related to altered striatal $D_1$ and $D_2$ receptor density (Powell *et al.*, 1999). Thus although deer mouse stereotypy is associated with SERT changes (Wolmarans *et al.*, 2013) as well as selective response to an SSRI and not an NRI (Korff *et al.*, 2008), a disturbance in serotonin may *not* be the immediate cause for excessive stereotypy in these animals. In fact, SSRI-resistant OCD often responds better to augmentation with a $D_2$ receptor antagonist, such as risperidone (Erzegovesi *et al.*, 2005; Fineberg *et al.*, 2006), suggesting cooperation between serotonin and other monoamines or with other signaling pathways such as glutamate. Considering the paradox that deer mouse stereotypy (Korff *et al.*, 2008) and human OCD (Fineberg *et al.*, 2006) are reversed by a D2 receptor agonist and antagonist, respectively, suggests a mutual role for receptor state *and* neurotransmitter release in response to a dopaminergic agent. The role of neuronal adaptation in disease re-affirms the importance of using a pathological animal model in drug discovery research (see Section 4.2.2.). Considering that DA transmission appears to be unaltered in H mice (Powell *et al.*, 1999) prompts a deeper look at other mechanisms that may be involved. Similarly, failure to engage a deeper mechanism also explains the partial response to SSRI's.

One such mechanism may involve oxidative stress, evidence of which has been described in OCD (Behl *et al.*, 2010; Chakraborty *et al.*, 2009; Selek *et al.*, 2008). OCD is associated with polymorphisms of the neuronal glutamate transporter (EAAC1) gene, which mediates cysteine uptake necessary for neuronal glutathione (GSH) production

(Aoyama *et al.*, 2006; Monteiro and Feng, 2016). Add-on N-acetyl cysteine (NAC), a GSH precursor, has distinct clinical benefits in OCD (Afshar *et al.*, 2012; Paydary *et al.*, 2016). Importantly, disturbances in frontal cortical GSH redox balance are correlated with severity of stereotypy in deer mice (see Figure 6) (Guldenpfennig *et al.*, 2011), suggesting increased cycling and utilization of GSH and confirming a causal association between oxidative stress and symptom severity in deer mice and possibly in OCD. Moreover, the aforementioned clinical benefit of NAC in OCD and also its ability to target glutamate transmission (Berk *et al.*, 2013) reinforces current thinking as to the clinical value of glutamate modulators in treating OCD (Grados *et al.*, 2013; Pittenger *et al.*, 2006).

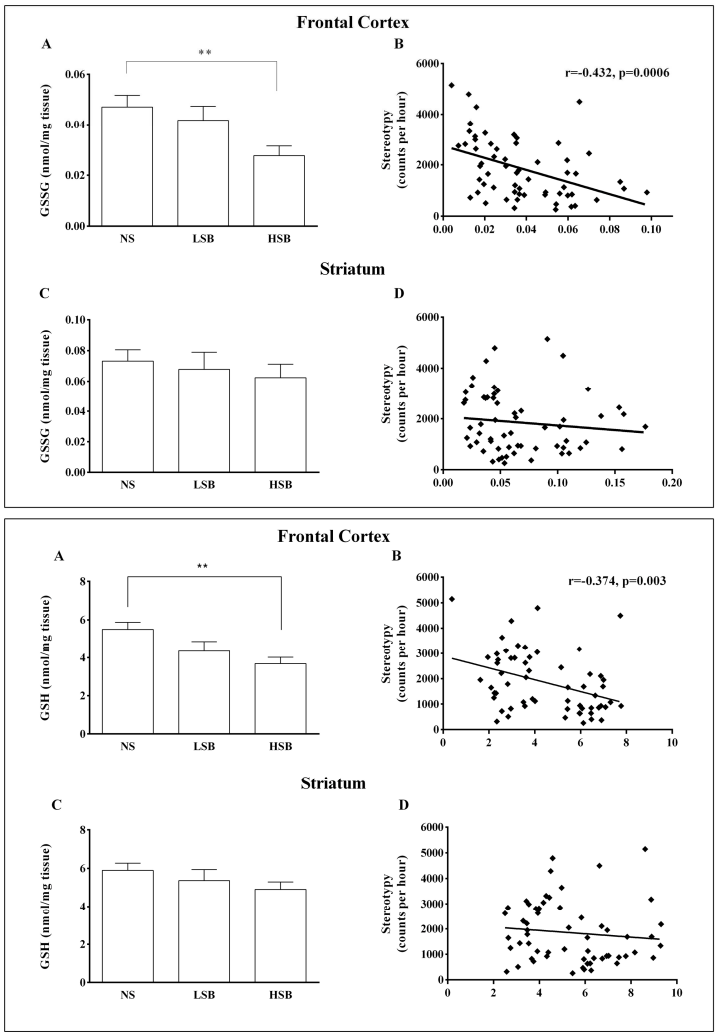



**Figure 6**

Figure 6: **Cortico-striatal glutathione redox imbalance is correlated with severity of stereotypy in deer mice**. Comparative oxidized (GSSG; *top* panel) and reduced (GSH; *bottom* panel) glutathione in the frontal cortex and striatum of non-stereotypic (NS), low stereotypic (LSB) and high stereotypic (HSB) deer mice (n=20, 16 and 24, respectively; **p<0.01, Bonferroni), as well as appropriate correlations between stereotypy count and GSSG or GSH in all animals (n=60). (From Guldenpfennig *et al.*, 2011).

4.2.2. How a naturalistic model reveals more about OCD neurocircuitry

OCD represents a bias in the direct vs. indirect basal ganglia pathway within the CBGTC circuit, with separation of these pathways mediated through $D_1$ and $D_2$ receptors as well as serotonergic regulation of striatal DA activity via the raphae nucleus (Korff and Harvey, 2006). Despite this knowledge, uncertainty prevails as to how DA and 5-HT are co-involved in OCD, especially from a neurotherapeutics point of view. Thus, although $D_2$ receptor antagonists benefit treatment, a number of studies have failed to demonstrate a hyper-dopaminergic state in OCD (Brambilla *et al.*, 2000; Pitchot *et al.*, 1996). Further, although direct and indirect acting DA agonists *exacerbate* obsessive-compulsive (OC) symptoms, they may also improve such symptoms (Denys *et al.*, 2004). Concerning 5-HT, despite the clinical efficacy of SSRI's, broad-spectrum 5-HT agonists may exacerbate OCD symptoms (Hollander *et al.*, 1991) or not (Khanna *et al.*, 2001). Similarly, paradoxical data are observed with $5HT_{1D}$ agonists, while $5HT_{1A}$ and $5HT_{2C}$ receptor agonists have no effect on OC symptom severity (Aouizerate *et al.*, 2005). Different 5-HT receptors are probably involved in different OCD behaviors, e.g., $5HT_{2C}$ receptors in reward-seeking behavior (Millan *et al.*, 1998), and it is therefore incumbent to delineate the sub-cellular pathways involved to assist in the drug discovery endeavor. A model that presents with behavioral heterogeneity (see later in this section and Section 6) would be invaluable in acquiring a deeper understanding of OCD and its treatment.

Although DA is *not* altered in the CBGTC of deer mice (Guldenpfennig *et al.*, 2011; Powell *et al.*, 1999), deer mouse stereotypy *is* abrogated by the $D_{2/3}$ agonist QNP (Korff *et al.*, 2008), thus also paradoxical. That QNP induces 'compulsive checking' in rats (Szechtman *et al.*, 1998a) suggests that DA agonists precipitate OC-like behavior in a non-pathological (drug-induced) animal model but suppress such behaviors in naturalistic models, e.g., deer mice, bank voles (Korff *et al.*, 2008; Vandebroek and Odberg, 1997). DA pathology likely *already* exists in a naturalistic (pathological) animal model but is absent in an acute drug-induced model. The basis for subversive

dopaminergic function in deer mice, such as DA-mediated changes in redox balance noted earlier, is a primer for deeper translational research.

The non-selective $5HT_{1A/2A/2B/2C}$ agonist, m-chlorophenylpiperazine, attenuates deer mouse stereotypy (Korff *et al.*, 2008), as well as suppresses QNP-induced checking in rats (Tucci *et al.*, 2013; Tucci *et al.*, 2015). Perseverative locomotor paths are indeed associated with $5HT_{1B/1D}$ receptor stimulation (Shanahan *et al.*, 2011). More importantly, $5HT_{1A}$ receptor desensitization involves adenylate cyclase-cAMP signaling (Hensler *et al.*, 1996), while the ameliorative effects of SSRIs in OCD are said to involve desensitization of these receptors (El Mansari and Blier, 2006; Pineyro and Blier, 1999). Severity of stereotypy in deer mice is associated with elevated frontal-cortical (not striatal) cAMP and reduced PDE4 activity, while chronic fluoxetine significantly reduces both stereotypy *and* cortical (but not striatal) cAMP and PDE4 activity in H animals (see Figure 7) (Korff *et al.*, 2009). Such concordance between predictive and construct validity is especially significant. $5HT_{1A}$ agonists reduce stereotypy (Korff *et al.*, 2008; Tucci *et al.*, 2013; Tucci *et al.*, 2014b), while 5-$HT_{1A}$ receptor activation promotes adenylyl cyclase sensitization (Hensler *et al.*, 1996), supporting a role for $5HT_{1A/B}$ $G_i$ dependent adenylate cyclase-cAMP coupling in OCD (Marazziti *et al.*, 2001; Perez *et al.*, 2001) and its response to treatment. Indeed, clinically effective OCD treatments prevent 5-$HT_{1B}$ receptor-induced repetitive behavior and striatal activation (Ho *et al.*, 2015). Furthermore, elevated cAMP in H mice could be related to increased $5HT_{1A}$-adenylate cyclase-cAMP signaling with reduced hydrolysis by PDE4 (Korff *et al.*, 2009). Interestingly, the PDE4 inhibitor rolipram decreases methamphetamine-induced stereotypy (Iyo *et al.*, 1995), suggesting that PDE4 active compounds may represent novel treatment options for OCD.

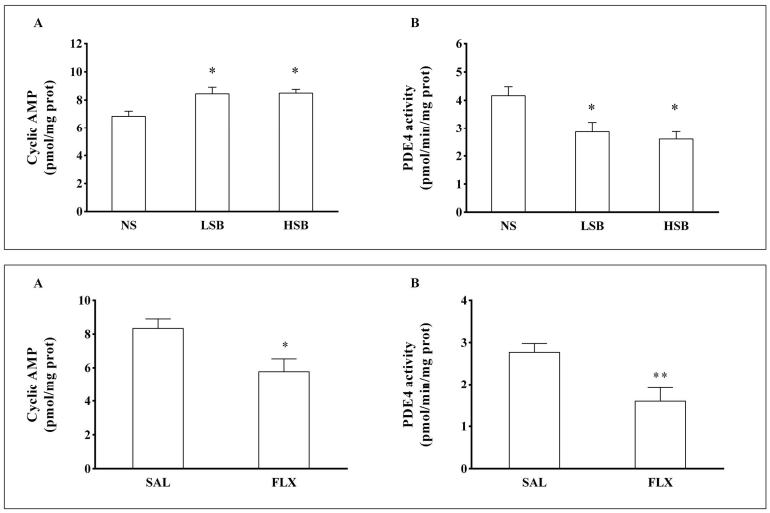



**Figure 7**

Figure 7: **cAMP-PDE4 signaling in stereotypic deer mice, and response to fluoxetine.** *Top panel*: Frontal cortical cAMP levels (A) and PDE4 enzyme activity (B) in low stereotypic (LSB) and high stereotypic (HSB) deer mice compared to non-stereotypic (NS) mice. Significant differences versus control NS mice are indicated by an asterisk (one-way ANOVA followed by the Tukey test; $p<0.05$). Data are expressed as mean±S.E.M. *Bottom panel*: Effect of chronic fluoxetine or saline treatment (x 21 days) on cAMP levels and PDE4 activity in the frontal cortex of HSB mice. Significant differences versus control SAL are indicated by an asterisk (Students t-test; $p<0.05$). Data shown represent the mean±S.E.M. (From Korff *et al.*, 2009).

4.3. The need for an animal model presenting with multiple OCD phenotypes

OCD animal models are limited in their ability to address the cognitive-obsessive manifestations of OCD. In order to more closely relate to human OCD (American Psychiatric Association, 2013), assessment of co-presenting symptoms of anxiety, social impairment and specific compulsive behaviors has been realized with the deer mouse preparation. This work has demonstrated different behavioral patterns in deer mice that cannot simply be regarded as compulsive repetition and formally establishes *a cognitive-psychobiological link* in their behavior.

When considering the link between stereotypy and social deficits and anxiety, the ventromedial PFC and OFC function as the cortical inputs of the limbic loop, while the caudate functions as the striatal entry point for the associative loop (Mannella *et al.*, 2013). This arrangement implicates a possible role for cross-talk between these two pathways in the pathology of OCD. Therefore stereotypy involves motor and limbic elements, making these two parameters and their associated behaviors important targets to be considered in an animal model of OCD.

4.3.1. Are deer mice anxious?

Although previously regarded as an anxiety disorder, OCD is now classified under the OC spectrum (American Psychiatric Association, 2013). Typical anxiolytics also have no clinical value in treating OCD (Fineberg and Craig, 2007). Nevertheless, OCD is often comorbid with social anxiety disorder (Assunção *et al.*, 2012; Kim *et al.*, 2012) or poor social adjustment (Rosa *et al.*, 2012), while it is widely recognized that OCD-related obsessions are accompanied with severe anxiety that in turn is alleviated by the apparent “anxiolytic” effect brought about by compulsive and repetitive acts.

H deer mice *do not* present with altered marble burying behavior, a measure of compulsivity or anxiety (neophobia), compared to non-stereotypic (N) mice (Wolmarans *et al.*, 2016a). In fact, *all* deer mice exhibit a level of inherent burying behavior, thereby

*dissociating* severity of stereotypy with anxiety. Moreover, a characteristically different within-species form of high burying behavior is evident in certain animals, although neither inherent nor high burying behavior responds to chronic SSRI treatment (Wolmarans *et al.*, 2016a). Since chronic SSRI treatment is effective in OCD *and* anxiety, as well as in attenuating deer mouse stereotypy (Korff *et al.*, 2008, 2009; Wolmarans *et al.*, 2013), we conclude that anxiety is not a driving force for perseverative behavior in the deer mouse, which may be in line with the recent DSM-5 reclassification of OCD.

4.3.2. Social behavior in deer mice, what does it reveal about OCD?

Despite being a prominent symptom of OCD, social impairment is poorly studied in animals. Higher rates of unemployment, marital discord and financial instability occur among adult OCD patients (Kim *et al.*, 2012), while children with OCD display impaired abilities for making and keeping friends (Kim *et al.*, 2012; Piacentini *et al.*, 2003). Social phobia and OCD show varying symptom intensity, are characterized by severe occupational infringement, and respond preferentially to SSRI's (Baldwin *et al.*, 2008; Lochner *et al.*, 2003; Niederauer *et al.*, 2007). Furthermore, comorbid OCD and social impairment demonstrate greater OC symptom severity and treatment resistance (Alarcon *et al.*, 1993; Khanna *et al.*, 1988), while greater OC severity with poor social functioning predict a poor treatment outcome (Stewart *et al.*, 2010). Finally, greater OCD severity may worsen social impairment and vice versa (Rosa *et al.*, 2012). Considering children, young OCD sufferers tend to be more socially isolative in scenarios where normal peers may observe their behavior (Piacentini *et al.*, 2003).

Wolmarans et al. (2016b) noted distinctly different treatment-naive social behavior in N and H animals within and between cohorts. Also, a greater tendency of N animals to interact with one another and not with an H animal was observed from before to after chronic SSRI treatment, where such treatment also increased the sociability of H animals towards one another but not towards N animals. Deer mouse behavior therefore provides a unique insight into the social behavior of OCD patients and their social experiences in the presence of healthy peers. Thus, deer mice not only resemble the compulsive nature of motor repetition, but H behavior is also associated with changes in cognitive ability and emotional perception, as indicated by altered social interactivity and its response to treatment.

4.3.3. Does deer mouse behavior in general present with different OC behavioral phenotypes?

OCD is a phenotypically heterogeneous condition characterized by intrusive thoughts and/or compulsions of varying nature, of which four major OC symptom dimensions

have been described, viz: 1) contamination obsessions and washing compulsions, 2) harm obsessions and checking compulsions, 3) symmetry obsessions and ordering compulsions, and 4) unacceptable thoughts and neutralizing compulsions (Abramovitch and Cooperman, 2015).

Nest-building (NB) behavior forms part of the normal behavioral repertoire of rodents, although differences in NB behavior (i.e., aberrant vs. normal NB) may resemble OC-like symptoms (e.g., work in rabbits by Hoffman and Morales, 2009). NB behavior in deer mice is highly variable, with no evident differences as a function of severity of stereotypy (Wolmarans *et al.*, 2015). However, as described for marble burying behavior above, a sub-population from *both* H and N cohorts present with large NB behavior. However, in this instance large NB behavior *is* reversible with chronic SSRI treatment, confirming that deer mouse behavior, like human OCD, presents with symptom heterogeneity.

Deer mouse behavior therefore resembles the inter-patient differences in OC phenomenology in that normal non-pathological (viz. N) and aberrant (viz. OC; H) stereotypical behavior is present. Moreover, different forms of OC phenotypes (viz. stereotypy and aberrant NB behavior) are present, with *both* abrogated by chronic SSRI treatment. Different psychological constructs of OC behavior are thus presented, with stereotypy resembling motor-associated compulsive behavior and aberrant NB reflecting a cognitive foundation in that it implicates a reason for compulsivity, i.e., concerns about security (Section 5). The latter would involve thoughtfulness in the expression of OC behavior.

### 4.4. Concluding remarks

Deer mouse stereotypy is a promising model for research into the neurobiology and behaviour of OCD, as well as a platform for novel drug discovery and research into the genetics of OCD. It has provided confirmatory facts about OCD phenomenology, as well as new knowledge pertaining to its neurobiology and treatment.

## 5. Insights from analysis and synthesis of compulsive checking in rats: Indications that OCD is a disturbance of motivation

### 5.1. Description of the quinpirole sensitization rat model of OCD

The notion that the transformation in behavior induced by chronic treatment with the DA agonist QNP could serve as an animal model of OCD arose by serendipity, during the course of research with animal models of psychosis. Specifically, experimental attempts to obtain from the behavior of QNP rats evidence of a psychotic state—expected from

the DA hypothesis of schizophrenia (Carlsson, 1988; Willner, 1997)—did not yield the predicted result of disorganized activity (Szechtman *et al.*, 1994b). Instead, watching these rats gave the impression of QNP behavior being "compulsive," suggesting OCD pathology. To translate this impression into an experimental framework, Szechtman and colleagues followed Reed (1985) who argued that the structure of OCD symptoms, rather than their content, is more clinically relevant and revealing of mechanisms. Hence, they searched for the spatiotemporal structure of OCD compulsions in the clinical literature and derived from it the following set of salient features of compulsive checking: (a) preoccupation with and an exaggerated hesitancy to leave the item(s) of interest; (b) presence of a ritual-like quality in the performance of checking; (c) dependence of checking activity on environmental context; (d) attachment of checking activity to stimuli with a plausible relationship to safety and security; and, (e) an ability to interrupt checking behavior temporarily. They translated those features into a set of objective criteria by identifying specific tests and quantifiable dependent variables that indexed those criteria and showed that QNP-treated rats met the stated criteria for compulsive checking (Ben Pazi *et al.*, 2001; Dvorkin *et al.*, 2006; Szechtman *et al.*, 2001; Szechtman *et al.*, 1998a; Zadicario *et al.*, 2007). Thus, because the spatiotemporal structure of QNP-induced behavior matched the salient features of OCD checking in the human, it was proposed that the QNP preparation constitutes an animal model of OCD compulsions and compulsive checking in particular (Szechtman *et al.*, 1998a). A comprehensive description of the logic and details of this model has been reviewed (Eilam and Szechtman, 2005b; Szechtman *et al.*, 1999; Szechtman and Eilam, 2005) and evaluated by others (Ahmari, 2015; Ahmari and Dougherty, 2015; Albelda and Joel, 2012a; Albelda and Joel, 2012b; Alonso *et al.*, 2015; Camilla d'Angelo *et al.*, 2014; Diniz *et al.*, 2012; Hoffman, 2011; Joel, 2006a; Korff and Harvey, 2006; Man *et al.*, 2004; Pallanti *et al.*, 2014; Westenberg *et al.*, 2007).

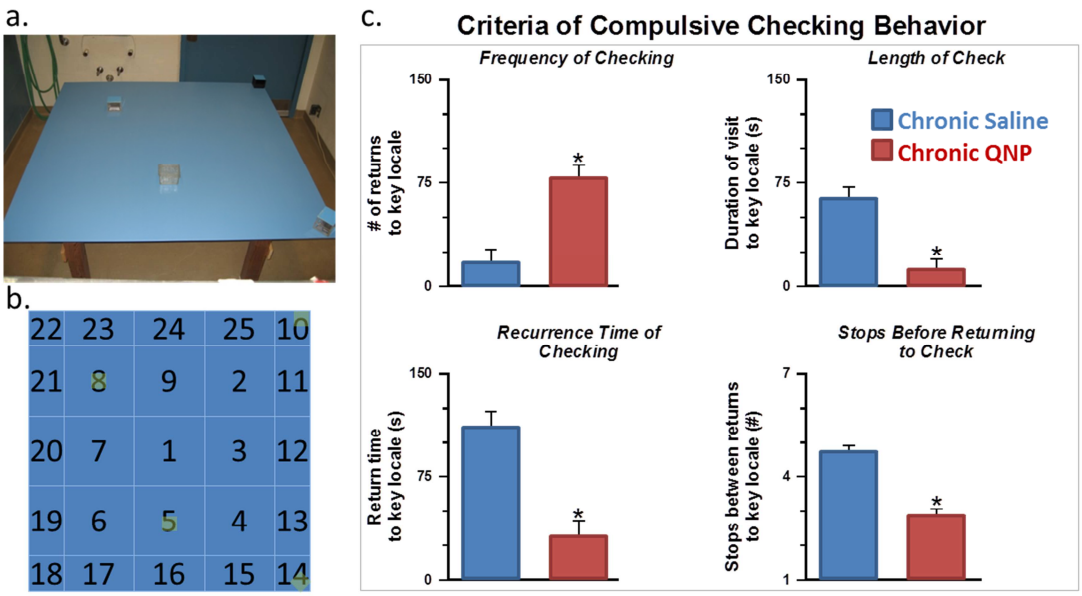



**Figure 8**

Figure 8: Experimental set-up and test for compulsive checking. (a.) The open field apparatus with 4 objects on it. (b.) Subdivision of the open field into 25 places. The software algorithm assigns the positions of *x,y* coordinates of a stop within these locales. (c.) Test for compulsive checking on the 8th injection of quinpirole (0.5 mg/kg). Rats are said to show compulsive checking behavior when their performance is significantly different from saline controls on all 4 measures: *frequency of checking* (# of stops in key locale); *length of check* (mean duration in seconds of stay in key locale); *recurrence time of checking* (mean duration in seconds of return times to key place); and, *# of stops before returning to check* (mean number of places visited between returns to key locale). *p<.05 *vs* saline controls. (Modified from Alkhatib *et al.*, 2013).

The standard protocol to induce compulsive checking is a dose of QNP every 3-4 days (0.5 mg/kg x 10); the rat is placed in the open field after each injection for 55 min. Control rats receive an injection of saline. The open field is a large table without walls (1.6 by 1.6 meters), with 4 small objects positioned at the same fixed locales throughout the study (see Figure 8a). For analysis of rat activity, the *x,y* coordinates of the rat's position in the open field are extracted from video records at a rate of 30 frames per second using EthoVision software (Noldus *et al.*, 2001) and the obtained track files processed to derive the criteria measures of compulsive checking (Dvorkin *et al.*, 2006; Dvorkin *et al.*, 2010). The open field is divided virtually into 25 locales (Figure 8b) and the criteria measures of compulsive checking are computed with reference to these locales. Evidence for compulsive checking requires the presence of a significant

difference between the QNP- and saline-treated rats on *all* 4 criteria measures, as shown in Figure 8c. Because repeated injections of QNP induce locomotor sensitization (Eilam and Szechtman, 1990; Einat *et al.*, 1996; Einat and Szechtman, 1993; Szechtman *et al.*, 1994a; Szechtman *et al.*, 1994b; Szechtman *et al.*, 1993; Szumlinski *et al.*, 1997), we often refer to the QNP preparation as the "quinpirole sensitization rat model of compulsive checking." In essence, in the QNP sensitization model, compulsive checking is manifested by exaggerated preoccupation with one location in the environment, to which the animal returns repeatedly (Figure 8c).

Overall, the QNP model of OCD is especially useful in two particular ways. First, it is open to a rich and sophisticated analysis of the behaviors that constitute the observable symptoms of the disorder. Indeed, the approach and methods developed to analyse compulsive checking in the rat were successfully applied to the analysis of rituals in OCD patients (see Section 7). Second, the model measures spontaneous behavior in an open-ended situation where there are no explicit rewards or contingencies. This simulates the condition which challenges OCD patients; namely, how to behave in situations of uncertainty where the environment does not dictate the optimal response (Boyer and Bergstrom, 2011; Cavedini *et al.*, 2006; Lind and Boschen, 2009; Starcke *et al.*, 2010; Tolin *et al.*, 2003; Woody and Szechtman, 2006). Below we highlight one interesting insight that emerged from studies with the QNP model, namely, an empiric description of the meaning of "compulsive" and relevance for a motivational theory of OCD.

5.2. Is "compulsive" behavior a unitary phenomenon?

In the research literature on mechanisms of OCD, behavior is often labelled as "compulsive" and displaying "compulsivity." However, as decried by Reed (1985) over 30 years ago, "the *meaning* of 'compulsive' is never examined; it seems to be regarded as so self-evident as to be unworthy of study or exposition" (p. 120, italics in original). One important question in the contrast between "compulsive behavior" and "normal behavior" (or "compulsivity" versus "normality") is whether the compulsive phenotype is a unitary whole or whether the behavioral phenomenon labelled as "compulsive" (or "compulsivity") is in fact comprised of discrete functional components. Because in the QNP model compulsive checking is characterized as an entire set of dependent measures, the question whether compulsive behavior is a unitary whole can be addressed by the method of nervous system fractionation (Teitelbaum, 1967; Teitelbaum, 2012; Teitelbaum and Pellis, 1992; Teitelbaum and Stricker, 1994). That is, if compulsive checking behavior is a unitary whole, then a lesion should affect the entire set as one entity. However, if the phenomenon is comprised of discrete functional

components then a lesion in a specific part of the brain should affect some components and not others, in essence fractionating the phenomenon into components. Two such lesion studies (Dvorkin *et al.*, 2010; Tucci *et al.*, 2014a) summarized below revealed that there exist at least two component processes underlying compulsive checking, both greatly exaggerated by QNP—one related to the vigour with which the behavior is performed and the other related to the focus with which checking is performed as a goal-directed activity.

5.2.1. Different lesions impact different checking measures

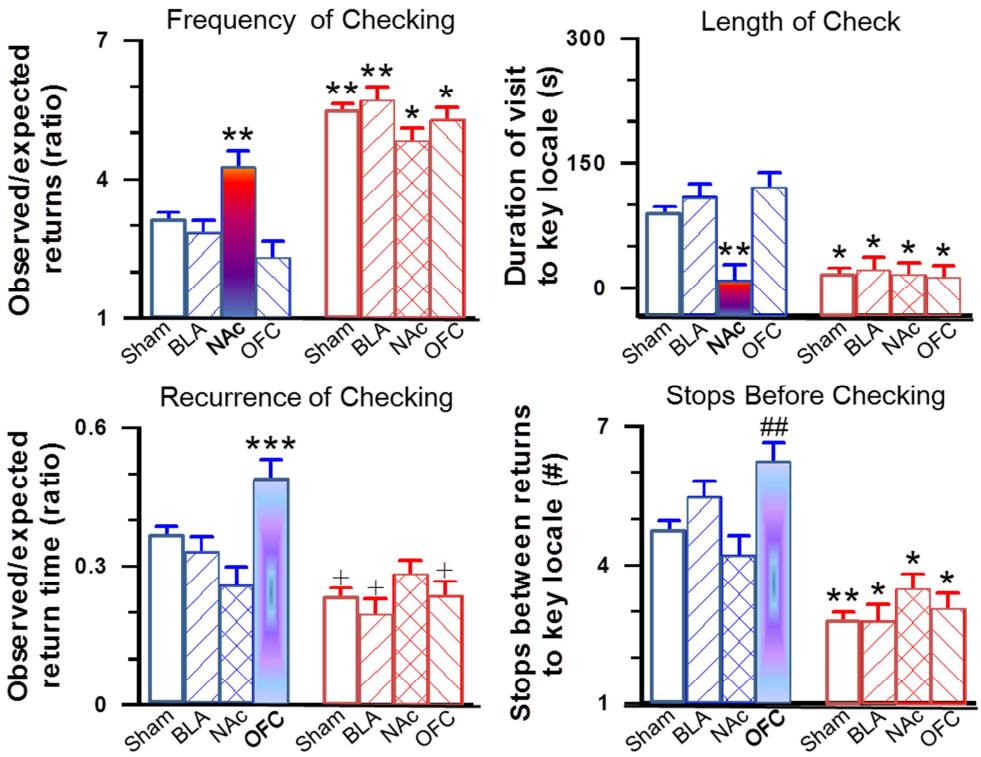



**Figure 9**

Figure 9**.** Performance on criteria measures of compulsive checking behavior shown by groups of rats with lesion to the basolateral amygdala (BLA), nucleus accumbens core (NAc), orbital frontal cortex (OFC) or sham lesion. Blue bars represent groups with chronic saline treatment (left cluster of each panel) and red bars represent groups with chronic quinpirole treatment (right cluster of bars of each panel). Solid fill bars in *top* row show effect of NAc lesion on *frequency of checking* and *length of check* while those in the *bottom* row show effect of OFC lesion on *recurrence of checking* and *stops before checking.* * $P < 0.05$ vs. sham controls, BLA lesion, and OFC lesion groups treated chronically with saline; ** $P < 0.05$ vs every group treated chronically with saline; *** P

< 0.05 vs. every other group; ## P < 0.05 vs. every group treated chronically with quinpirole as well as sham controls and NAc groups treated chronically with saline. (Modified from Dvorkin *et al.*, 2010).

In a study by Dvorkin *et al.* (2010), rats received repeated injections of saline or QNP (0.5 mg/kg, twice per week, x 8 injections) to induce compulsive checking, and then received NMDA lesions of the basolateral amygdala (BLA), NAc, OFC, or sham lesions. When retested two weeks post-surgery, results showed effects of NAc and OFC lesion on checking behavior but no effect of the BLA lesion. Tellingly, as shown in Figure 9, the set of criteria measures was split into two subsets – the NAc lesion affected the frequency of checking and length of check (top row), and the OFC lesion affected recurrence of checking and stops before checking (bottom row). These effects were evident on measures of checking behavior in saline-treated rats (blue colored bars; left bar cluster); the pertinent effects are indicated by the graph bar having a solid fill.

When it is analyzed whether the split into the two subsets reveals a meaningful subdivision, it becomes apparent that the measures in the *top* and *bottom* rows of Figure 9 capture two distinct aspects in the performance of checking. The *top* row measures behavior performed *at* the place of checking (how often the rat returns to check the place/object and how long it stays there to perform the check). The *bottom* row measures the behavior of *getting* to the place of checking (how long was the rat elsewhere and how many places did it visit before returning to check the place/object of interest). That is, NAc lesions affected measures indicative of the amount of checking behavior, whereas OFC lesions affected indices of staying away from checking. Consistent with the literature as to the function of NAc, Dvorkin et al. (2010) suggested that this region mediates the **vigor** of checking, and thus one component of compulsive checking is the vigor of its motor performance. Similarly, they suggested that a second component is the **focus or concentration** on the task of checking. Accordingly, "compulsive" checking reflects a QNP-induced exaggeration of at least two functional components: (a) vigor of checking; and, (b) the focus on checking. It is noteworthy that the anatomical substrates on these two components appear to include parts of the CBGTC circuit, the OFC, and a ventral region of the striatum, NAc.

5.2.2. Synthesis by experiment of compulsive checking from components

Following the proposition that the appropriateness of analysis ought to be confirmed with a synthesis of the behavior from its parts (Teitelbaum, 2012; Teitelbaum and Pellis, 1992), Szechtman and colleagues sought to re-synthesize compulsive checking from the identified components, without using QNP. In a study by Tucci *et al.* (2014a), the vigour component was reconstituted with a bilateral lesion of the NAc core, as this treatment

exaggerates vigor in saline-treated rats (Dvorkin *et al.*, 2010). To reconstitute focus, the employed treatment was a low dose of the 5-$HT_{1A}$ receptor agonist 8-hydroxy-2-(di-n-propylamino) tetralin hydrochloride (DPAT) (0.0625 mg/kg), as high doses of this drug induce compulsive behavior (Alkhatib *et al.*, 2013) and low doses show an effect on focus only. The study consisted of a 2 x 2 fully crossed factorial design where one of the between-group factors was *Lesion* (sham lesion *vs.* NAc core lesion) and the other one was *Drug* (saline *vs.* DPAT). As shown in Figure 10, neither the drug alone nor the NAc core lesion by itself produced compulsive checking but injection of DPAT to NAc core lesion rats did, confirming that vigour and focus are constitutive components of compulsive checking.

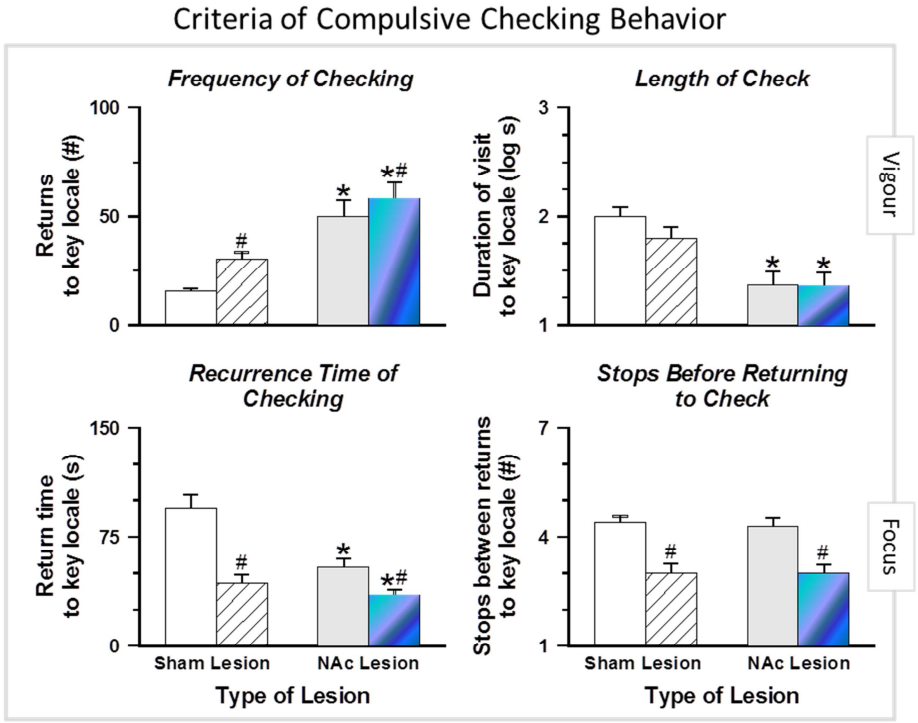



**Figure 10**

Figure 10: Performance on criteria measures for compulsive checking behavior shown by groups of sham controls and NAc core lesion rats treated with saline or DPAT. Open bars, sham controls injected with saline; right hatch, sham controls injected with DPAT; gray filled bars, NAc core lesion rats injected with saline; color filled bars, NAc core lesion rats injected with DPAT. * main effect of lesion; # main effect of drug. (From Tucci *et al.*, 2014a).

5.3. Diminished negative feedback in compulsive checking

Although compulsive checking appears comprised of vigorous performance and intense concentration, these two attributes are characteristic of any performance when motivation is high, and one normally would not label the performance of an individual who is highly motivated, as “compulsive.” Clearly, vigour and focus components are insufficient to mark a behavioral phenotype as "compulsive"— yet another component must operate to label checking as “compulsive”. Indeed, analysis revealed that performance of QNP-induced checking is characterized by yet another attribute, which sets compulsive behavior apart from normal motivation: Normally, when a goal object is attained, the output of a motivated state ends for a prolonged period of time before the motivation is awakened again. For instance, eating terminates hunger motivation by generating a negative feedback signal that shuts down or “satiates” the motivation for food and hence, one generally sees only one bout of the motivated behavior in a particular time period. However, QNP-induced checking behavior is characterized by a very abbreviated period of time after a bout of checking before the start of another checking bout (see Figure 11); consequently, there are several bouts of checking behavior in a relatively short period of time, suggesting a reduced negative feedback component between bouts of QNP-induced compulsive checking (Dvorkin *et al.*, 2006; Dvorkin *et al.*, 2010). Thus, by describing behavior as “compulsive” one is highlighting highly motivated performance *but without apparent satiation*.

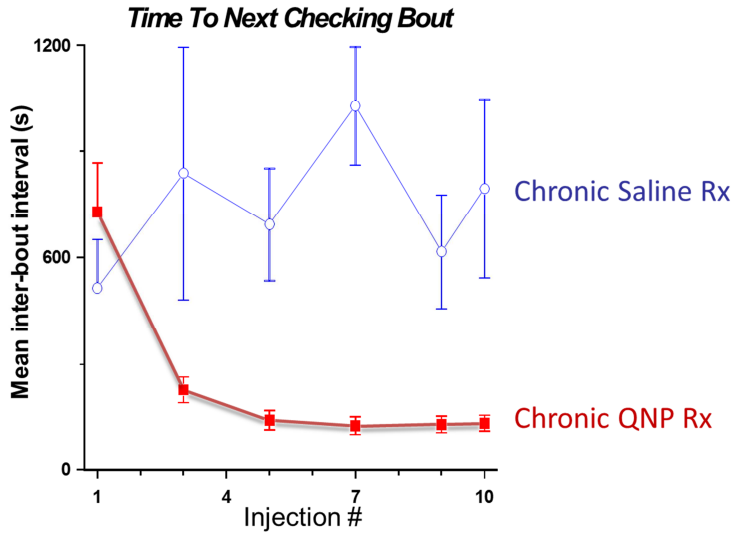



**Figure 11**

Figure 11: Duration of negative feedback signal as measured by *time to next checking bout* in rats treated chronically with saline (blue open circles) and quinpirole (red solid squares) during the course of treatment to induce compulsive checking. (From Dvorkin *et al.*, 2006).

5.4. Compulsive checking in the rat suggests a motivational disturbance in OCD

Because the identified components of compulsive checking— (a) vigour of performance (b) focus on the task, and, (c) rest or "satiation" after task completion—are also intrinsic parts of a motivational system, it is a reasonable formulation that checking behavior in the rat is a motivated behavior, and that compulsive checking reflects the exaggerated function of that particular motivation. Remarkably, this hypothesis brings the work with rats into the framework of the security motivation theory of OCD (Szechtman and Woody, 2004; Woody and Szechtman, 2005) that originated in a separate and independent line of research (Szechtman *et al.*, 1998b; Woody and Szechtman, 2000). It does so because the rat work hypothesis raises the question as to what is that particular motivation which would have as its output checking behavior, an answer contained in the security motivation theory of OCD (Szechtman and Woody, 2004; Woody and Szechtman, 2005). Specifically, it had been proposed that there exists a special motivation—Security Motivation—evolved to handle the uncertainties of potential threats, and that a dysfunction in security motivation produces OCD (Szechtman and Woody, 2004; Woody and Szechtman, 2005). The notion of a special motivation for potential danger was based on clinical literature that the domain of most OCD thoughts and behaviors is safety and security (Reed, 1985) and on evidence from ethological and ecological literatures that animals show species-typical behaviors for assessing various domains of potential harm, including potential threats related to predation and disease (e.g., Blanchard and Blanchard, 1988; Curio, 1993; Lima and Bednekoff, 1999; Wingfield *et al.*, 1998). These considerations suggested that a security motivation system would produce not only the urge to engage with cues of potential danger but produce also species-typical precaution and preventive responses such as checking or washing (Hinds *et al.*, 2010; Szechtman and Woody, 2004; Woody and Szechtman, 2011, 2013). Accordingly, it was theorized that OCD symptoms emerge if there is a malfunction that prevents the normal de-activation of security motivation because preoccupation with issues of potential danger would continue, driving repeated performance of security-related behaviors such as checking or washing and the associated thoughts and ideas characteristic of OCD (Szechtman *et al.*, 2014; Szechtman and Woody, 2004; Szechtman and Woody, 2006; Woody *et al.*, 2005; Woody and Szechtman, 2005). Recent experimental support for this theory has come from studies showing that in individuals with OCD, performance of precautionary behaviors is indeed deficient in turning off an activated security motivation (Hinds *et al.*, 2010; Hinds *et al.*, 2012). Moreover, the neuroanatomical structures associated with the component behaviours of the compulsive checking system are common elements of the CBGTC circuit implicated in OCD and have been proposed as the neural circuit of the security motivation system (Szechtman *et al.*, 2014; Szechtman and Woody, 2004; Woody and Szechtman, 2011).

The reviewed decomposition of compulsive checking behavior in the rat into functional components and the characterization of compulsive checking as highly motivated performance but without apparent satiation, provides strikingly convergent support from an animal model for the security motivation theory of OCD (Szechtman and Woody, 2004; Woody and Szechtman, 2005).

## 6. Insights into OCD from neuromodulation in the QNP and signal attenuation (SA) models

### 6.1. Endophenotypes in OCD

In concordance with the existence of a heterogeneous group of patients, OCD patients do not show consistent responsiveness to treatment, as some patients respond well whereas others show partial or no response. In other words, the capacity of a treatment strategy to modulate specific pathophysiological disease substrates may not suffice as an efficient treatment for all OCD patients due to the existence of endophenotypes entailing a specific neurobiological substrate of behavior. It needs to be considered that: i) the same neuropathological mechanism may translate into different expressions of disease, ii) the same disease expression and symptom profile may result from different neurobiological trajectories and iii) a specific neurobiological substrate may translate into a specific symptom. Such considerations are mandatory when evaluating optimal therapeutic strategies, i.e. those that specifically interact with the pathophysiological substrate only at those times when symptom alleviation is needed and only in those brain regions and networks that are implicated in the disease process. As such, a pool of therapeutic options that are accurately defined with respect to their specific potential to interact with the underlying pathology of a specific endophenotype and its correlated neurobiological substrate may be appealing and entail the future of effective treatment of psychiatric disorders. While these challenges will ultimately need to be met in the clinic, model rodents have aided considerably in addressing them at the proof-of-concept level.

### 6.2. Using two different animal models of compulsive behavior in parallel

As noted in the Introduction (Section 1), animal models do not recapitulate the full phenotype of a human disorder such as OCD. However, a phenotype or pathophysiological constructs of specific aspects of a psychiatric disorder including OCD may be modeled and the parallel use of different animal models ultimately leads to a more complex picture of the modeled disorder. The *QNP model* (Section 5) considers the pathophysiological relevance of the DA system in the manifestation of a repetitive symptom: The combination of an environmental context and repeated dopaminergic

challenge with the DA D2/D3 receptor agonist QNP induces compulsive behavior that resembles compulsive checking behavior in the human (Szechtman *et al.*, 1998a). The *signal attenuation (SA) model* is based on the theory that OC-behavior results from a disrupted feedback following the accomplishment of goal-directed behavior (Joel, 2006b). In this model, an external cue indicating the successful accomplishment of a specific goal-directed behavior (lever pressing) is attenuated by repeated exposure to the cue in the absence of the goal. This leads to a greater number of lever presses that are not "completed" by checking the feeder for food. The uncompleted lever presses are seen as excessive or compulsive, modeling compulsive behavior in OCD.

Consequently, the mechanisms by which compulsions are induced differ between the two models. Compulsions in the QNP model are provoked pharmacologically, whereas compulsions in the SA model are induced in drug-free rats following a behavioural paradigm. Therefore, the underlying neurobiological alterations mediating compulsive behaviour may differ between the two models and result in different aspects of OCD. There is no doubt that both the SA and the QNP model of OCD constitute rodent models of strong face, predictive and construct validity. The differential way of manipulation leading to the induction of distinct symptoms suggests that the parallel investigation of these models may help define both neurobiological substrates specific for each of the distinct symptom profiles as well as those substrates related to common pathological pathways. By this, it becomes possible to envision the development of therapeutic strategies that either selectively target a specific symptom profile or generally interact with common pathological substrates of aberrant behavior.

6.3. DBS in the QNP and SA models

Deep brain stimulation (DBS) has been established for the treatment of several movement disorders and currently is discussed as a therapeutic alternative for the treatment of intractable psychiatric disorders. Yet, DBS is more than merely an effective therapeutic tool. By its nature to selectively modulate activity within the DBS target itself and the associated networks, an evaluation of DBS effectiveness across pathologies allows for conclusion on the pathophysiological relevance of specific brain sites and networks. Further, evaluation of DBS effectiveness across endophenotypes of a single disease allows for conclusions on the specific pathological substrates of a specific symptom.

In this context, the QNP and the SA model of OCD were used in parallel to study the symptom-specific therapeutic effects of DBS and to conclude on the pathological involvement of several brain sites in the manifestation of OCD subtypes: i) the STN, ii) the GP differentiated into the lateral GP (LGP, rodent equivalent to external segment of

the human GP) and the EP [rodent equivalent to internal segment of human GP (GPi)], iii) NAc, divided into the functionally and anatomically distinct NAc core and NAc shell. The overall effectiveness of STN- and NAc-DBS in ameliorating OC-symptoms has been validated clinically (Denys *et al.*, 2010; Mallet *et al.*, 2008). This also goes for DBS applied to the GPi - shown to alleviate symptoms in patients with Tourette's syndrome patients comorbid with OC-symptoms (Nair *et al.*, 2014). Therapeutic responses are still largely restricted, however, suggesting the need for further investigation into the underlying pathology and subsequent effects of DBS in OCD-subtypes.

6.3.1. DBS of the GP, EP or STN

In studies with rodents, high frequency DBS applied to the GP and EP reduces compulsions in the SA model, whereas EP-DBS only partly reduces compulsive behaviour and GP-DBS not at all in the QNP model (Djodari-Irani *et al.*, 2011; Klavir *et al.*, 2011) (Figure 12A). This observation that the two models do not react in the same manner towards neuromodulating interventions corroborates the notion that the underlying neurobiological alterations mediating compulsive behaviour differ between the two models and thus result in different aspects of OCD (Djodari-Irani *et al.*, 2011). Despite these differences, there might still be a final common pathway leading to compulsive behaviour in both models. This is apparent as functional modification of the STN following DBS application reduces compulsions in both the SA and QNP model. The anti-compulsive effect of STN-DBS links the indirect pathway of the CBGTC circuit to the compulsive manifestations in both models (Klavir *et al.*, 2009; Winter *et al.*, 2008c). The QNP model is thought to express a hyperactive dopaminergic system due to repetitive QNP application. Since STN-DBS reduces compulsivity in both the QNP and SA model (e.g., drug-naive rat) this suggests that the anti-compulsive effect is not restricted to a hyper-dopaminergic system (Klavir *et al.*, 2009).

6.3.2. DBS of nucleus accumbens and the possible role of DA and 5-HT

Modification of the dopaminergic system indeed seems to be an important aspect of the anti-compulsive effect of DBS especially in the QNP model as DBS applied to the NAc reduces compulsive behaviour in the QNP model (Mundt *et al.*, 2009). Since the NAc itself projects to dopaminergic neurons innervating the striatum, the anti-compulsive effects may be related to a normalisation of the abnormal dopaminergic activity induced by repetitive QNP application (Mundt *et al.*, 2009). STN-DBS has furthermore been coupled to an increase in DA levels in the striatum and NAc (Meissner *et al.*, 2003; Winter *et al.*, 2008b). Interestingly, EP-DBS that only partially affects compulsive behaviour in the QNP model, does not affect DA release in the striatum (Meissner *et al.*, 2004). In the SA model, both STN and OFC lesions increase compulsive behaviour. This

behaviour is coupled to a decrease in both 5-HT and DA content in the striatum (caudate putamen) and can subsequently be reversed by a SSRI. This indicates that normalisation of especially a dysfunctional striatal serotonergic system may be important for the anti-compulsive effect in the SA model (Schilman *et al.*, 2010; Winter *et al.*, 2008a). Taken together, there is the possibility that both the dopaminergic and serotonergic neurotransmitter systems are involved in compulsions, yet one or the other may dominate in each of the two models, giving rise to the different model subtypes (Figure 12B).

### 6.4. Inactivation of CBGTC circuit targets

Direct inactivation of some targets within the CBGTC circuit abolishes compulsive behaviour regardless of the model. Direct inactivation of the STN, GP or EP by administration of the GABA agonist muscimol decreases compulsion in the SA and QNP model (Djodari-Irani *et al.*, 2011; Klavir *et al.*, 2009; Winter *et al.*, 2008c). The behavioural effect of STN inactivation corresponds to that observed following STN-DBS in both models – initially indicating a common mechanism of both interventions. Yet, the differential effect mediated by muscimol and EP- or GP-DBS in the QNP model, states otherwise. This shows that DBS effects are different from a direct silencing and further may indicate that the neuromodulating effect of DBS depends on the cellular arrangement of the target structure (Djodari-Irani *et al.*, 2011). If this is indeed the case, the cellular arrangement of the EP and GP may ultimately differ between the two models, which further highlight differences between the two models.

### 6.5. Conclusions

These data suggest that there is not just one pathophysiological mechanism underlying the whole spectrum of OCD manifestation but rather that specific neurobiological profiles translate into specific symptom profiles. The well-accepted inability of animal models to recapitulate the full phenotype of uniquely human disorders such as OCD simultaneously constitutes their strength in modeling specific aspects of the whole phenotype. The parallel use of different model rodents of different subtypes allows for evaluation of neurobiological substrates of the specific disease expressions and the establishment of therapeutic strategies that directly interact with the endophenotypic neurobiological substrate. Based on these findings, we may conclude that of the DBS targets investigated in the QNP and SA animal models of OCD, the STN constitutes a region where DBS elicits symptom-comprehensive effects, whereas the GP and NAc may be selected for DBS treatment of OCD patients with symptom profiles resulting from

predominantly serotonergic or dopaminergic deficits, respectively.

**A**

| Anti-compulsive DBS effects | SA model | QNP model |
|---|---|---|
| **STN** | ↓↓ | ↓↓ |
| **LGP** (GPe equivalent) | ↓↓ | ÷ |
| **EP** (GPi equivalent) | ↓↓ | ↓ |
| **NAc** | Not known | ↓↓ |

**B**

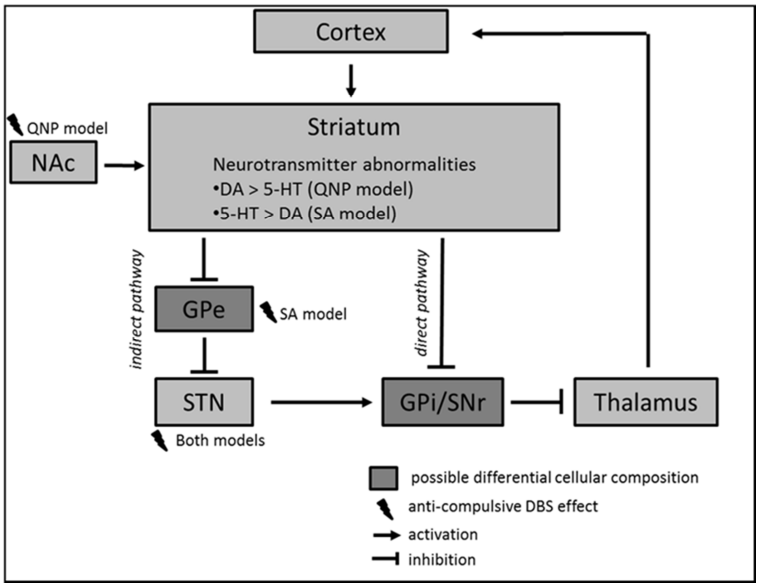



**Figure 12**

Figure 12: A) the degree of anti-compulsive effects in the signal attenuation (SA) and quinpirole (QNP) model following high-frequency deep brain stimulation (DBS) to brain targets of the cortical-basal ganglia-thalamo-cortical circuit (CBGTC) ÷ = no effect; B) the CBGTC loop, including the differential neuropathology between the two models with respect to striatal neurotransmitter systems and cellular arrangement. DBS applied to the STN elicits symptom-comprehensive effects, whereas the NAc and GPe selectively reduce compulsivity in the QNP and SA model, respectively. 5-HT, serotonin; DA, dopamine; EP, entopeduncular nucleus; GPe, external globus pallidus; GPi, internal globus pallidus; LGP, lateral globus pallidus; NAc, nucleus accumbens; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus

7. From the quinpirole rat model for OCD to clinical OCD patients: Translating an animal model into practice

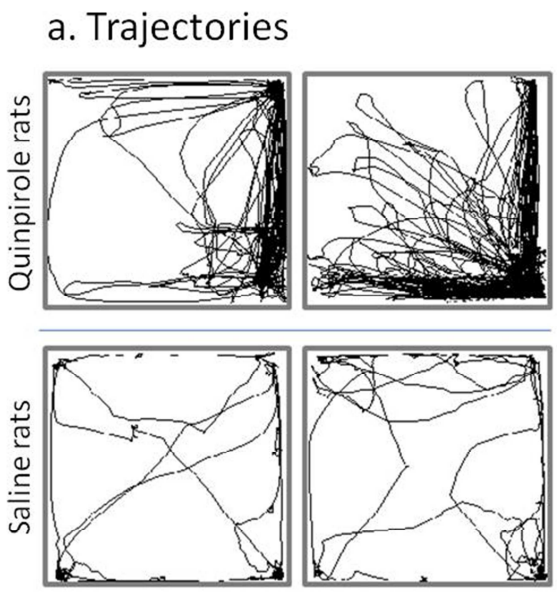
### 7.1. Translational research

The field of translational research was introduced to promote the application of basic research in clinical practice (Zerhouni, 2003). In other words, this field of research offers an interface between basic science and clinical medicine, coined by Woolf (2008) as 'bench to bedside'. Relying on Darwin's notion that the difference between humans and non-humans is one of degree, not of kind (Dalgleish, 2004; Darwin, 1871), the concept of translational research in animals may seem obvious. Indeed, while there are clear differences between humans and other animals, there are also many similarities. Nevertheless, there is a large mental gap between humans and non-humans (Penn *et al.*, 2008), and this gap hinders the translational studies of animal models for psychiatric disorders. To overcome this obstacle in developing an animal model for OCD, a descriptive and analytic approach that originated in studying movement in humans was utilized. Specifically, this approach borrowed tools from the Eshkol-Wachman Movement Notation (EWMN), which was designed to describe the movements of ballet dancers in the same way that notes describe music (Eshkol and Wachman, 1958). The EWMN had been previously applied in the study of animal behavior in general (Golani, 1992) and specifically in studying spatial behavior in rats (Eilam and Golani, 1988, 1989). In those studies, behavior was regarded as intervals of travel that are interrupted by stops (stationary episodes). Accordingly, the analysis was based on scoring: (i) the sets of movements that rats perform when they are stationary in a specific locale; and (ii) the trajectories of the routes connecting these locales, assuming that during locomotion rats cannot perform movements like rearing and grooming that they perform when stationary (Eilam and Golani, 1989; Eilam *et al.*, 1989; Weiss *et al.*, 2012). Notably, the application of this approach revealed numerous similarities between spatial behavior in humans and in rodents (for a comprehensive review, see Eilam, 2014). In the context of OCD, this analytic approach was first applied to the study of behavior of rats sensitized to the $D_{2/3}$ DA agonist QNP (Eilam *et al.*, 1989).

### 7.2. Compulsive behavior as a set of trajectories bounded by sets of acts

Following several injections of QNP to rats in a large (1.6 x 1.6 m) open field, activity increased to as much as 16-fold higher than after the first injection. However, the rats' activity was limited to specific paths in the open field (Eilam *et al.*, 1991). Moreover, the rats seemed to travel hurriedly from place to place with unbounded curiosity as if performing an important mission, and they did not appear to habituate to the environment or succumb to fatigue (Szechtman *et al.*, 1994b). This behavior of QNP rats was suggested as a model for compulsive checking (Szechtman *et al.*, 1998a) and was further supported in a large set of studies (e.g., Alkhatib *et al.*, 2013; Tucci *et al.*, 2013;

Tucci *et al.*, 2014b). This compulsive-like behavior of QNP rats in the open field is based on two types of performance: (i) path stereotypy; and (ii) fixed sets of acts in specific locations (see Section 5 and Figure 13).




b. Behavior at one corner

| Visit # | Arrival | Touch the box | Climb the box | Lateral movement | Departure |
|---|---|---|---|---|---|
| 1 | A | B | C | D | H |
| 2 | A | B | C | D | H |
| 3 | A | B | | D | H |
| 4 | A | B | C | D | H |
| 5 | A | | | 2 x D | H |
| 6 | A | | | 2 x D | H |
| 7 | A | B | | D | H |
| 8 | A | B | C | D | H |
| 9 | A | B | C | D | H |
| 10 | A | B | | D | H |
| 11 | A | B | C | D | H |
| 12 | A | B | C | D | H |

**Figure 13**

Figure 13: The method of tracing the trajectories of locomotion and scoring the behavior in stopping places. The figure is based on data from (Zadicario *et al.*, 2007). **a.** Trajectories of traveling of two rats after the 18th injection of 0.5 mg/kg quinpirole (top) or saline (bottom). The trajectories represent the activity during the 60 min after the injection in a 2x2 m arena. As shown, the quinpirole rats traveled repeatedly the same paths in a restricted portion of the arena whereas the lesser activity of the saline rats spans over the entire arena, with seldom passing the same paths. **b**. Behavior of a quinpirole rat during 12 visits to the bottom right arena corner at which a small box was placed. Each row represents one visit, and the characters represent the following behaviors: A – arriving at a diagonal direction; B – snout contact with the box; C – climbing on top of the box; D – performing a large lateral turn; E – departure from the corner to the left. As shown, there is high regularity in the behavior of the rat over repeated visits to the corner.

In parallel with reinforcing the QNP rat as a model for OCD, Eilam and colleagues commenced experiments aimed at materializing the translational potential of this model, seeking to scrutinize the compulsive behavior of OCD patients on the basis of the same separation that was used in rats: the sets of movements that patients perform when stationary in a specific locale and the trajectories of the routes connecting these

locales. This method is illustrated in Figure 15, in which the routes and movements of an OCD patient are depicted, based on an excerpt from the diary of that patient published in Rasmussen and Eisen (1991).

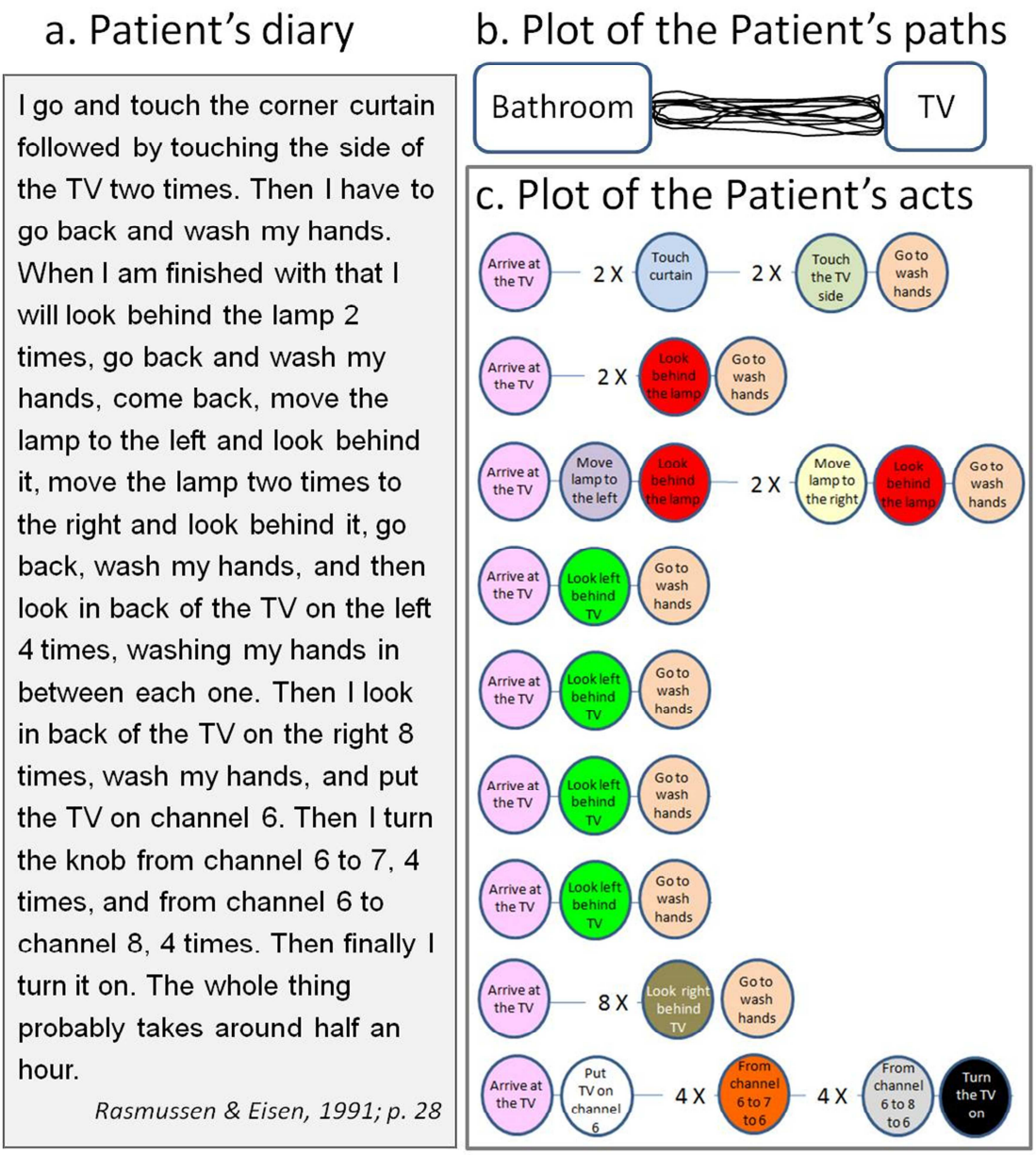



**Figure 14**

Figure 14: Excerpt from the patient's diary (**a.**) describing the ritual of turning on the TV. Behavior comprised systematic traveling between the bathroom and the TV, which could be schematically depicted as shown (**b.**). In the description of the acts when at the

TV (**c.**), each visit to the TV during the ritual is depicted along one row, and each circle represents one act (similar acts are depicted in the same color).

7.3. Compulsive OCD rituals: predominance of idiosyncrasy and repetitions

What is lacking in Figure 14 is an appropriate control that could highlight what is abnormal in this behavior, in addition to the apparent long duration and numerous repetitions. The need for appropriate reference for OCD behavior is a major obstacle, considering the great variability in patients' behavior, where one could have a compulsive checking of the door, another washes hands compulsively, a third one has a ritual when lighting a cigarette, and so on. To overcome this variability, a control individual was matched to each OCD ritual. Specifically, after an OCD patient performed on camera, a matched healthy individual of similar age and gender was asked to perform the same task that formed the OCD ritual. For example, if a patient described his/her ritual as locking the house door, the respective control was requested to lock his house door too. After scoring the acts performed by an OCD patient and his control individual, their act repertoire was divided into common acts performed by both and idiosyncratic acts performed by only one of them. Moreover, it was suggested that the common acts are compulsory for performance of that specific task, whereas the idiosyncratic acts are unnecessary for its completion (Zor *et al.*, 2009). The idea that idiosyncratic acts are unnecessary rests on the fact that one actor (the patient or the control individual) was able to complete the task without these acts. Figure 15 depicts the set of acts by a control individual (top) and OCD patient (bottom) when each was locking his car. The large circles depict common acts whereas the small circles depict idiosyncratic acts.

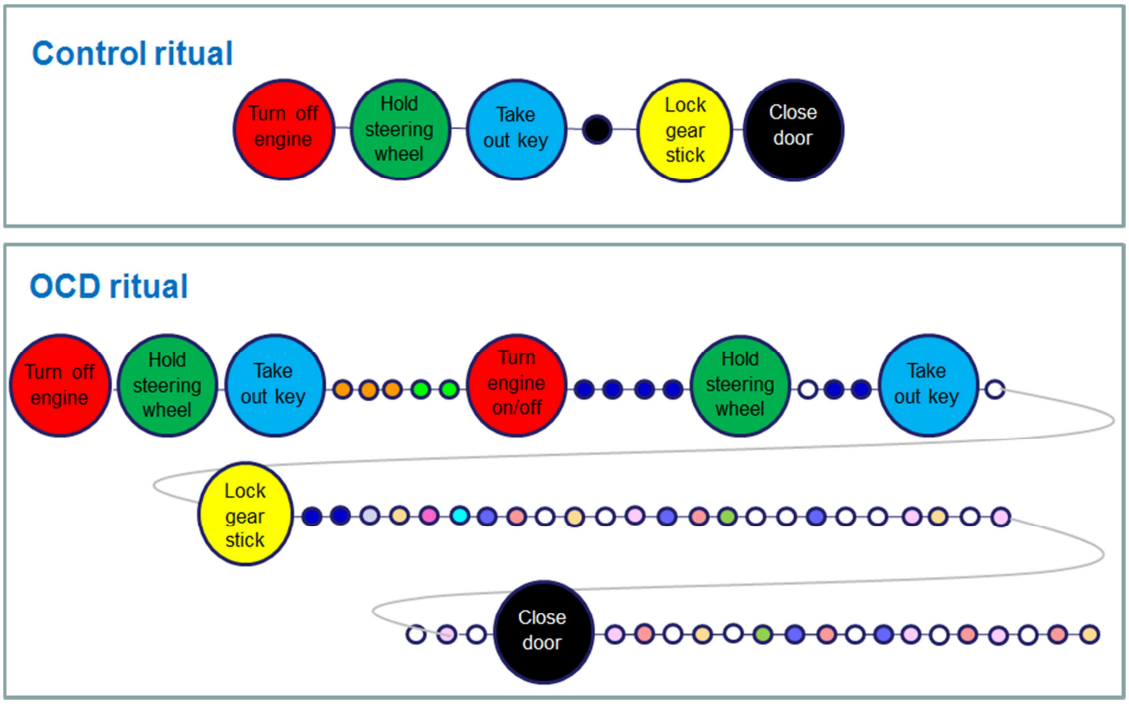



**Figure 15**

Figure 15: The sequence of acts performed by a control individual (upper box) and an OCD patient (bottom box) as they lock and walk away from their car. Large circles depict common acts and small circles depict idiosyncratic acts. As shown, the control individual had only one idiosyncratic act and no repetition of acts, whereas the OCD patient had numerous idiosyncratic acts, repetition of common acts, and a long "tail" of idiosyncratic acts at the end of the task.

Applying the division to common and idiosyncratic acts for the repertoire of acts (repetitions excluded) of 43 rituals performed by 39 OCD patients revealed that there were three-fold more idiosyncratic acts in OCD patients compared with their respective control individuals (Figure 16). Accordingly, the performance of OCD patients was termed pessimal (antonym of optimal) behavior (Zor *et al.*, 2009). A discussion on the possible role of idiosyncratic acts in OCD as well as in normal behavior is available elsewhere (Eilam, 2015).

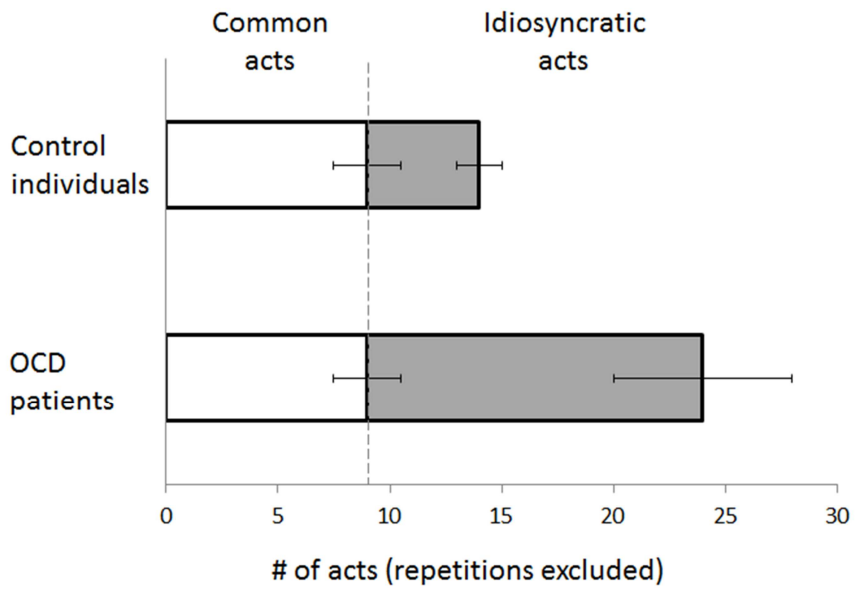



**Figure 16**

Figure 16**:** The number (mean ± SEM) of common acts (open bars) and idiosyncratic acts (gray bars) in the repertoire of acts (repetitions excluded) of 43 OCD rituals (bottom) and their non-OCD controls (top). The number of common acts performed in OCD and control rituals was identical (open bars). However, the number of idiosyncratic acts in OCD was three-fold that of controls (gray bars). The overall act repertoire was almost twice as large in OCD as in control rituals. Moreover, in the controls there were more common than idiosyncratic acts, whereas in the OCD patients it was the opposite: more idiosyncratic than common acts. (Based on data from Eilam *et al.*, 2012).

Further scrutiny of the temporal order of acts revealed that OCD rituals typically end with a long chain of idiosyncratic acts (see Figure 15 for example). Since these acts are considered unnecessary for task completion, it was suggested that the prevalence of activity after the functional end of the task increased the non-functionality in OCD motor rituals and supports the theory of ‘‘lack of stop signal’’ as the underlying mechanism in OCD (Zor *et al.*, 2011). The same methodology was also used to compare cleaning and checking rituals, with the findings indicating that these rituals are sufficiently different to justify their division into different subtypes, which presumably are sub-served by different mechanisms (Zor *et al.*, 2011). Similarly, the division into common and idiosyncratic acts also revealed that between-country and/or culture differences among OCD patients were mild, possibly overridden by the conspicuous impact of OCD pathology that resulted in a similar OCD phenotype (Zor *et al.*, 2010).

Finally, the overt and eye-catching prevalence of idiosyncratic acts has been recently implemented as a bed-sign in clinical OCD patients (Amitai *et al.*, 2015).

7.4. Summary: bench to bedside

In psychiatry, the diagnosis of mental disorders is established on the basis of behavior and, therefore, the assessment of movement patterns offers a common baseline for the comparison and study of different syndromes. This seems especially true for compulsions and stereotypies, which are primarily associated with repetitive behaviors and rigid routines. Here, it was demonstrated how movement notation, which is a sign language for the description of movement in humans, was applied in a study of the QNP rat model for OCD and ultimately led to implementing the approach in the clinic. In other words, this translational model provided us with tools that could be applied directly for studies of motor rituals in OCD patients, studies that are now implemented in OCD clinics. The model demonstrated here thus offers an illustration of the path of a translational model from the bench (animal behavioral analysis lab) to the bedside (OCD clinics).

8. Conclusions

Good models generate novel insights, and this should be the case for animal models of psychiatric disorders as well. The present review considered the use and utility of animal models in research on mechanisms underlying the psychiatric disorder, OCD. This review was not intended to summarize the growing area of research using animal models of OCD, as a number of such first-rate publications already exists (Ahmari, 2015; Ahmari and Dougherty, 2015; Albelda and Joel, 2012a; Albelda and Joel, 2012b; Alonso *et al.*, 2015; Boulougouris *et al.*, 2009; Camilla d'Angelo *et al.*, 2014; Diniz *et al.*, 2012; Eilam and Szechtman, 2005b; Eilam *et al.*, 2012; Grados *et al.*, 2015; Gunaydin and Kreitzer, 2016; Hoffman, 2011; Joel, 2006a; Korff and Harvey, 2006; Man *et al.*, 2004; Ting and Feng, 2011b; Wang *et al.*, 2009; Westenberg *et al.*, 2007). Instead, the current synthesis is unique in that it brings together several independent investigators to highlight a few features of their research where animal models serve as exemplars of fruitful questions and areas of investigation into OCD. Some key points that emerged from each section above include:

(1) Establishment of a cause-effect relation between neural circuit hyperactivity and OCD symptoms requires the experimental manipulation of the neural circuit to induce the symptoms in question and this can be done in animals as shown with the optogenetic studies in mice where optical stimulation of VMS led to excessive grooming that was still present up to 2 weeks after the last stimulation (reviewed in section 2).

(2) Because OCD presents with different symptom combinations, this suggests the presence of endophenotypes and the likelihood that specific symptom profiles would respond best with targeted therapeutics. Parallel use of several animal models is a fruitful paradigm to examine the mechanisms of treatment effects of DBS in distinct OCD endophenotypes, as suggested by differential effects of DBS at several sites within the CBGTC circuit of QNP-treated and SA model rats (reviewed in section 6).
(3) Features of spontaneous behavior in a subpopulation of deer mice show many properties of OCD compulsions, providing a naturalistic model of compulsive behaviors. This preparation constitutes a rich platform to investigate the neurobiology of OCD, the social ramifications of a compulsive phenotype, and a vehicle for drug discovery that includes the possibility of therapeutics for OCD which target pathways of oxidative stress and PDE4 activity within the CBGTC circuits (reviewed in section 4).
(4) Mechanisms underlying comorbidity of OCD with other psychiatric disorders such as schizophrenia may involve shared neural circuits controlling expression of compulsive behavior, as suggested by enhanced SIP in various animal models and associated brain changes in parts of the CBGTC circuit implicated in OCD (reviewed in section 3).
(5) Analysis of compulsive behavior into its constitutive functional components provides evidence from an animal model for a motivational perspective on OCD, as suggested by findings in QNP-sensitized rats that 'compulsive' checking has the attributes of highly motivated performance but without apparent satiation, consistent with the theory that a malfunction in a negative feedback signal that shuts-down an activated security motivation produces OCD (reviewed in section 5).
(6) Because in psychiatry diagnosis of mental disorders is largely from behavioral data, assessment of movement patterns in animals and humans offers a common methodology to study psychiatric syndromes in animal models. Applied successfully to implement the QNP model of OCD, methods from this animal model were used to dissect compulsive rituals in OCD patients, with findings ultimately leading to a bed-side test with patients, so illustrating the translational path to the clinic (reviewed in section 7).

In all, the reviewed studies show the use and utility of animal work in directing research on OCD and the insights gained from behavioral neuroscience research on this disorder.

Competing interests

Brian H. Harvey has participated in advisory boards and received honoraria from Servier®, and has received research funding from Servier® and Lundbeck®. Except for income from the primary employer and the exceptions noted above, and research funding provided by the above-mentioned funders, no financial support or compensation has been received from any individual or corporate entity over the past

three years for research or professional services, and there are no personal financial holdings that could be perceived as constituting a potential conflict of interest. Remaining authors declare no competing interests.

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Figure captions

Figure 1: MK-801 significantly increased daily mean (±SEM) water drinking across days in the schedule-induced polydipsia (SIP) paradigm. Experimental groups received saline (1.0 ml/kg) or the NMDA receptor blocker MK-801 (0.5 mg/kg) twice daily for 7 days followed by a 4-day washout prior to the beginning of testing. Control groups received the same drug treatments but instead of receiving one food pellet each minute according to the fixed time schedule during daily 2-hr sessions, they received 120 pellets in a dish placed next to the feeder cup in the test chamber. Only the experimental groups showed SIP and the MK-801 group drank more. *Analysis of variance revealed a significant 3-way interaction [group (MK-801 and saline) x condition (experimental and control) x day], $F(1,36) = 5.88$, $p = 0.02$. MK-801 Experimental and Saline Experimental groups did not differ significantly on day 1, $t(22) = 0.98$, $p = .34$, but by day 21 the MK-801 Experimental group was drinking more, $t(22) = 3.30$, $p = .004$. (From Hawken *et al.*, 2011)

Figure 2: Y-maze test used to identify different response strategies in rat. During the training phase, food-restricted rats are started in the same arm on each trial and learn to choose the arm baited with a food pellet (Reward). On probe test trials, rats are

started in the arm that was neither the usual start arm nor the arm where a food pellet was found. At the choice point, a right turn reflects a habit learning (striatal) strategy and a left turn reflects a place learning (hippocampal) strategy. No food reward is provided on probe trials.

Figure 3: Number of animal that used response (habit) or place-learning strategies in groups pre-treated for 5 days with amphetamine (AMPH; 1.5 mg/kg) or saline. H = significantly greater proportion than expected by chance in binomial probability test. (From Gregory et al., 2015).

Figure 4: **The heterogeneous nature of deer mouse stereotypy**. Deer mouse stereotypy is heterogeneous within a given population of animals, with 45% of animals classified as having high stereotypic behavior (HSB), 41% as having low stereotypic behavior (LSB), and 16% as being non-stereotypic (NSB). In this graph, deer mice are compared to C57Bl/6 mice as control. (From Korff *et al.*, 2008).

Figure 5: **Differential response of deer mouse stereotypy to chronic fluoxetine and desipramine treatment**. Effect of treatment with 20 mg/kg fluoxetine, 20 mg/kg desipramine and saline on stereotypic behaviour of deer mice. Baseline (untreated) stereotypic activity for each treatment group (solid bars) is provided for high stereotypic behavior (H) mice. Data represent the average of three behavioural assessment sessions for the baseline score and a once-off measurement for the treatment altered score (open bars), and expressed as the mean ± SEM. The number of animals (*n*) is shown below the indicated drug treatment. Locomotor effects following the various drug treatments were minimal (data not shown). *$p<0.05$ end-point vs baseline analysis for each treatment group (Student's t-test). #$p<0.05$ end-point analysis compared to post-saline treatment (Dunnett's test). (From Korff *et al.*, 2008).

Figure 6: **Cortico-striatal glutathione redox imbalance is correlated with severity of stereotypy in deer mice**. Comparative oxidized (GSSG; *top* panel) and reduced (GSH; *bottom* panel) glutathione in the frontal cortex and striatum of non-stereotypic (NS), low stereotypic (LSB) and high stereotypic (HSB) deer mice (n=20, 16 and 24, respectively; **$p<0.01$, Bonferroni), as well as appropriate correlations between stereotypy count and GSSG or GSH in all animals (n=60). (From Guldenpfennig *et al.*, 2011).

Figure 7: **cAMP-PDE4 signaling in stereotypic deer mice, and response to fluoxetine.** *Top panel*: Frontal cortical cAMP levels (A) and PDE4 enzyme activity (B) in low stereotypic (LSB) and high stereotypic (HSB) deer mice compared to non-stereotypic (NS) mice. Significant differences versus control NS mice are indicated by an asterisk

(one-way ANOVA followed by the Tukey test; $p<0.05$). Data are expressed as mean±S.E.M. *Bottom panel*: Effect of chronic fluoxetine or saline treatment (x 21 days) on cAMP levels and PDE4 activity in the frontal cortex of HSB mice. Significant differences versus control SAL are indicated by an asterisk (Students t-test; $p<0.05$). Data shown represent the mean±S.E.M. (From Korff *et al.*, 2009).

Figure 8: Experimental set-up and test for compulsive checking. (a.) The open field apparatus with 4 objects on it. (b.) Subdivision of the open field into 25 places. The software algorithm assigns the positions of *x,y* coordinates of a stop within these locales. (c.) Test for compulsive checking on the 8th injection of quinpirole (0.5 mg/kg). Rats are said to show compulsive checking behavior when their performance is significantly different from saline controls on all 4 measures: *frequency of checking* (# of stops in key locale); *length of check* (mean duration in seconds of stay in key locale); *recurrence time of checking* (mean duration in seconds of return times to key place); and, *# of stops before returning to check* (mean number of places visited between returns to key locale). *p<.05 *vs* saline controls. (Modified from Alkhatib *et al.*, 2013).

Figure 9**.** Performance on criteria measures of compulsive checking behavior shown by groups of rats with lesion to the basolateral amygdala (BLA), nucleus accumbens core (NAc), orbital frontal cortex (OFC) or sham lesion. Blue bars represent groups with chronic saline treatment (left cluster of each panel) and red bars represent groups with chronic quinpirole treatment (right cluster of bars of each panel). Solid fill bars in *top* row show effect of NAc lesion on *frequency of checking* and *length of check* while those in the *bottom* row show effect of OFC lesion on *recurrence of checking* and *stops before checking.* * $P < 0.05$ vs. sham controls, BLA lesion, and OFC lesion groups treated chronically with saline; ** $P < 0.05$ vs every group treated chronically with saline; *** $P < 0.05$ vs. every other group; ## $P < 0.05$ vs. every group treated chronically with quinpirole as well as sham controls and NAc groups treated chronically with saline. (Modified from Dvorkin *et al.*, 2010).

Figure 10: Performance on criteria measures for compulsive checking behavior shown by groups of sham controls and NAc core lesion rats treated with saline or DPAT. Open bars, sham controls injected with saline; right hatch, sham controls injected with DPAT; gray filled bars, NAc core lesion rats injected with saline; color filled bars, NAc core lesion rats injected with DPAT. * main effect of lesion; # main effect of drug. (From Tucci *et al.*, 2014a).

Figure 11: Duration of negative feedback signal as measured by *time to next checking bout* in rats treated chronically with saline (blue open circles) and quinpirole (red solid

squares) during the course of treatment to induce compulsive checking. (From Dvorkin *et al.*, 2006).

Figure 12: A) the degree of anti-compulsive effects in the signal attenuation (SA) and quinpirole (QNP) model following high-frequency deep brain stimulation (DBS) to brain targets of the cortical-basal ganglia-thalamo-cortical circuit (CBGTC) ÷ = no effect; B) the CBGTC loop, including the differential neuropathology between the two models with respect to striatal neurotransmitter systems and cellular arrangement. DBS applied to the STN elicits symptom-comprehensive effects, whereas the NAc and GPe selectively reduce compulsivity in the QNP and SA model, respectively. 5-HT, serotonin; DA, dopamine; EP, entopeduncular nucleus; GPe, external globus pallidus; GPi, internal globus pallidus; LGP, lateral globus pallidus; NAc, nucleus accumbens; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus

Figure 13: The method of tracing the trajectories of locomotion and scoring the behavior in stopping places. The figure is based on data from (Zadicario *et al.*, 2007). **a.** Trajectories of traveling of two rats after the 18th injection of 0.5 mg/kg quinpirole (top) or saline (bottom). The trajectories represent the activity during the 60 min after the injection in a 2x2 m arena. As shown, the quinpirole rats traveled repeatedly the same paths in a restricted portion of the arena whereas the lesser activity of the saline rats spans over the entire arena, with seldom passing the same paths. **b**. Behavior of a quinpirole rat during 12 visits to the bottom right arena corner at which a small box was placed. Each row represents one visit, and the characters represent the following behaviors: A – arriving at a diagonal direction; B – snout contact with the box; C – climbing on top of the box; D – performing a large lateral turn; E – departure from the corner to the left. As shown, there is high regularity in the behavior of the rat over repeated visits to the corner.

Figure 14: Excerpt from the patient's diary (**a.**) describing the ritual of turning on the TV. Behavior comprised systematic traveling between the bathroom and the TV, which could be schematically depicted as shown (**b.**). In the description of the acts when at the TV (**c.**), each visit to the TV during the ritual is depicted along one row, and each circle represents one act (similar acts are depicted in the same color).

Figure 15**:** The sequence of acts performed by a control individual (upper box) and an OCD patient (bottom box) as they lock and walk away from their car. Large circles depict common acts and small circles depict idiosyncratic acts. As shown, the control individual had only one idiosyncratic act and no repetition of acts, whereas the OCD patient had numerous idiosyncratic acts, repetition of common acts, and a long "tail" of idiosyncratic acts at the end of the task.

Figure 16: The number (mean ± SEM) of common acts (open bars) and idiosyncratic acts (gray bars) in the repertoire of acts (repetitions excluded) of 43 OCD rituals (bottom) and their non-OCD controls (top). The number of common acts performed in OCD and control rituals was identical (open bars). However, the number of idiosyncratic acts in OCD was three-fold that of controls (gray bars). The overall act repertoire was almost twice as large in OCD as in control rituals. Moreover, in the controls there were more common than idiosyncratic acts, whereas in the OCD patients it was the opposite: more idiosyncratic than common acts. (Based on data from Eilam *et al.*, 2012).