Review

Biological Psychiatry

Learning From Animal Models of Obsessive-Compulsive Disorder

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ABSTRACT

Obsessive-compulsive disorder (OCD) affects 2%–3% of the population worldwide and can cause significant distress and disability. Substantial challenges remain in the field of OCD research and therapeutics. Approved interventions alleviate symptoms only partially, with 30%–40% of patients being resistant to treatment. Although the etiology of OCD is still unknown, research evidence points toward the involvement of cortico-striato-thalamocortical circuitry. This review focuses on the most recent behavioral, genetics, and neurophysiologic findings from animal models of OCD. Based on evidence from these models and parallels with human studies, we discuss the circuit hyperactivity hypothesis for OCD, a potential circuitry dysfunction of action termination, and the involvement of candidate genes. Adding a more biologically valid framework to OCD will help researchers define and test new hypotheses and facilitate the development of targeted therapies based on disease-specific mechanisms.

Keywords: Animal models, Basal ganglia, CSTC, Obsessive-compulsive disorder, OCD, Striatum, Synapse

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Neuropsychiatric disorders encompass a wide range of diseases that manifest as one or many altered behaviors, including, but not limited to, self-injurious behavior, impaired social-emotional communication, and cognitive deficits. Because of the lack of biomarkers and overlapping behavioral symptoms, diagnosis of neuropsychiatric disorders sometimes relies on exclusion of other underlying conditions.

Obsessive-compulsive disorder (OCD) has a 2%–3% worldwide prevalence (1,2) and is characterized by excessive preoccupations (obsessions) associated with specific rituals (compulsions). Current treatments to alleviate symptoms include cognitive behavioral therapy and selective serotonin reuptake inhibitors (3,4). In cases in which patients do not respond to cognitive behavioral therapy or medication or both, other interventions have been used, such as deep brain stimulation (5–7). Because abnormalities in the glutamatergic system also have been proposed in the pathology of OCD, some *N*-methyl-D-aspartate receptor antagonists including ketamine and memantine are being tested as possible therapies (4,8).

Previously considered under the spectrum of anxiety disorders, OCD is now categorized in the recently revised DSM-5 with other obsessive-compulsive–related disorders, including trichotillomania, body dysmorphic disorder, skin picking disorder, and hoarding disorder. The reclassification is based on behavioral similarities and common features of these disorders —obsessive preoccupations and repetitive actions. Such categorization is thought to help guide diagnostic criteria and ensure consistency among health care providers. However, a more "biologically valid framework" for mental disorders has been proposed by the U.S. National Institute of Mental Health. This new research framework, designated Research Domain Criteria, aspires to emphasize mental disorders as biological constructs that span specific domains of behavior, emotion, and cognition (e.g., social interactions, mood) that can co-occur in a range from normal to extreme. Future goals include using brain mapping, genetic studies, and modeling of cognitive aspects of mental disorders to help understand and target therapeutically the biological bases of complex neuropsychiatric diseases, including OCD. Animal models can contribute to this dimensional approach by providing means to test biological causality. This review discusses several areas of research including neurophysiology, behavior, and genetics in animal models of compulsive/repetitive behavior that can serve as foundations for understanding the basic biology of such behavior.

NEUROPHYSIOLOGY OF OCD—INSIGHTS FROM ANIMAL MODELS

Cortico-striato-thalamocortical Circuitry

One of the most replicated findings in human OCD studies is the involvement of cortico-striato-thalamocortical circuitry (CSTC) (9,10). Human striatum is anatomically subdivided by the internal capsule into caudate nucleus and putamen. Caudate nucleus receives mostly excitatory inputs from orbitofrontal, prefrontal, and cingulate cortex areas, whereas putamen receives most of its cortical inputs from sensorimotor areas (11,12). Increased activity in the anterior cingulate/caudal medial prefrontal cortex, orbitofrontal cortex (OFC), and caudate region (areas implicated in some aspects of executive function and evaluation of significance (12)) has been reported in OCD (13). How can we connect these

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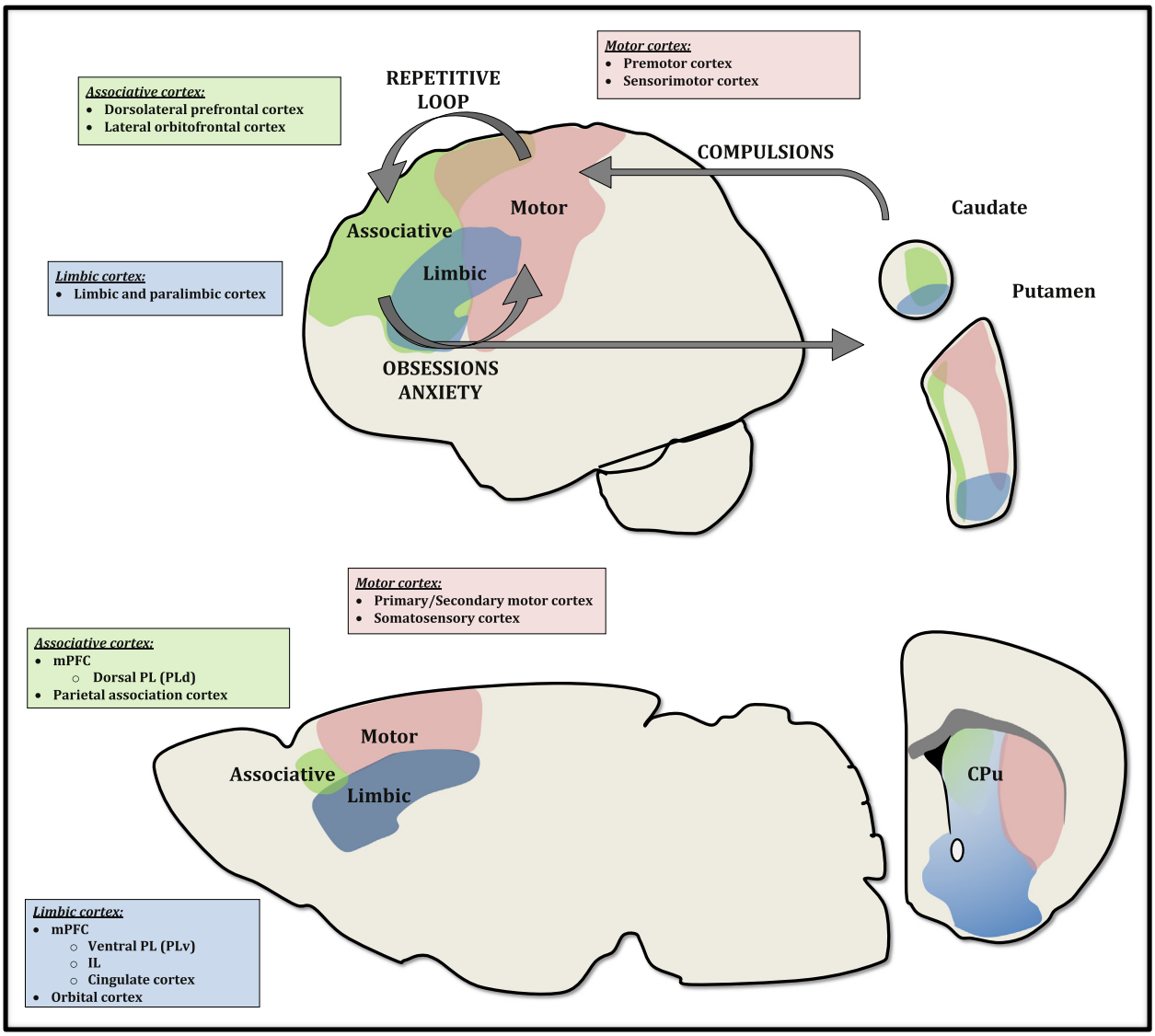

Figure 1. Simplified neuroanatomic models of corticostriatal circuitry within the human (top) and mouse (bottom) brain. Human motor cortex is represented by premotor and sensorimotor cortical regions that mainly project to the posterolateral putamen (11). Mouse motor cortex is represented by somatosensory and motor cortex that mainly project to the dorsolateral striatum region (16). Human associative cortex, represented by the dorsolateral prefrontal cortex and lateral orbitofrontal cortex, projects to the caudate and anteromedial portion of the putamen (11). Mouse associative cortex is represented by dorsal prelimbic and parietal association cortices that mainly project to the dorsomedial striatum region (15). Human limbic cortex, represented by the paralimbic and limbic cortices (including entorhinal cortex [area 28], perirhinal cortex [area 35], medial orbitofrontal cortex [area 11], and anterior cingulate cortex [area 24]) (11,101), projects to the ventral striatum (ventral region of the caudate nucleus and putamen, including nucleus accumbens). Mouse limbic cortex is represented by orbitofrontal cortex and prefrontal cortex (ventral prelimbic, infralimbic, and cingulate cortices) that mainly project to the ventromedial striatum region (including nucleus accumbens) (15,16). Human associative and limbic circuits are implicated in stimuli significance and might generate obsessive thoughts that cause anxiety. Interconnections with motor cortex and basal ganglia circuits lead to execution of compulsive actions. Based on the perceived outcome, actions can be reinforced and propagated through this repetitive loop. All regions depicted are representative and are not intended to provide accurate anatomic locations. CPu, caudate putamen; IL, infralimbic; mPFC, medial prefrontal cortex; PL, prelimbic.

findings with behavioral manifestations in OCD? A major advantage of studying animal models is the ability to manipulate neural circuits directly and test behavioral outcomes. It is important to define neuroanatomic parallels between CSTC structures in humans and mice so that their (dys)function and relevance to OCD can be tested (Figure 1).

Based on behavioral studies in mice, a loose definition of limbic, associative, and motor striatal territories can be adopted as well as definition of their respective sources of cortical inputs (14,15). Mouse medial prefrontal cortex seems to be organized in a dorsal-ventral gradient of connectivity such that dorsal-prelimbic input projects to dorsomedial regions of striatum (DMS; associative striatum), and ventral-

prelimbic input projects mainly to ventral striatum (limbic striatum) (16). These ventromedial striatum regions are considered to be caudate-like in rodents (15,17,18). Finally, motor cortex projects mainly to the mouse dorsolateral striatum (DLS), a region considered similar to the primate putamen (15,17). However, despite some functional resemblance, there are important species-specific differences, with mice lacking certain neuroanatomic connectivity possessed by primates (14–17,19,20).

Similar to the connectivity patterns observed between cortex and striatum, it is believed that downstream basal ganglia territories are equally well organized into associative, limbic, and sensorimotor regions. Evidence for this cognitive, emotional, and motor organization of basal ganglia has been clarified through groundbreaking studies in monkeys (21,22). Bicuculline injections into limbic regions of globus pallidus (GP) can induce stereotypies, whereas injections into associative regions can lead to attention deficit/hyperactivity. Abnormal movements are not observed unless injections occur within sensorimotor regions of GP, suggesting a particular role for associative and limbic territories in the etiology of compulsive behaviors (21).

In rats, DLS is known to be required for grooming syntax (23–26), a normal physiologic behavior that appears hyperactive in some OCD mouse models with self-injurious overgrooming (27,28). Can dysfunction of the rodent putamen-like structure, DLS, and seemingly purposeless repetitive routines/stereotypies be related to caudate dysfunction and compulsive behaviors in human OCD? Neurophysiology and behavior studies suggest that DLS and DMS regions support an important behavioral transition in rodents: intentional goal-directed actions, encoded by DMS, that, on repetition, become habitual automated responses, encoded by DLS (16–18,29–33). A dynamic competition is thought to occur between these two striatal regions during habit acquisition. DMS activation likely guides the expression of behaviors as they transform into habits, but once this DMS activity decreases, DLS circuits assume control over behaviors (34). Evidence from DMS lesioned mice that show tendencies for action generalization strategies (i.e., habitual responses) indicating that DLS guides behavioral performance when DMS function is compromised (29). This evidence might help to explain results from a clinical study in which a deficit in goal-directed control and an overreliance on habits were observed in patients with OCD (35). Dysfunctional associative circuitry could be affecting the performance of related sensorimotor circuits.

Striatum Microcircuitry

Medium spiny neurons (MSNs) are the major cell type within the striatum and can be classified into two main subtypes: striatonigral (dopamine 1 receptor–positive direct-pathway cells; project to substantia nigra pars reticulata) and striatopallidal (dopamine 2 receptor–positive indirect-pathway cells; project to GP) (36,37). The classic model of basal ganglia motor output function postulates that direct-pathway activation facilitates movement and indirect-pathway activation suppresses movement (38–41). Validity of this model was called into question through more recent mouse studies showing concurrent activation of both pathways during action initiation (42), whereas other mouse studies substantiated the classic model (43). One possible unifying explanation for these disparate results is that activation of both pathways could be important for specific action selection and initiation: Direct-pathway cells could be activated to promote a specifically intended motor program, whereas indirect-pathway cells could be concomitantly activated to inhibit specific competing motor programs. In this scenario, one could imagine that nonspecific activation of all indirect-pathway cells could lead to inhibition of all motor programs, as in bradykinesia, whereas overall ablation or silencing of all indirect-pathway cells could lead to hyperkinesia.

In addition to MSNs, the striatum contains three main classes of interneurons that regulate striatal function: fast-spiking (FS) interneurons that are cytochemically parvalbumin-positive and project to both MSN types but are more likely to target dopamine 1 receptor–positive cells; low-threshold–spiking interneurons; and choline acetyltransferase–positive interneurons (Figure 2) (36,37,44,45). Despite their relative sparsity, these interneurons can strongly modulate MSNs, greatly influencing final output of the striatum (46). In patients with Tourette's syndrome, a disorder often comorbid with OCD, histology of postmortem striatal tissues revealed decreased density of parvalbumin-positive and choline acetyltransferase–positive interneurons in caudate and putamen regions (47,48). A potential bridge between Tourette's syndrome, OCD, and striatal interneuron dysfunction is also suggested by a study, summarized subsequently, in which increased MSN activity and lower striatal parvalbumin-positive cell density were observed in a mouse model of OCD (49). Although interneuron dysfunction is a less commonly explored hypothesis in animal models of OCD, it is possible that defective interneuron activity might result in or contribute to abnormal striatum activation associated with pathology. In future studies, it will be important to define exactly how these interneuron populations modulate striatum output and how, if at all, they are relevant to OCD.

Hyperactive Circuitry in OCD

Among the various tools that have become available to study neural circuits, one holds great promise: optogenetics (50,51). Using this strategy, a study directly tested the CSTC hyperactivity hypothesis of OCD (52). The authors expressed and activated ChR2 in mouse medial OFC excitatory neurons that project to ventromedial striatum. Repeated direct hyperactivation of these cells over 5 consecutive days led to a progressive increase in repetitive grooming. However, acute stimulation was insufficient to induce increased grooming patterns, suggesting the need for a reinforcing circuitry loop in repetitive OCD-like behaviors.

Another finding in support of the CSTC hyperactivity hypothesis is derived from the *Slitrk5*-knockout (KO) mouse model. Staining for FosB, a cellular marker of sustained neuronal activity (53), showed its levels to be increased specifically at OFC, suggesting hyperactivity of this brain region. These results may be particularly relevant to understanding the increased metabolic activity observed in OFC and caudate nucleus of patients with OCD (54).

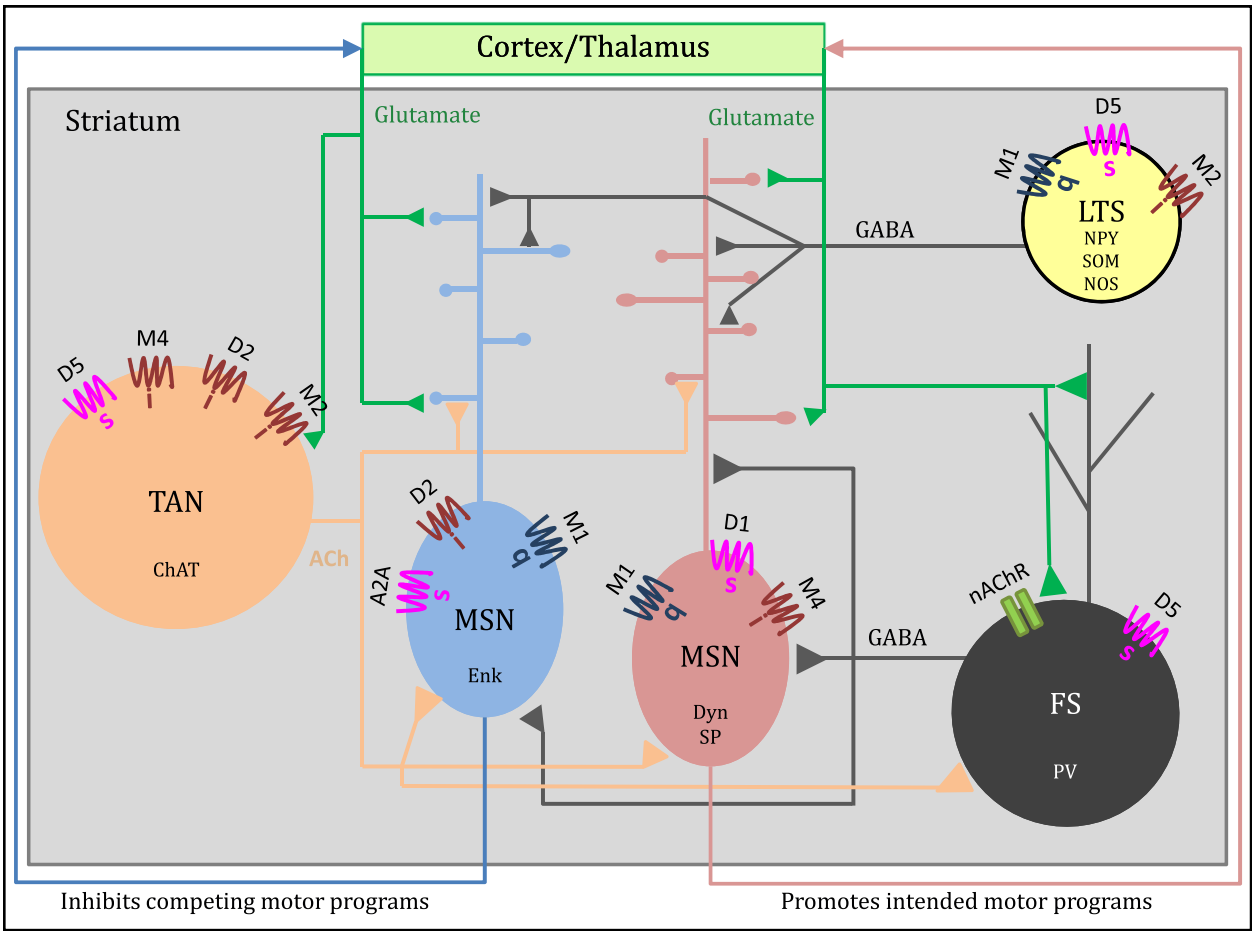

Figure 2. Representation of intrastriatal microcircuitry. Corticostriatal and thalamostriatal excitatory axons target the dendritic spines of medium spiny neurons (MSNs) and dendritic shafts and soma of striatal interneurons. Fast-spiking (FS) interneurons receive more cortical contacts and are more responsive to cortical inputs than MSNs (102,103); FS interneurons synapse proximally onto both MSN types (104) with a bias toward direct-pathway dopamine 1 receptor-positive MSNs (45); FS interneurons also synapse with other FS cells, but not low-threshold spiking neurons or TANs (45). Low-threshold spiking interneurons send sparse inhibitory projections onto MSN dendrites (45,105,106). TANs send inputs to dendritic spines, shafts, and somata of MSNs (107) and provide powerful excitatory cholinergic input to FS interneurons (108,109). Dopamine 1 receptor-positive MSNs have more elaborate dendritic arbors (110), and their axons project to substantia nigra pars reticulata (37) (not represented); this direct pathway promotes the execution of intended motor programs (42). Dopamine 2 receptor-positive MSNs project to globus pallidus (37) (not represented); this indirect pathway may inhibit the execution of competing motor programs (42). G protein–coupled receptors are depicted with their associated G protein: Gs (pink), Gi (brown), Gq (blue). A2A, A2A adenosine receptor; ChAT, choline acetyltransferase; D, dopamine receptors; Dyn, dynorphin; Enk, enkephalin; LTS, low-threshold spiking; M, muscarinic acetylcholine receptors; nAChR, ionotropic nicotinic acetylcholine receptor; NOS, nitric oxide synthase; NPY, neuropeptide Y; PV, parvalbumin; SOM, somatostatin; SP, substance P; TANS, tonically active neurons.

A recent study by Rothwell *et al.* (55) showed that imbalanced basal ganglia activity can clearly influence the formation of repetitive motor routines. In this study, the authors showed that disinhibition of direct-pathway MSNs in ventral striatum can enhance the formation of repetitive motor routines, observed as increased rotarod learning. Although direct-pathway MSNs in dorsal striatum are important for overall motor coordination, the observed phenotype is independent of cerebellum or dorsal striatum. Such studies support the idea that different symptom dimensions might be associated with distinct neural substrates (56). Proper balance between direct-pathway and indirect-pathway activity and proper dynamic interaction between different striatal subregions seem crucial for normal behavior. Repetitive behaviors observed in OCD may arise from brief but repeated bursts of neuronal activity in specific brain areas, facilitating their reactivation by subsequent stimuli.

Dysfunction of Termination (Stop Signal) in OCD?

Hyperactivity of CSTC circuitry in OCD and consequent propagation of positive-feedback loops could be due to augmented sensitivity to initial triggering stimuli (too much start signal) or to deficiency in motivation to break the initiated behavioral ritual (too little stop signal). More recent work tried to address this question by studying security-related behaviors that arise from exposure to contamination cues (57). The results indicated that the cause of patients' symptoms relied on dysfunctional termination (stop signal) rather than dysfunctional activation (start signal). The root cause of this improper

action termination may be weakened "motivational satiety." In line with this hypothesis, a report by Burguière *et al.* (49) corroborated an insufficiency of the stop signal and reinforced the importance of the OFC-striatal pathway in the genesis of compulsive behaviors. Electrophysiologic recordings obtained over a long-term period in *Sapap3*-KO mice, an established model of OCD-like behaviors (see later), revealed abnormally high spontaneous MSN activity in the centromedial striatum, in further support of the hyperexcitability hypothesis. These mice not only showed deficits in adaptive grooming response during a conditioned grooming task (tone-delay-water) but also showed impaired striatal physiology, in which MSNs were incapable of adapting and refining their activity during task shaping. These findings point toward acquired maladaptive behavior to an initially neutral stimulus. *Sapap3*-KO mice further showed reduced striatal FS interneuron density, suggesting that deficient inhibition within striatum might contribute to MSN hyperactivity (58). Optogenetic stimulation of lateral OFC somata or afferent terminals in the striatum can successfully alleviate conditioned overgrooming as well as naturally occurring compulsive grooming in *Sapap3*-KO mice (49). In vivo recording data demonstrated that stimulation of the lateral OFC–striatal pathway increased FS-MSN inhibitory efficacy and helped to restore behavioral inhibition, presumably through increasing striatal inhibitory tone. Given that FS interneurons synapse onto both MSN subtypes but are more likely to target direct-pathway MSNs (45), it is tempting to speculate that the altered feedforward inhibition of striatal MSNs observed in *Sapap3*-KO mice more profoundly affects the direct pathway to lead to disinhibition of specific motor compulsions.

Although the aforementioned animal studies by Ahmari *et al.* (52) and Burguière *et al.* (49) might at first appear discrepant—medial OFC stimulation increases grooming, while lateral OFC stimulation reduces grooming—it is critical to note that results were derived from different cell populations. Both studies implicated OFC dysregulation in compulsive behaviors and suggested that lateral OFC and medial OFC might be playing different roles in OCD, as hypothesized earlier by Milad and Rauch (59).

BEHAVIORAL STUDIES IN OCD ANIMAL MODELS

To evaluate OCD-like behaviors in animal models, specific behavioral paradigms have been developed in recent decades to assess multiple factors, such as anxiety and compulsivity. Tests of anxiety include open field and elevated zero or plus mazes, where patterns of exploratory activity can be evaluated by quantifying time spent in typically anxiogenic open areas versus time spent in perimeter or protected areas. Despite the relevance of anxiety in OCD, anxiety is an equally relevant trait to other non–OCD spectrum disorders. Similarly, OCD itself shares important links with other anxiety disorders, although this is not true for all other OCD spectrum disorders (60). Additional behavioral paradigms focus on compulsive behaviors, considering them as closer translational manifestations of the human condition. Time spent in repetitive tasks, such as nonnutritive chewing, grooming, or shifting/digging in bedding as in the marble burying test, can be simply observed. Other, more complex tests involve learned tasks in which the presence of compulsive traits can be tested under specific conditioning paradigms. The delayed reinforcement task helps to dissociate impulsive choices from the motor impulsivity observed in OCD. In addition, reversal learning tasks or serial reaction time tasks, in which duration, frequency, and perseverance of choices are assessed, can distinguish between impulsive and compulsive responses (14,61).

Animal models of neuropsychiatric disorders should exhibit at least one of the following characteristics: atypical behaviors that resemble human symptoms (face validity); shared biological grounds with human conditions, such as mutation of a specific gene (construct validity); or successful response to the same therapeutic agents prescribed to patients, allowing outcome predictability (predictive validity). Several animal models exhibit OCD-like behaviors and have been useful in underpinning distinct aspects of the neurobiology of OCD. The first genetic mouse model presenting face, construct, and predictive validity for OCD was published in 2007 (28). These mice lack SAPAP3, a scaffolding protein normally enriched at corticostriatal glutamatergic synapses. Besides impaired corticostriatal transmission, these mice display self-injurious grooming and increased anxiety as assessed by the open field, elevated zero maze, and dark-light emergence tests. Anxiety and compulsive grooming can be partially alleviated by fluoxetine treatment. A key finding is that restoring SAPAP3 expression in the striatum alone can rescue self-injurious grooming and corticostriatal transmission, further emphasizing the role of the striatum in compulsive behaviors. A more recent study in this OCD mouse model suggested exaggerated stimulus-response habit formation. When mice are conditioned to groom in response to delivery of a water drop to the forehead preceded by a tone, *Sapap3*-KO mice promptly groom in response to the tone and are unable to reshape this acquired behavior, even when delivery of the water drop is subsequently omitted. This behavior contrasts sharply with wild-type mice that respond primarily to the water drop rather than the tone, suggesting an abnormal adaptive process to conditioned stimuli in OCD.

Other interesting findings have emerged from the deletion of the *Slitrk5* gene in mice. SLITRK family proteins are involved in neurite outgrowth (62), and absence of SLITRK5 protein in mice leads to increased anxiety, as assessed by elevated plus maze and open field tests, and compulsivity, as assessed by increased marble burying behavior and self-injurious grooming (27). Long-term fluoxetine treatment can alleviate this phenotype. *Slitrk5*-KO mice provide researchers with another promising mouse model for studying OCD-like behaviors.

GENETIC STUDIES OF OCD—INSIGHTS FROM HUMAN PATIENTS AND ANIMAL MODELS

Common acts carried out by patients with OCD involve actions such as checking, washing, and ordering. The fact that these themes are not random and occur consistently in patients across distinct sociocultural backgrounds worldwide raises the possibility of common genetic bases (63,64). Twin studies of OCD also support this prediction, yielding the strongest evidence for a genetic contribution in OCD. An extensive review published by van Grootheest *et al.* (65) using a dimensional approach for twin studies concluded that OCD

symptoms are highly heritable, ranging from 45%–65% in childhood-onset OCD and 27%–47% in adult-onset OCD.

Slc1a1/Eaac1

The first genome-wide linkage study for OCD was carried out in 2002 to identify susceptible chromosomal regions for early-onset OCD (66). The results suggested a link to chromosomal region 9p24 with the closest gene being *Slc1a1* (solute carrier family 1, member 1), a glutamate transporter also known as *Eaac1* (67). Since then, several linkage studies have supported OCD association with this genomic region, but with modest cross-validation, as different studies support different single nucleotide polymorphisms associated with the disease (68–70). An *Eaac1*-KO mouse was first generated and published in 1997, albeit with apparently nominal relevance to the study of OCD neurobiology and behavior (71). *Eaac1*-KO mice develop dicarboxylic aminoaciduria and show reduced spontaneous locomotion in the open field. Later studies reported reduced neuronal glutathione levels and age-dependent neurodegeneration, evidenced by cortical thinning and ventricular enlargement (72,73). Despite the absence of a strong OCD-like phenotype in *Eaac1*-KO mice, several studies implicated the human *EAAC1* gene in at least some cases of OCD (68,74). It is plausible that *Eaac1* functional deficits are not well recapitulated in mice or that this gene is involved rather in polygenic susceptibility to OCD by interacting with other factors.

Sapap and *Slitrk*

An effort has been made to search for common single nucleotide polymorphisms predisposing individuals to OCD. More than 20 research groups have collaborated to accomplish the first genome-wide association study for human OCD (75). Results from this study suggested the involvement of two single nucleotide polymorphisms located within the *Dlgap1* gene that encodes the SAPAP1 protein. Previously, another member from the same family of proteins, SAPAP3, had been implicated in the *Sapap3*-KO mouse model that exhibits OCD-like behavior (see earlier) (28,76–78). Smaller association studies supported a role for *SAPAP3* in human trichotillomania and OCD (79–81), reinforcing the idea that proteins from this family might play a role in OCD-related behaviors.

Another group, the OCD Collaborative Genetics Association Study (82), found an association of a marker on chromosome 9 near the *PTPRD* gene, although no genome-wide significance was achieved. The PTPRD protein seems to play a role in regulating development of inhibitory synapses through its interaction with SLITRK3. SLITRKs (SLITRK1 through SLITRK6) are a relatively recently discovered family of proteins (62) that have emerged as candidate genes in neuropsychiatric disorders (83). Human genetic studies suggested an association link between *SLITRK1* and Tourette's syndrome, a neuropsychiatric disorder characterized by motor and vocal tics (84). *Slitrk1*-KO mice display increased anxiety and noradrenergic abnormalities (85), consistent with reports of increased norepinephrine levels in cerebrospinal fluid of patients with Tourette's syndrome (86). The hypothesis of *SLITRK1* involvement in Tourette's syndrome and the fact that SLITRKs are highly expressed in mammalian central nervous system (87) motivated the generation of a *Slitrk5*-KO mouse to explore possible phenotypes (27). As described earlier in this review, *Slitrk5*-KO mice display OCD-like behaviors and impaired corticostriatal circuitry. Given that *Slitrk5*-KO mice and *Sapap3*-KO mice display impaired corticostriatal transmission and OCD-like behaviors that are responsive to treatment with fluoxetine, one of the pharmacologic agents used in patients with OCD, it would be interesting to address whether these mutations of these genes lead to common defects in molecular pathway or circuitry function.

Hoxb8

Another hypothesis concerning OCD etiology comes from genetic deletion of the *Hoxb8* gene in mice, which suggests a link between the immune system and OCD expression (88). This transcription factor is detected in the adult brain, being expressed in bone marrow–derived microglia cells that migrate into the OFC, cingulate cortex, limbic system, and other regions of the brain during the postnatal period (88,89). *Hoxb8*-KO mice display self-injurious and cage-mate excessive grooming that can be rescued by bone marrow transplantation from wild-type mice. Although this link between the immune system and OCD might seem puzzling at first, it was previously shown that microglia play roles in regulating neuronal cell death and in modulating neural networks (90,91). A subset of children with OCD can experience worsening of symptoms after streptococcal infection. One brain region that is affected in pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections is the basal ganglia (immunobiology of OCD and pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections reviewed by Murphy *et al.* (92)). Although expressed brain-wide in the mouse, *Hoxb8* is predominantly found in adult brainstem, olfactory bulb, cortex and striatum (88,89), the latter two regions being highly implicated in OCD, as discussed earlier.

Although *Hoxb8*-KO mice, *Sapap3*-KO mice, and *Slitrk5*-KO mice have grooming phenotypes that are unique in their biological origins, all genes share an enriched corticostriatal expression. In regard to human OCD, these mice studies suggest that a commonly shared pathologic behavior, compulsivity, may arise from different causal insults that impact the same brain circuits.

Other Genes

Currently approved treatments to alleviate OCD symptoms include medications that modulate the serotoninergic system. Although the exact mechanisms are unknown, it is thought that 5-hydroxytryptamine 2C serotonin receptor agonism might contribute to therapeutic benefits in OCD (93). Genetic deletion of 5-hydroxytryptamine 2C receptor in mice led to enhanced sensitivity to induced motor stereotypy and compulsive-like behaviors, such as nonnutritive chewing and increased head dipping (94–97), supporting serotoninergic involvement in compulsivity. In contrast to other OCD models, these mice showed less anxiety than wild-type mice in open field, elevated plus maze, novel object, and mirrored chamber tests, suggesting that compulsivity and anxiety symptoms might be dissociable.

Another useful method to look for candidate genes involved in OCD, besides hypothesis-driven gene deletion in mice, is

Table 1. Candidate Genes From Animal Models With OCD-like Behaviors

Gene	Genetic Evidence	Behavioral Phenotype	Neurophysiology	Notes	References
Hoxb8	Global *Hoxb8*-KO mice with relevant phenotype	Self-injurious grooming	*Hoxb8* expressed in bone marrow–derived microglia that migrate into brain OFC, cingulate cortex, and basal ganglia regions	WT bone marrow transplantation rescues excessive grooming	(88,89)
	Conditional-KO mice (hematopoietic cells) exhibit global KO phenotype	Cage mate overgrooming		KO bone marrow transplantation induces excessive grooming in WT	
Sapap3	Global *Sapap3*-KO mice with strong phenotype	Self-injurious grooming	*Sapap3* mainly expressed in neocortex, striatum, hippocampus, and thalamus	Striatum infection using lentivirus-*Sapap3* rescues self-injurious grooming and fEPSP	(28,49,75,78)
	Two SNPs located in *Sapap1* (family member) found in human OCD GWAS study	Increased anxiety (open field test, elevated zero maze, and dark-light emergence)	Impaired corticostriatal function (reduced fEPSP, mEPSC and AMPA/NMDA ratio; increased silent synapses and eCB-LTD)	Fluoxetine treatment partially alleviates compulsive grooming and anxiety	
		Deficit in adaptive grooming response during conditioning task	Increased spontaneous MSN firing activity in centromedial striatum		
			Reduced interneuron PV number in centromedial striatum		
Slitrk5	Global *Slitrk5*-KO mice with strong phenotype	Self-injurious grooming	*Slitrk5* mainly expressed in neocortex, striatum, and hippocampus	Fluoxetine alleviates overgrooming	(27)
		Increased anxiety (open field test, elevated plus maze)	Impaired corticostriatal function (reduced fEPSP)		
		Compulsive-like behavior (marble burying test)	OFC hyperactivity (increased FosB staining levels)		
			Decreased striatal volume and decreased MSN dendritic arbor complexity		
Slc1a1/ Eaac1	Human OCD genetic studies	Human OCD	*Slc1a1* is highly expressed in human cortex, striatum, and thalamus	Age-dependent cortical thinning and ventricular enlargement in *Eaac1*-null mice	(67,71–73)
	Eaac1-null mice show modest phenotype	*Eaac1*-KO mice show cognitive and motivational impairment at old age		Dicarboxylic aminoaciduria	
		Reduced spontaneous locomotion in open field test			
Cdh2	Dog OCD small GWAS	Canine OCD (incessant tail chasing, relentless paw chewing)	ND in dogs	*Cdh2*-KO mice die during early embryonic stages	(98–100)
Ht2rc	Global 5-HT_{2C}-R-KO mice show compulsive phenotype	Nonnutritive chewing	Decreased corticotropin hormone release from extended amygdala in response to anxiogenic stimuli	Midlife obesity (due to hyperphagia)	(94,97)
		Increased head-dipping		Prone to death from spontaneous seizures	
		Reduced anxiety (open field test, elevated plus maze, novel object, mirrored chamber)		Altered sleep homeostasis	

Genes listed in this table have emerged from human sequencing studies or animal single-gene knockout studies that resulted in OCD-like phenotypes.

AMPA/NMDA, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid/*N*-methyl-D-aspartate; 5-HT_{2C}-R, 5-hydroxytryptamine 2C receptor; eCB-LTD, endocannabinoid-mediated long-term depression; fEPSP, field excitatory postsynaptic potentials; GWAS, genome-wide association study; KO, knockout; mEPSC, miniature excitatory postsynaptic currents; MSN, medium spiny neuron; ND, not defined; OCD, obsessive-compulsive disorder; OFC, orbitofrontal cortex; PV, parvalbumin; SNP, single nucleotide polymorphism; WT, wild-type.

genomic sequencing from animals displaying spontaneously occurring pathologic behaviors. Some dog breeds display OCD-like behaviors, including incessant tail chasing and relentless paw chewing. Given that the dog genome is less complex than the human genome, the first canine OCD genome-wide association study was carried out recently, which identified four synaptic genes with case-only variations (*Cdh2*, *Ctnna2*, *Atxn1*, *Pgcp*) (98). Previous studies in mice showed that *Cdh2* gene disruption, although embryonically lethal, caused synaptic dysfunction in cultured neurons (99,100).

Together, the ever-expanding genetic studies of human, mouse, and dog seem to converge toward CSTC synaptic dysfunction in OCD pathology (Table 1). Although animal

models never can fully recapitulate the human OCD spectrum because of species-specific limitations, they do allow us to study precisely neurobiological mechanisms of gene-linked phenotypes by limiting some of the many confounds inherent to studies of humans, including variability in one's environment and genetic background.

FUTURE PERSPECTIVES AND CONCLUSIONS

Much is still to be unraveled in terms of the detailed neurobiology of CSTC circuits in OCD: What neuromodulators are imbalanced? Are OCD compulsions dissociable from obsessions or anxiety in general? What specific ensemble of neurons encode for motor programs of compulsions? What brain areas initiate the obsession-compulsion process?

Human functional imaging data seem to suggest hyperactivity in OFC of patients with OCD. It is possible that this area could be important for generating specific thoughts that in a person without OCD are easily resolved by performing a particular act, such as double-checking something in case of doubt. This behavioral ritual could serve a perfectly banal physiologic need. However, patients with OCD might have insufficient "motivational satiety" that prevents resolution and proper termination of the obsession.

To answer the many unresolved questions regarding OCD, continued efforts to understand the circuitry involved need to be undertaken, with particular attention to distinct brain regions, cell types, and the roles of modulatory neurotransmitters. Some OCD animal models discussed in this review point toward specific dysregulations that might be relevant as OCD endophenotypes—CSTC hyperactivity and dysfunctional task-specific behavioral performance, including in adaptive switching to novel stimulus-reinforcement associations. Despite the limitations in using animal models to study neuropsychiatric disorders, these findings in the evolutionally conserved CSTC circuitry might be relevant across DSM diagnoses and help to guide future translational studies.

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Review article

Obsessive-compulsive disorder: Insights from animal models☆

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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.

Contents

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.

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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 1–2% (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 modeling 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 behavior 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, behavioral 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, 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, 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 the orbitofrontal cortex (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., 2009; Posner et al., 2014), ACC (Anticevic et al., 2014; Posner et al., 2014), ventral (Anticevic et al., 2014; Harrison et al., 2013, 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

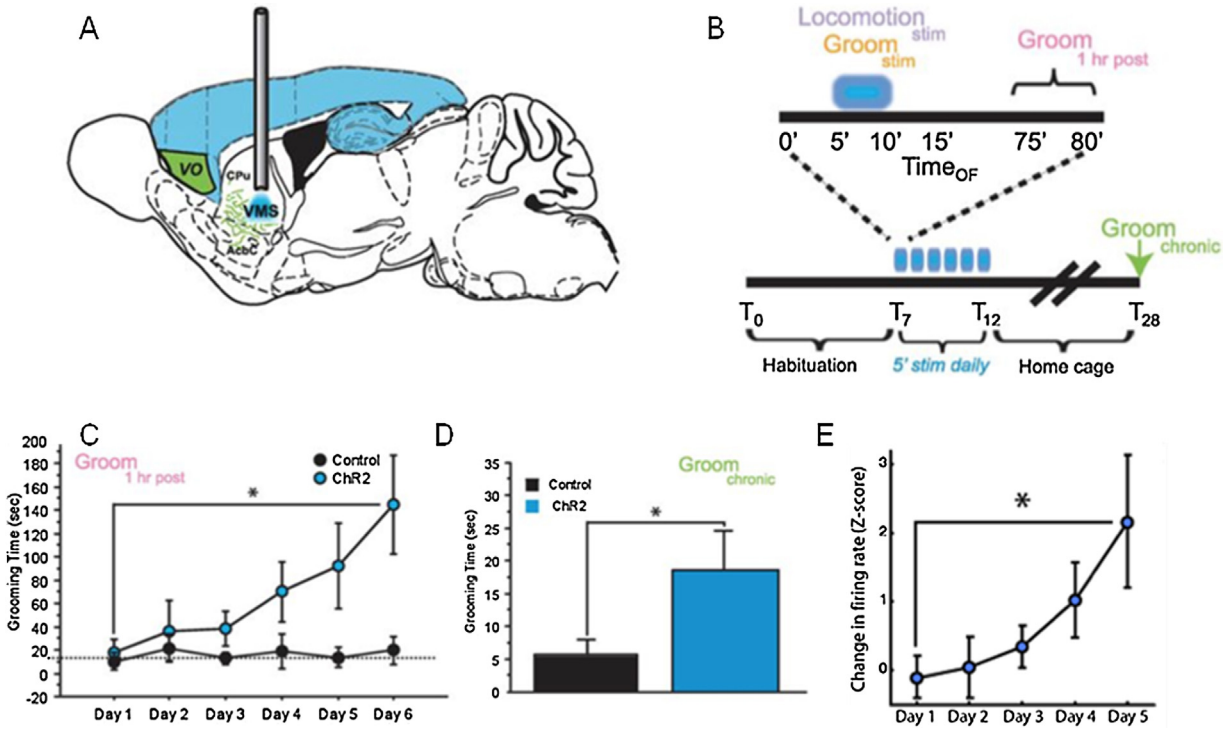


Fig. 1. Optogenetically induced increase in perseverative grooming. A) Channelrhodopsin (ChR2) is expressed in the ventromedial orbitofrontal cortex (VO), and a chronic fiberoptic implant in ventromedial striatum (VMS) is used to stimulate ChR2+ terminals projecting from VO. B) ChR2+ VO-VMS projections were stimulated 5 min/day for 6 days (T7 to T12). C) 6 days of stimulation led to a progressive increase in grooming 1 h post stimulation. D) 2 wk after repeated stimulation (T28), ChR2+ animals still demonstrate significantly increased grooming (Groomchronic *P < 0.03) despite no intervening stimulation. E) Progressive increase in evoked firing rate over course of multiple days. Z-scores indicate activity before vs. after light. (Modified from Ahmari et al., 2013).

[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 ms, 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 h and 24 h 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 (Fig. 1). 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 serotonergic drugs including chronic SSRIs (e.g., fluoxetine, clomipramine), 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 frontal cortical 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 h 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, 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, 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 N-methyl-D-aspartate (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 Fig. 2). This observation extends the face validity of the sub-chronic NMDA receptor-blockade model to include increased susceptibility to compulsive behaviors such as polydipsia.

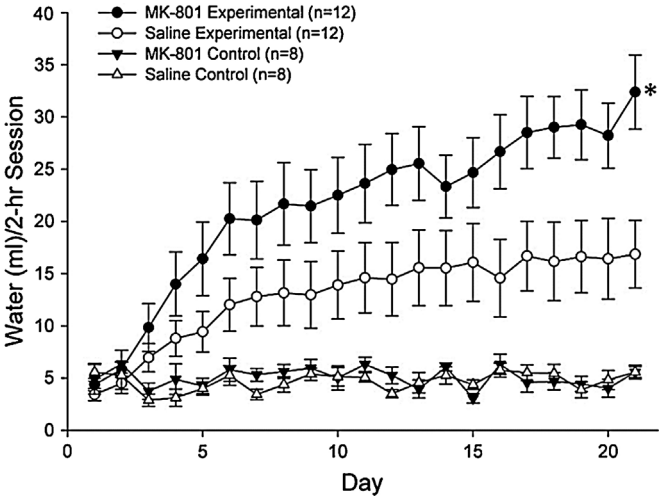


Fig. 2. MK-801 significantly increased daily mean (±SEM) water drinking across days in the schedule-induced polydipsia (SIP) paradigm. Experimental groups received saline (1.0 ml/kg) or the NMDA receptor blocker MK-801 (0.5 mg/kg) twice daily for 7 days followed by a 4-day washout prior to the beginning 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-h 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) × condition (experimental and control) × day], $F(1,36) = 5.88$, $p = 0.02$. MK-801 Experimental and Saline Experimental groups did not differ significantly on day 1, $t(22) = 0.98$, $p = 0.34$, but by day 21 the MK-801 Experimental group was drinking more, $t(22) = 3.30$, $p = 0.004$. 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, 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 neu-

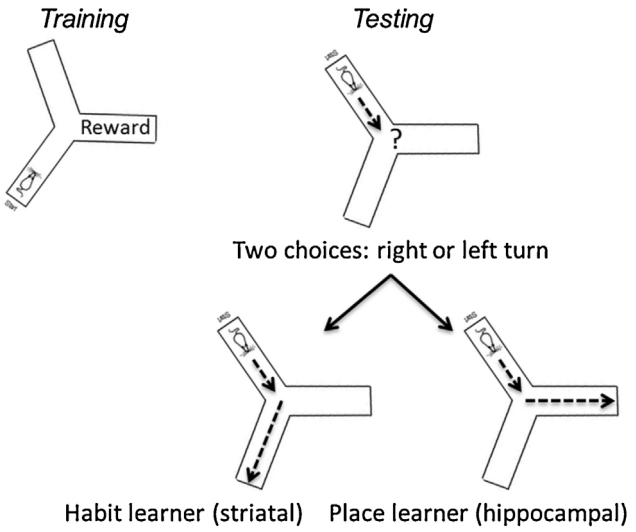


Fig. 3. Y-maze test used to identify different response strategies in rat. During the training phase, food-restricted rats are started in the same arm on each trial and learn to choose the arm baited with a food pellet (Reward). On probe test trials, rats are started in the arm that was neither the usual 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.

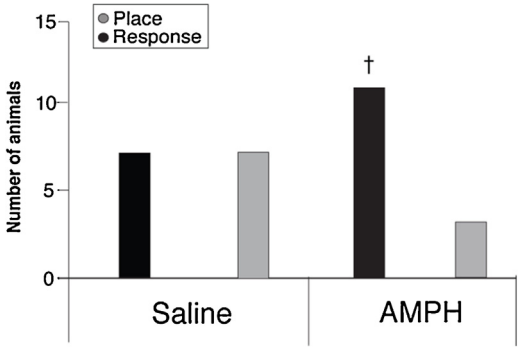


Fig. 4. Number of animal that used response (habit) or place-learning strategies in groups pre-treated for 5 days with amphetamine (AMPH; 1.5 mg/kg) or saline. † = significantly greater proportion than expected by chance in binomial probability test. From Gregory et al. (2015).

rocognitive 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 h 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 Fig. 3, *Training*). On periodic probe trials, they were started in the third arm that was neither the usual start box nor the goal box (Fig. 3, *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 (Fig. 3, 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).

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 (Fig. 4). These results reveal that groups of rats that show a greater level of SIP are overrepresented by rats that use a habit strategy.

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. Pellon 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, behavior 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 Fig. 5) (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%, Fig. 5), 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 Fig. 5 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

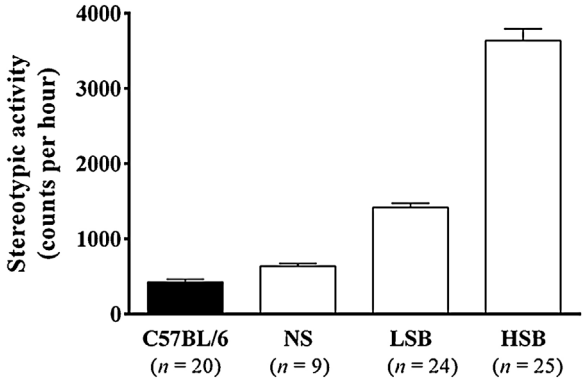


Fig. 5. The heterogeneous nature of deer mouse stereotypy. Deer mouse stereotypy is heterogeneous within a given population of animals, with approximately 45% of animals classified as having high stereotypic behavior (HSB), 41% as having low stereotypic behavior (LSB), and 16% as being non-stereotypic (NSB). In this graph, deer mice are compared to C57Bl/6 mice as control. From Korff et al. (2008).

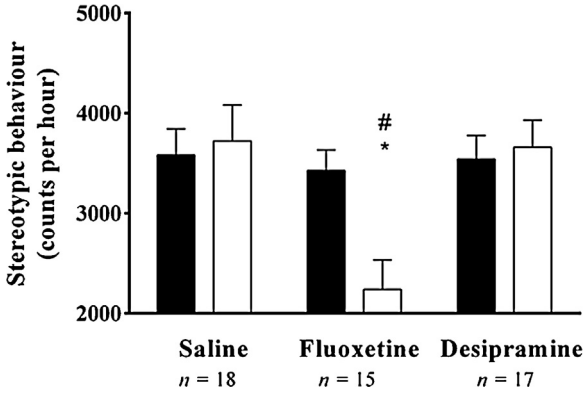


Fig. 6. Differential response of deer mouse stereotypy to chronic fluoxetine and desipramine treatment. Effect of treatment with 20 mg/kg fluoxetine, 20 mg/kg desipramine and saline on stereotypic behavior of deer mice. Baseline (untreated) stereotypic activity for each treatment group (solid bars) is provided for high stereotypic behavior (H) mice. Data represent the average of three behavioral 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).

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 Fig. 6) (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., 2016a,b,c). 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)

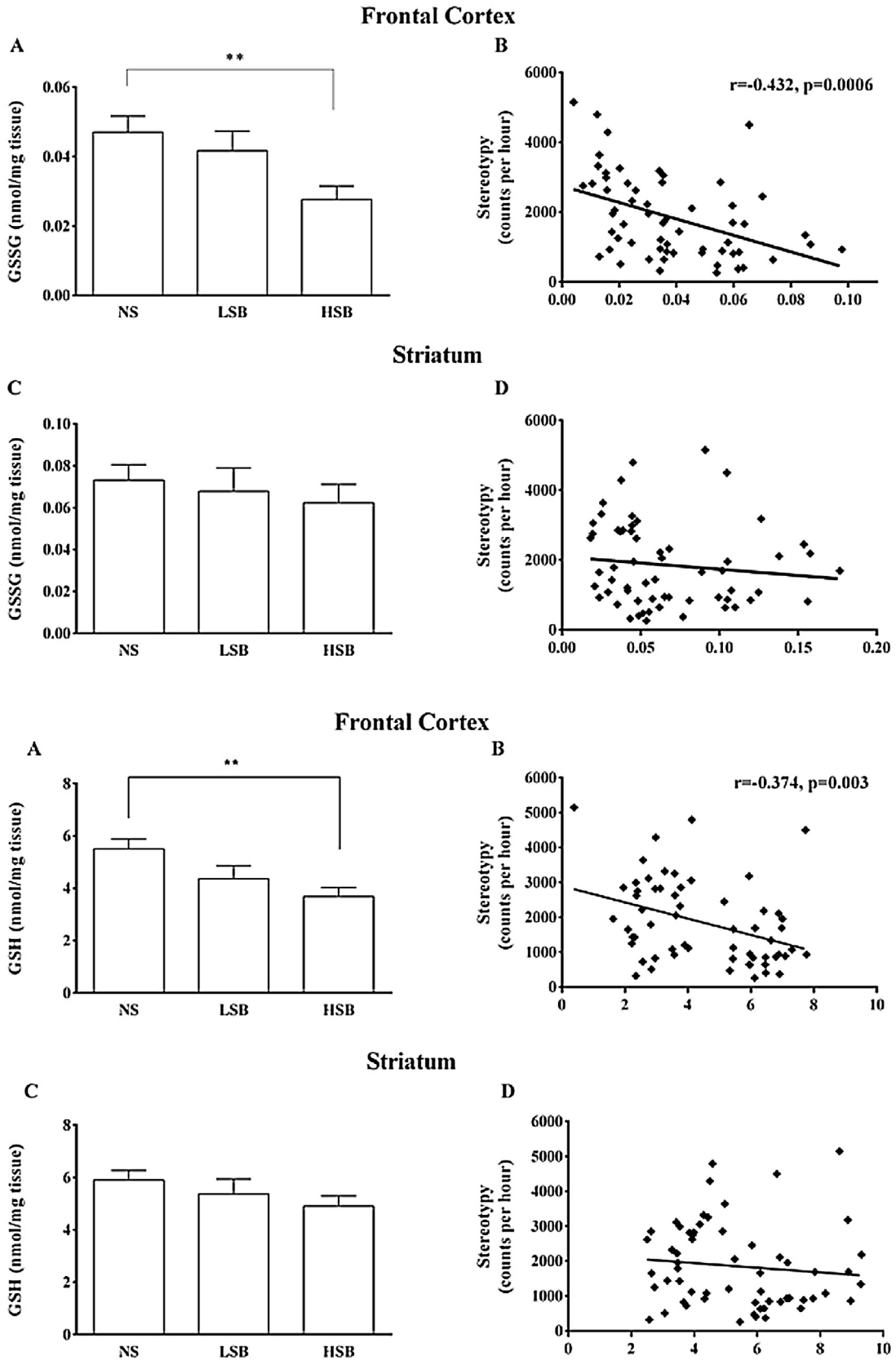


Fig. 7. Cortical but not striatal glutathione redox imbalance is correlated with severity of stereotypy in deer mice. Comparative oxidized (GSSG; *top* panel) and reduced (GSH; *bottom* panel) glutathione in the frontal cortex and striatum of non-stereotypic (NS), low stereotypic (LSB) and high stereotypic (HSB) deer mice (n = 20, 16 and 24, respectively) are shown; **p < 0.01, Bonferroni). Also shown are appropriate correlations between stereotypy count and GSSG or GSH in all animals (n = 60). From Guldenpfennig et al. (2011).

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.

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, this highlights the complex nature of treatment response and suggests a mutual role for receptor state *and* neurotransmitter release in response to a dopaminergic agent. Furthermore, the role of neuronal adaptation in disease re-affirms the importance of using a pathological animal model in drug discovery research as this may provide a better understanding of treatment variability and treatment resistance in OCD (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 reduced (GSH) and oxidized (GSSG) glutathione are correlated with severity of stereotypy in deer mice (see Fig. 7) (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).

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, 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 Fig. 8) (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, 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

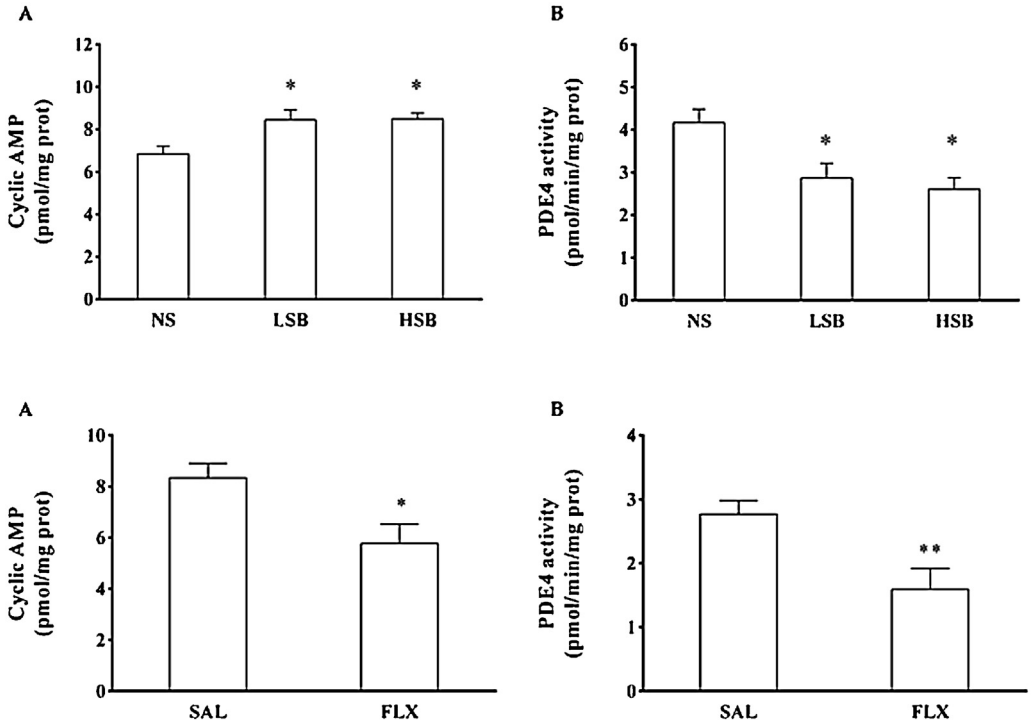


Fig. 8. cAMP-PDE4 signaling in stereotypic deer mice, and response to fluoxetine. *Top panel*: Frontal cortical cAMP levels (A) and PDE4 enzyme activity (B) in low stereotypic (LSB) and high stereotypic (HSB) deer mice compared to non-stereotypic (NS) mice. Significant differences versus control NS mice 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 (×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).

methamphetamine-induced stereotypy (Iyo et al., 1995), suggesting that PDE4 active compounds may represent novel treatment options for OCD.

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 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., 2016c). 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, implying 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 also 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 behavior 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, 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, 2012ab; 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).

The standard protocol to induce compulsive checking is a dose of QNP every 3–4 days (0.5 mg/kg × 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 m), with 4 small objects positioned at the same fixed locales throughout the study (see Fig. 9 a). 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, 2010). The open field is divided virtually into 25 locales (Fig. 9b) 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 Fig. 9c. Because repeated injections of QNP induce locomotor sensitization (Eilam and Szechtman, 1990, 1983; Einat et al., 1996; Einat and Szechtman, 1993; Szechtman et al., 1994a,b, 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 (Fig. 9c).

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

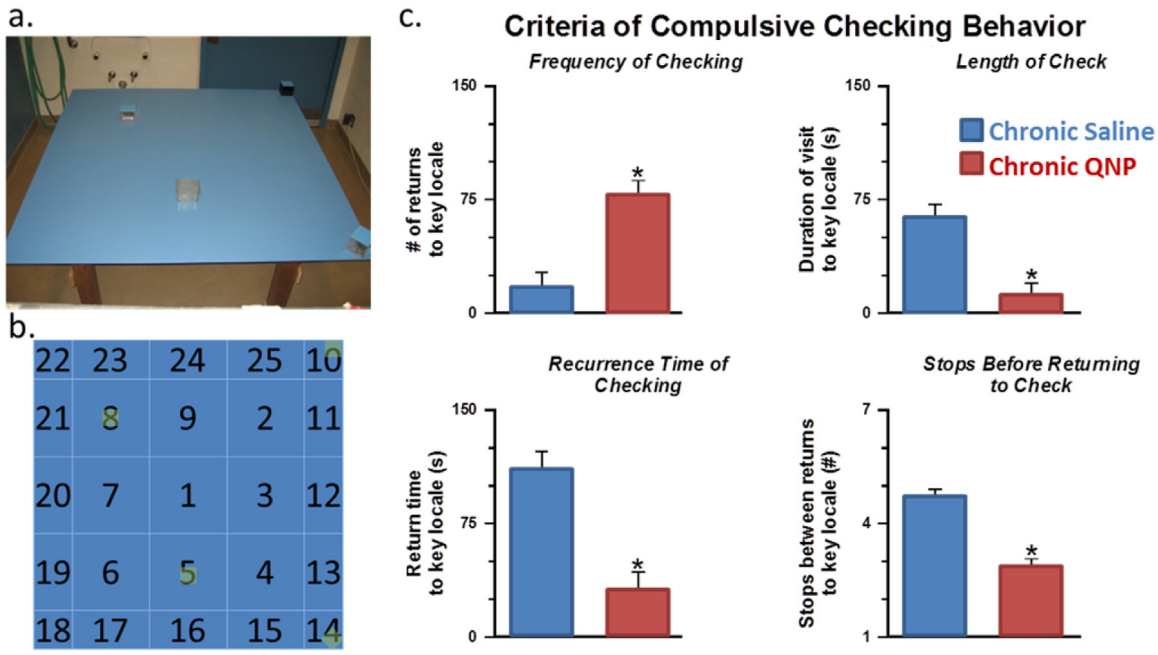


Fig. 9. Experimental set-up and test for compulsive checking. (a.) The open field apparatus with 4 objects on it. (b.) Subdivision of the open field into 25 places. The software algorithm assigns the positions of *x,y* coordinates of a stop within these locales. (c.) Test for compulsive checking on the 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 stay in key place); and, *# of stops before returning to check* (mean number of places visited between returns to key locale). *p < 0.05 vs saline controls. Modified from Alkhatib et al. (2013).

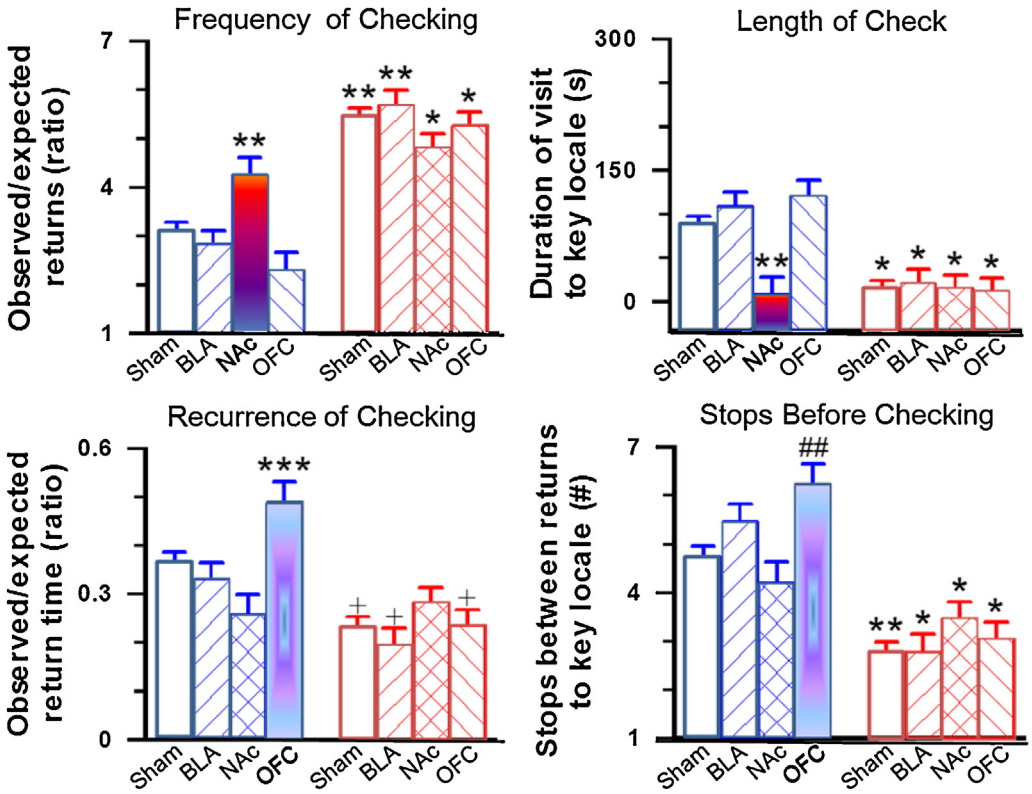


Fig. 10. Performance on criteria measures of compulsive checking behavior shown by groups of rats with lesion to the basolateral amygdala (BLA), nucleus accumbens core (NAc), orbital frontal cortex (OFC) or sham lesion. Blue bars represent groups with chronic saline treatment (left cluster of each panel) 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). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

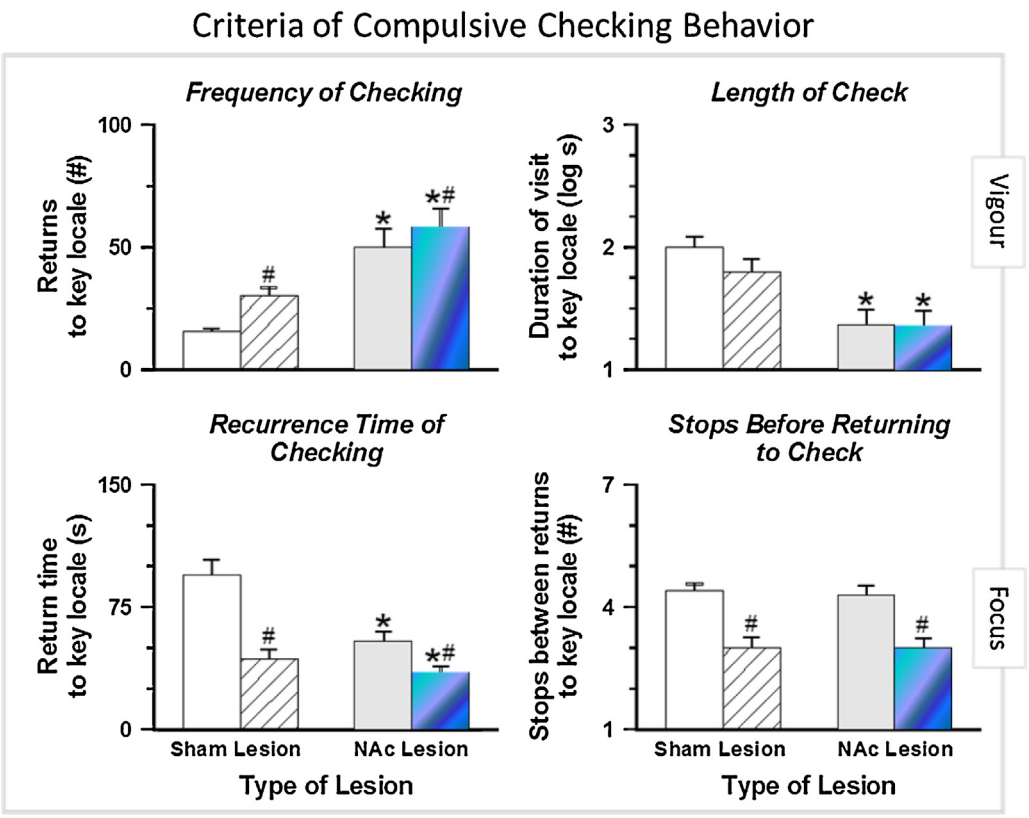


Fig. 11. Performance on criteria measures for compulsive checking behavior shown by groups of sham controls and NAc core lesion rats treated with saline or DPAT. Open bars, sham controls injected with saline; right hatch, sham controls injected with DPAT; gray filled bars, NAc core lesion rats injected 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).

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, 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

In a study by Dvorkin et al. (2010), rats received repeated injections of saline or QNP (0.5 mg/kg, twice per week, × 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 Fig. 10, 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 Fig. 10 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 **vigour** of checking, and thus one component of compulsive checking is the vigour 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) vigour 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 vigour 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 2×2 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 Fig. 11, 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.

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 Fig. 12); 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*.

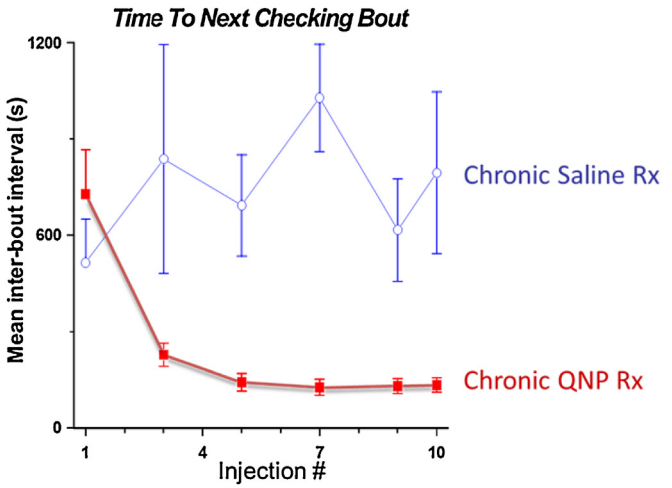


Fig. 12. Duration of negative feedback signal as measured by *time to next checking bout* in rats treated chronically with saline (blue open circles) and quinpirole (red solid squares) during the course of treatment to induce compulsive checking. From Dvorkin et al. (2006). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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 raises the question what particular motivation has checking behavior as its output, 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, 2006; Woody et al., 2005; Woody and Szechtman, 2005). Recent experi-

mental 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, 2012). Moreover, the neuroanatomical structures associated with the component behaviors 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 behavioral paradigm. Therefore, the underlying neurobiological alterations mediating compulsive behavior 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 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 behavior and GP-DBS not at all in the QNP model (Djodari-Irani et al., 2011; Klavir et al., 2011) (Fig. 13A). 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 behavior 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 behavior in both models. This is apparent as functional modification of the STN following DBS application reduces compul-

A

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

B

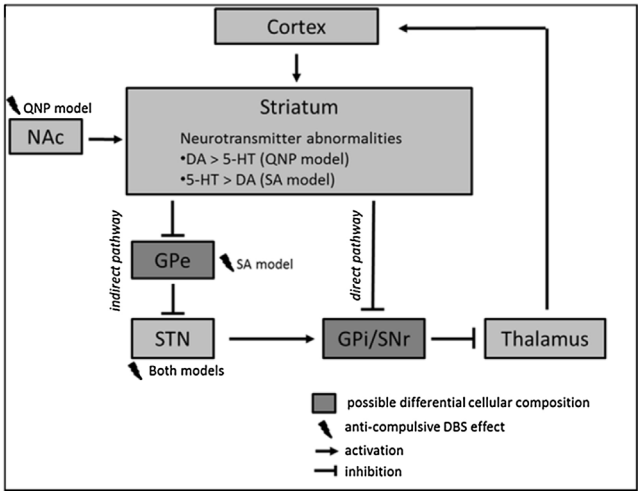


Fig. 13. A) the degree of anti-compulsive effects in the signal attenuation (SA) and quinpirole (QNP) model following high-frequency deep brain stimulation (DBS) to brain targets of the cortical-basal ganglia-thalamo-cortical circuit (CBGTC) ÷ = no effect; B) the CBGTC loop, including the differential 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.

sions 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 where DBS applied to the NAc reduces compulsive behavior (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 behavior 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 behavior. This behavior 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 (Fig. 13B).

6.4. Inactivation of CBGTC circuit targets

Direct inactivation of some targets within the CBGTC circuit abolishes compulsive behavior 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 behavioral 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.

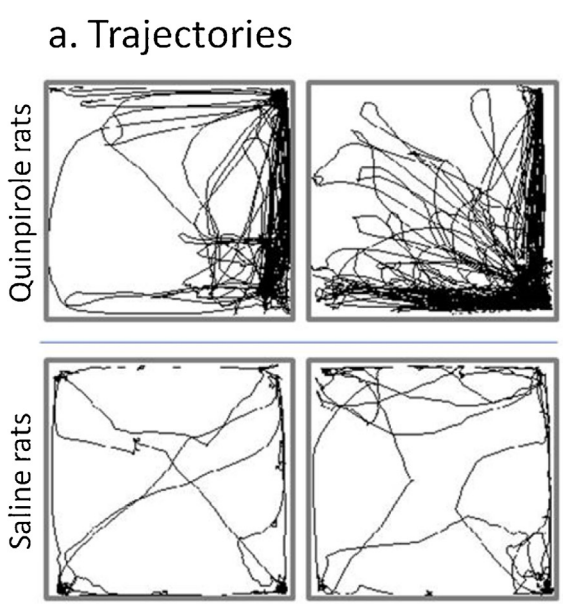
6.5. Conclusions

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.

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



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

Fig. 14. 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 2 × 2 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; H—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.

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 × 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, 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 Fig. 14).

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 Fig. 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).

7.3. Compulsive OCD rituals: predominance of idiosyncrasy and repetitions

What is lacking in Fig. 15 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.,

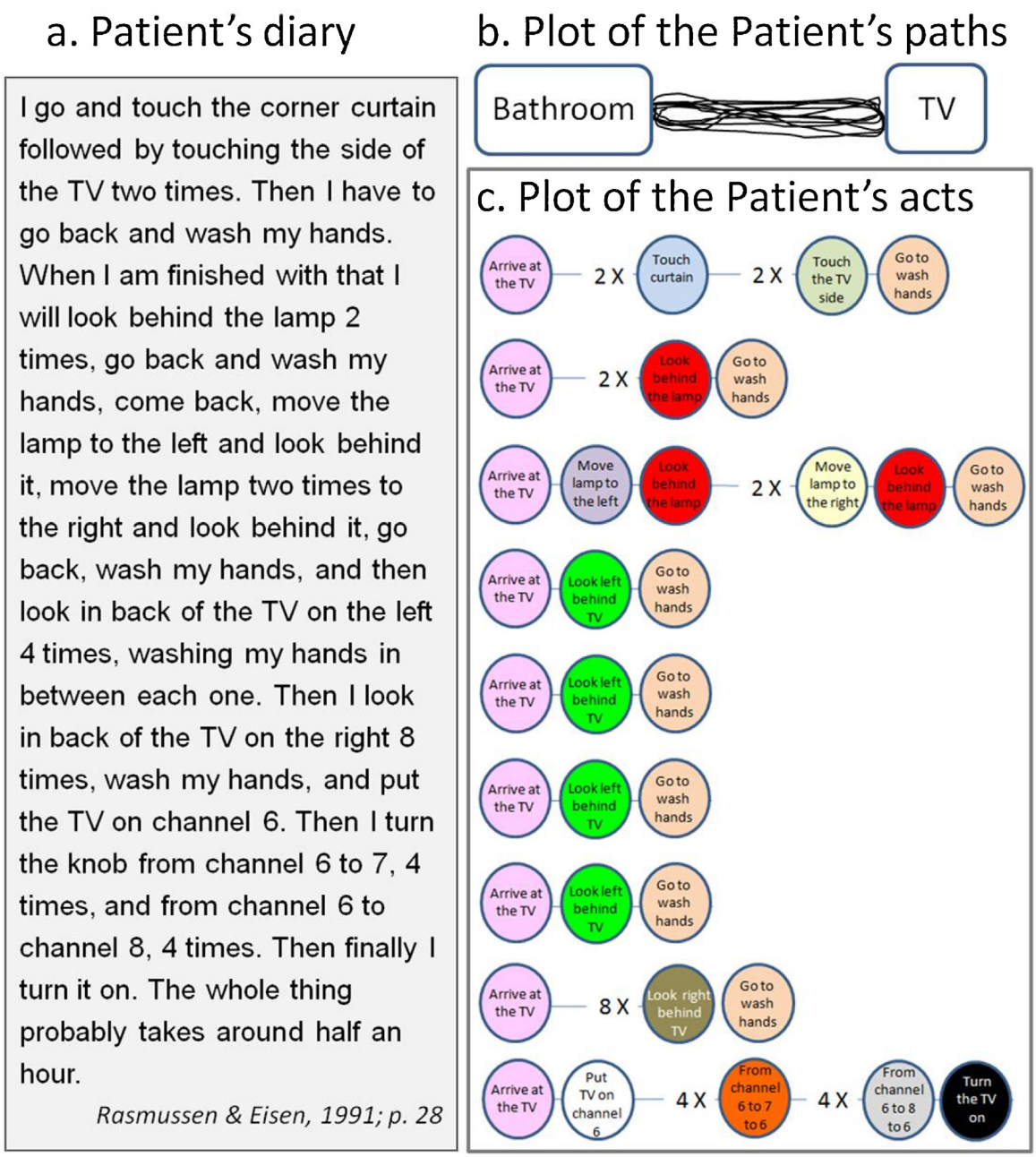


Fig. 15. Excerpt from the patient's diary a. describing the ritual of turning on the TV. Behavior comprised systematic traveling between the bathroom and the TV, which could be schematically depicted as shown b. In the description of the acts when at the TV c., each visit to the TV during the ritual is depicted along one row, and each circle represents one act (similar acts are depicted in the same color).

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. Fig. 16 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.

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 (Fig. 17). 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).

Further scrutiny of the temporal order of acts revealed that OCD rituals typically end with a long chain of idiosyncratic acts (see Fig. 16 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

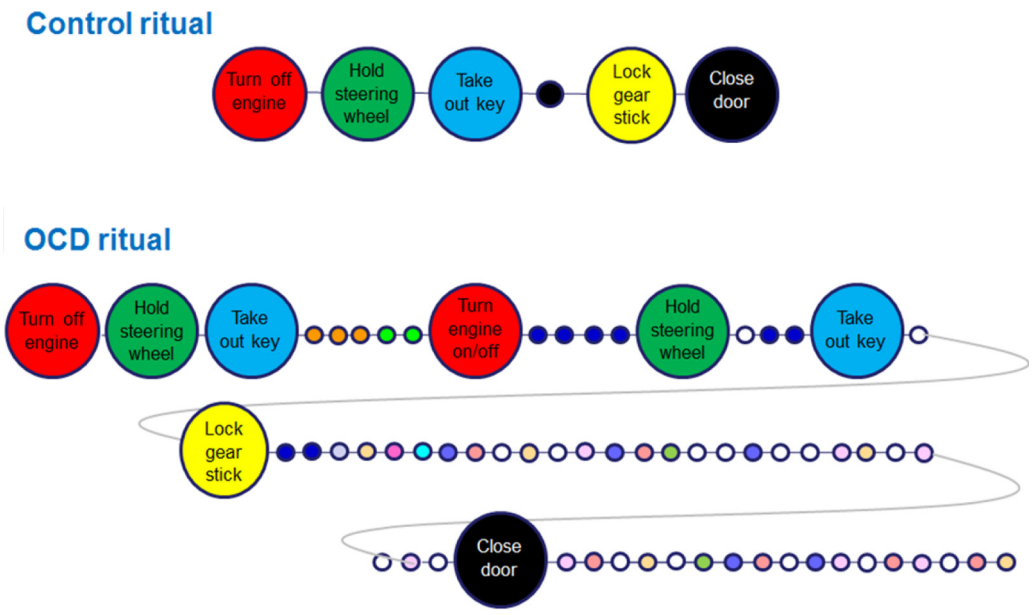


Fig. 16. The sequence of acts performed by a control individual (upper box) and an OCD patient (bottom box) as they lock and walk away from their car. Large circles depict common acts and small circles depict idiosyncratic acts. As shown, the control individual had only one idiosyncratic act and no repetition 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.

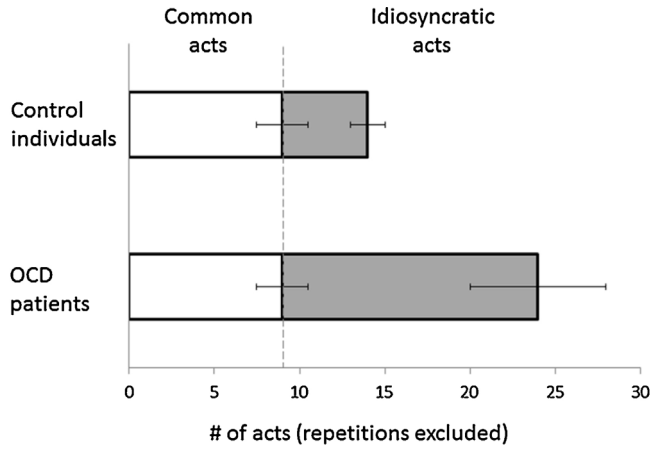


Fig. 17. The number (mean ± SEM) of common acts (open bars) and idiosyncratic acts (gray bars) in the repertoire of acts (repetitions excluded) of 43 OCD rituals (bottom) and their non-OCD controls (top). The number of common acts performed in OCD and control rituals was identical (open bars). However, 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).

(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., unpublished manuscript).

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,b; 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. The latter has emphasized targeting pathways of oxidative stress and PDE4 activity within the CBGTC circuits as possible treatment options for OCD (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. This is 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.

Conflict of interests

Brian H. Harvey has participated in advisory boards and received honoraria from Servier®, and has received research funding from Servier® and Lundbeck®. BHH acknowledges that opinions, findings and conclusions or recommendations expressed in any publication generated by National Research Foundation (NRF) supported research are those of the authors, and that the NRF accepts no liability whatsoever in this regard. Remaining authors declare no competing interests.

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Research Paper

Lateral orbitofrontal dysfunction in the *Sapap3* knockout mouse model of obsessive–compulsive disorder

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Background: Obsessive–compulsive disorder (OCD) is a common psychiatric disorder that affects about 2% of the population, but the underlying neuropathophysiology of OCD is not well understood. Although increasing lines of evidence implicate dysfunction of the orbitofrontal cortex (OFC) in OCD, a detailed understanding of the functional alterations in different neuronal types in the OFC is still elusive. **Methods:** We investigated detailed activity pattern changes in putative pyramidal neurons and interneurons, as well as local field potential oscillations, in the lateral OFC underlying OCD-relevant phenotypes. We applied in vivo multichannel recording in an awake OCD mouse model that carried a deletion of the *Sapap3* gene, and in wild type littermates. **Results:** Compared with wild type mice, the lateral OFC of *Sapap3* knockout mice exhibited network dysfunction, demonstrated by decreased power of local field potential oscillations. The activity of inhibitory and excitatory neurons in the lateral OFC showed distinct perturbations in *Sapap3* knockout mice: putative interneurons exhibited increased activity; putative pyramidal neurons exhibited enhanced bursting activity; and both putative pyramidal neurons and interneurons exhibited enhanced discharge variability and altered synchronization. **Limitations:** To exclude motor activity confounders, this study examined functional alterations in lateral OFC neurons only when the mice were stationary. **Conclusion:** We provide, to our knowledge, the first direct in vivo electrophysiological evidence of detailed functional alterations in different neuronal types in the lateral OFC of an OCD mouse model. These findings may help in understanding the underlying neuropathophysiology and circuitry mechanisms for phenotypes relevant to OCD, and may help generate and refine hypotheses about potential biomarkers for further investigation.

Introduction

Obsessive–compulsive disorder (OCD) is a debilitating neuropsychiatric condition with a lifetime prevalence of 2%.[1] It is characterized by persistent intrusive thoughts (obsessions) and repetitive actions (compulsions). Although dysfunction of the cortico–striato–thalamo–cortical circuitry has been implicated in the pathogenesis of OCD[2–5] and is supported by neuroimaging studies in patients,[6–9] the underlying neuropathological changes are still not well understood. The orbitofrontal cortex (OFC) may be central to our understanding of OCD, because it is the most frequently reported region of structural, functional and connectivity alterations in patients with OCD.[10–12] The OFC is thought to update outcome expectations when rules linking stimuli to outcomes are changed.[13–15] Therefore, the OFC is essential for behaviour flexibility and goal-directed behaviours, both of which are impaired in people with OCD.[16,17] For this reason, the OFC is well suited as a neural substrate for OCD pathogenesis.

Although a large number of functional neuroimaging studies have shown altered metabolic activity in the OFC of people with OCD, a detailed understanding of the functional alterations is still elusive. For example, a majority of studies have reported increased resting metabolic activity in the OFC of people with OCD,[18–22] which is exacerbated by symptom provocation[23,24] and alleviated after successful treatment.[25–30] However, these studies can only measure metabolic levels to indirectly reflect general neuronal activity levels. The noninvasive methods used in clinical studies also have limited spatial and temporal resolution. Direct electrophysiological evidence of detailed activity change of different neuronal types in the OFC of people with OCD or animal models is still lacking. Furthermore, there are discrepancies in the directionality of findings in clinical neuroimaging studies that may be due

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to the heterogeneity of the disorder, comorbidities, medication history or different subregions of the OFC analyzed.

In the present study, we investigated detailed functional change in different neuronal types in the lateral OFC (lOFC) that underlie OCD-relevant phenotypes by applying in vivo multichannel recording in an awake OCD mouse model that carried a deletion of the *Sapap3* gene. These *Sapap3* knockout (KO) mice demonstrate several OCD-like behaviours, including excessive and pathological self-grooming and increased anxiety-like behaviours, suggesting potential relevance to OCD. As well, the entire constellation of OCD-like behaviours in *Sapap3* KO mice is alleviated by chronic fluoxetine, a first-line treatment for OCD.[31] Human genetics studies also support a role for *Sapap* genes in OCD.[32–34] Therefore, a detailed understanding of functional alterations in the OFC of *Sapap3* KO mice could help identify potential circuit mechanisms for behaviours relevant to OCD. The OFC consists of lateral and medial subregions. The lateral and medial OFC may perform different functions, such as processing negative versus positive valence.[35,36] A previous study from our group found that selective stimulation of the lOFC suppressed overexpression of both spontaneous and conditioned repetitive grooming behaviours, suggesting involvement of the lOFC in these behaviours in *Sapap3* KO mice.[37] To investigate functional alterations in the OFC in *Sapap3* KO mice, we focused on the lOFC subregion in the current study. Using single-unit and local field potential (LFP) recording in the lOFC, we studied activity pattern changes in different neuronal populations and alterations in LFP oscillations in *Sapap3* KO mice. Our goal was to shed light on the neuropathophysiology underlying OCD-like behaviours and advance our circuit-level understanding of phenotypes relevant to OCD. Our findings may help to generate and refine hypotheses for further investigation. For example, LFP alterations and increased burst firing in lOFC may be useful biomarker candidates for further examination in people with OCD.

Methods

Animal use

All experiments were conducted according to protocols approved by the Institutional Animal Care and Use and Institutional Biosafety committees of the Capital Medical University (Beijing, China) and the Massachusetts Institute of Technology (Cambridge, Massachusetts). Our group had previously found that from age 2 to 3 months, *Sapap3* KO mice exhibited significantly increased self-grooming that resembled compulsive OCD behaviours.[31] Therefore, we performed all of our experiments on adult *Sapap3* KO mice aged 3 to 10 months, and on age-matched, wild type (WT) littermates of either sex.

Surgery

Our method of electrophysiological recording in head-restrained, mobile mice was based on previous studies with modifications.[38,39] Briefly, for head-plate implantation, mice were anesthetized by intraperitoneal injection of Avertin solution (20 mg/mL, 0.5 mg/g body weight) and then mounted in a stereotactic holder and kept warm (37°C) with an electric heating pad (BrainKing Biotech). A small skull region (~1 mm in diameter) located posterior to the lOFC based on stereotactic coordinates (anterior–posterior = 2.3 mm, medial–lateral = 1.3 mm) was thinned but not broken with a high-speed drill. A custom-made head plate with a hole 2 mm in diameter was placed on the skull, with the hole centred over the thinned region above the lOFC. The head plate was affixed to the skull with Meta-bond (Parkell Inc.), and the thinned skull and hole in the head plate were then covered with Kwik-sil (World Precision Instruments) for protection. Mice were individually housed after surgery and allowed to recover for 3 to 5 days before habituation training. To minimize potential stress effects, mice were trained to habituate to a head-fixed spherical treadmill for 2 to 4 hours each day for 4 consecutive days before recording. Mice quickly learned to balance and walk on the apparatus and stayed quiet for most of the time during recording, indicating low stress.

Electrophysiological recording

During electrophysiological recording, the mouse's head was restrained by a head plate, and the mouse was able to manoeuvre on the top surface of an air-supported floating styrofoam ball. Immediately before recording, we opened a small craniotomy in the thinned skull area above the lOFC. We detected extracellular spiking signals and LFP using a 32-channel silicon probe (A4×8–5mm-50–200–413-A32–15; NeuroNexus) arranged in a 4 × 8 pattern (4 shanks with 8 recording sites in each shank), lowered to the lOFC (anterior–posterior = 2.5–2.8 mm; medial–lateral = 1.0–1.6 mm, dorsal–ventral = 1.3–2 mm) and tilted rostrally at an angle of 15° to the vertical plane. Based on the above coordinates, we discarded neural activities recorded outside the lOFC from analysis. We sampled unit activity at 30 kHz and high-pass filtered it at 250 Hz using a Blackrock Cerebus data acquisition system (Blackrock Microsystems LLC). We sampled LFP at 1 kHz and low-pass-filtered it at 250 Hz. To avoid possible noise contamination in low-frequency oscillations, we discarded LFP data below 1.5 Hz.

Spike sorting and single-unit classification

We sorted unit activity containing spikes of multiple neurons manually offline using Offline Sorter (Plexon Inc.) and a combination of template-matching and principal-components analyses. A total of 362 single units were well isolated. Units with a trough half width within 100–200 μs, a peak half width within 467–700 μs and a trough:peak ratio within 1.2–2.8 were classified as putative pyramidal neurons. Units with a trough half width within 67–167 μs, a peak half width within 100–300 μs and a trough:peak ratio within 1.1–1.8 were classified as putative interneurons.[37,40] Using these criteria, we identified 294 units as putative pyramidal neurons and 51 units as putative interneurons.

Detailed explanations of these cell-type classification criteria are provided in Appendix 1, available at jpn.ca/180032-a1.

Statistical analysis

All analyses used custom Matlab software (H.L.). For LFP oscillation power, the mean baseline firing rate of putative pyramidal neurons and interneurons, the percentage of spikes in the bursting mode per neuron and the number of bursts per minute per neuron, we determined statistical significance between WT and *Sapap3* KO mice using the Wilcoxon rank sum test. For LFP oscillation power, n was the number of animals. For single-unit activity, n was the number of neurons. We measured the correlation between firing rate and the depth of the neurons using the Spearman rank correlation coefficient.

We measured firing variability using C_{V2}.[41] We defined C_{V2} for spike i as the standard deviation of 2 adjacent interspike intervals (ISIs) divided by their mean and multiplied by √2.

$$C_{V2} = \frac{2|\Delta t_{i+1} - \Delta t_i|}{\Delta t_{i+1} + \Delta t_i}$$

Each C_{V2} corresponds to an ISI value that is the mean of the 2 adjacent ISIs used to compute C_{V2}. We computed mean C_{V2} by averaging all C_{V2} values corresponding to ISIs between a certain range. The ISI boundaries were logarithmically spaced with a ratio of 1.3. Because of the refractory period, we set the minimum ISI boundary at 1.69 ms. To access the significant difference of C_{V2} for different ISI ranges between WT and KO mice, we applied a Wilcoxon rank sum test to compare the mean C_{V2} values that corresponded to each ISI range. We then calculated the family-wise error rate to correct for multiple comparisons.

We calculated the spike-triggered average (STA) of the LFP at an interval of −5 s to 5 s, with LFP resampled at 200 Hz, so the bin size of the STA was 5 ms. We deemed STA fluctuation to be statistically significant when more than 10 consecutive bins (equal to a 50 ms time window) within an interval of −1 s to 1 s lay outside the minimum/maximum bound of its values at intervals of −5 s to −1 s and 1 s to 5 s. To access the significant difference for STA between WT and *Sapap3* KO mice, we applied the Wilcoxon rank sum test to the data points within the same corresponding bins of STA. If 20 or more consecutive bins had $p < 0.05$, we considered the STA during that time window to be significantly different.

Histology

To confirm recording location, mice were deeply anesthetized at the end of each recording (Nembutal, 50–100 mg/kg) and intracardially perfused with 50 mL 1 × PBS, followed by 50 mL 4% paraformaldehyde in PBS. Mouse brains were then postfixed in 4% paraformaldehyde/PBS overnight at 4°C and cryoprotected with 30% sucrose. Coronal sections were cut at 50 mm using a freezing microtome and reacted with Hoechst.

Results

Recording neuronal activity from the lOFC of awake mice

To identify changes in individual neuronal activity, we recorded extracellular single units and LFP from the lOFC of head-fixed, awake adult *Sapap3* KO mice (n = 24, 20 males and 4 females) and their age-matched, WT littermates (n = 21, 19 males and 2 females; Fig. 1A and B). Two-way analysis of variance (ANOVA) analysis showed a significant effect of genotype but no effect of sex (Appendix 1), so we pooled the data for male and female mice. To minimize stress, the mice were allowed to behave on an air-supported, frictionless spherical treadmill.[38] Because the activity of the lOFC is modulated by movement (Fig. 1C and D), we analyzed only the stationary epochs of the recordings to exclude movement or motor-directed activity confounders.

Reduced LFP oscillation power in the lOFC of Sapap3 *KO mice*

Brain rhythms are critical to coordinating the activity of neuronal populations across multiple spatial and temporal scales, and are involved in a wide range of cognitive and perceptual processes. To assess the rhythmic alterations of *Sapap3* KO mice, we recorded LFP at 64 sites, evenly distributed in a rectangular plane in the lOFC that was 600 μm in the medial–lateral dimension and 700 μm in the dorsal–ventral dimension, from a depth of 1300 μm to 2000 μm. We calculated the LFP power for each mouse by averaging the recordings across the 64 sites. The lOFC LFP oscillations in *Sapap3* KO mice exhibited reduced power at all frequency bands compared with their WT littermates (Fig. 2A and B). Specifically, the δ (1.5–4 Hz), θ (4–11 Hz), β (11–30 Hz) and γ (30–100 Hz) bands all had reduced power in *Sapap3* KO mice compared with WT mice (δ power normalized to WT mean: KO mean ± standard error of the mean [SEM] = 0.57 ± 0.05, WT = 1 ± 0.09, $p < 0.001$; θ power normalized to WT mean: KO = 0.59 ± 0.07, WT = 1 ± 0.09, $p < 0.001$; β power normalized to WT mean: KO = 0.54 ± 0.06, WT = 1 ± 0.11, $p < 0.001$; γ power normalized to WT mean: KO = 0.56 ± 0.06, WT = 1 ± 0.20, $p = 0.03$; Wilcoxon rank sum test; Fig. 2C, D, E and F). This is, to our knowledge, the first report of LFP alterations in the OFC in an OCD animal model. Because brain-rhythm alterations have been associated with several neuropsychiatric disorders including OCD,[42] alterations in OFC LFP oscillations may serve as a candidate biomarker to be further examined in people with OCD.

Increased activity of lOFC putative interneurons in Sapap3 *KO mice*

Brain rhythms are generated by the coordinated activity of multiple neuronal populations. The disrupted LFP oscillations found in the lOFC of *Sapap3* KO mice may indicate altered activity of multiple neuronal types. To dissect the role of individual neurons, we recorded a total of 362 single units that were isolated unambiguously using high spike-sort

quality. Among them, we recorded 215 single units from *Sapap3* KO mice: 182 were classified as putative pyramidal neurons and 30 were classified as putative interneurons, based on action potential waveforms. We recorded 147 single units from WT littermates: 112 were classified as putative pyramidal neurons and 21 were classified as putative interneurons (Fig. 3A and B).

The firing rate of putative interneurons while the mouse was at rest increased in *Sapap3* KO mice (WT mean ± SEM = 18.07 ± 1.50 Hz, median = 17.62 Hz; KO mean ± SEM = 22.56 ± 1.31 Hz, median = 23.30 Hz; $p = 0.02$ Wilcoxon rank sum test; Fig. 3C). Interestingly, however, the firing rate of putative pyramidal neurons at rest was unchanged between WT and *Sapap3* KO mice (WT mean ± SEM = 2.75 ± 0.30 Hz, median = 1.62 Hz; KO mean ± SEM = 2.78 ± 0.23 Hz, median = 1.50 Hz; $p = 0.63$ Wilcoxon rank sum test; Fig. 3D), suggesting intricate network imbalances in this mouse model with OCD-like behaviours. For both putative pyramidal neurons and interneurons, there was no correlation between firing rate and depth in either WT or *Sapap3* KO mice (Spearman rank correlation coefficient: WT putative interneurons $r = 0.02$, $p = 0.94$; KO putative interneurons $r = 0.29$, $p = 0.12$; WT putative pyramidal neurons $r = -0.15$, $p = 0.11$; KO putative pyramidal neurons $r = -0.04$, $p = 0.57$; Fig. 3E and F).

Increased bursting activity of lOFC putative pyramidal neurons in Sapap3 *KO mice*

The overall firing pattern (not merely the firing rate) determines neuronal function. Although we did not see any changes in the firing rate of pyramidal cells, we sought to compare their spike patterns between WT and *Sapap3* KO mice. In *Sapap3* KO mice, lOFC putative pyramidal neurons showed a notable enhancement of bursting activity compared with WT littermates (Fig. 4). Putative pyramidal neurons in *Sapap3* KO mice fired more bursts of doublet or triplet spikes with very short intra-burst ISI (< 10 ms). The number of bursts per minute per neuron was significantly increased

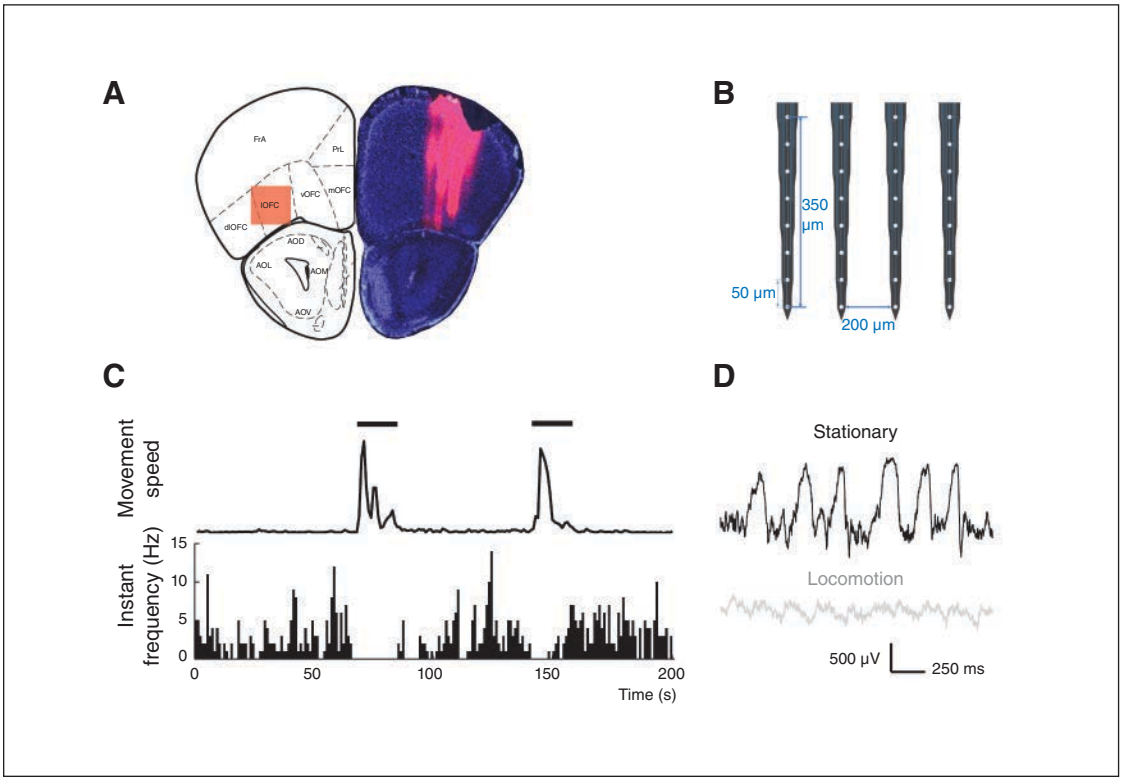

Fig. 1: Recording position and movement modulation of neuronal activity in lOFC. (A) Left: the red shadow summarizes the recording region, which was largely in the lOFC and sometimes also included the very medial portion of the dlOFC. Right: a histology example showing the tracks of the 4 electrode shanks reviewed by DiI (a fluorescent lipophilic cationic indocarbocyanine dye; red). (B) Electrode map. The recording electrodes had 4 shanks spaced by 200 µm. Each shank had 8 recording sites spaced by 50 µm. (C) An example of movement modulation of the spike activity of a putative pyramidal neuron in the lOFC of a WT mouse. This neuron decreased firing rate during locomotion. Horizontal bars indicate movement bouts. (D) An example of movement modulation of the LFP in the lOFC of a WT mouse. Black trace in the upper panel shows LFP when stationary. Grey trace in the lower panel shows LFP during locomotion. AOD = anterior olfactory area, dorsal part; AOL = anterior olfactory area, lateral part; AOM = anterior olfactory area, medial part; AOV = anterior olfactory area, ventral part; dlOFC = dorsolateral orbitofrontal cortex; FrA = frontal association cortex; LFP = local field potential; lOFC = lateral orbitofrontal cortex; mOFC = medial orbitofrontal cortex; PrL = prelimbic cortex; vOFC = ventral orbitofrontal cortex; WT = wild type.

in *Sapap3* KO mice (WT mean ± SEM = 12.4 ± 1.9 times/min, median = 5.8 times/min; KO mean ± SEM = 18.2 ± 2.0 times/min, median = 10.7 times/min; $p = 0.001$, Wilcoxon rank sum test; Fig. 4C). The percentage of spikes per neuron in the bursting mode was also significantly increased in *Sapap3* KO mice (WT mean ± SEM = 22.9 ± 2.1%, median = 16.1%; KO mean ± SEM = 32.3 ± 1.8%, median = 29.0%; $p < 0.001$, Wilcoxon rank sum test; Fig. 4D). The intra-burst ISI was significantly shorter in *Sapap3* KO mice compared with WT mice (WT mean ± SEM = 6.60 ± 0.13 ms; KO mean ± SEM = 6.23 ± 0.09 ms; $p = 0.016$, Wilcoxon rank sum test). Bursts with short intra-burst ISI are more reliable and efficient for eliciting synaptic transmission than tonic firing.[43] Therefore, the increased bursting activity seen in *Sapap3* KO mice may enable lOFC pyramidal neurons to provide a stronger output and drive increased activity in the downstream structures of the orbito–fronto–striatal circuit in this OCD mouse model, reflecting specific pathologic neural processes in lOFC that underlie phenotypes relevant to OCD.

Increased firing variability for both neuronal types in Sapap3 *KO mice*

Both lOFC putative pyramidal neurons and interneurons in *Sapap3* KO mice exhibited enhanced discharge variability compared to WT littermates. To measure firing variability,

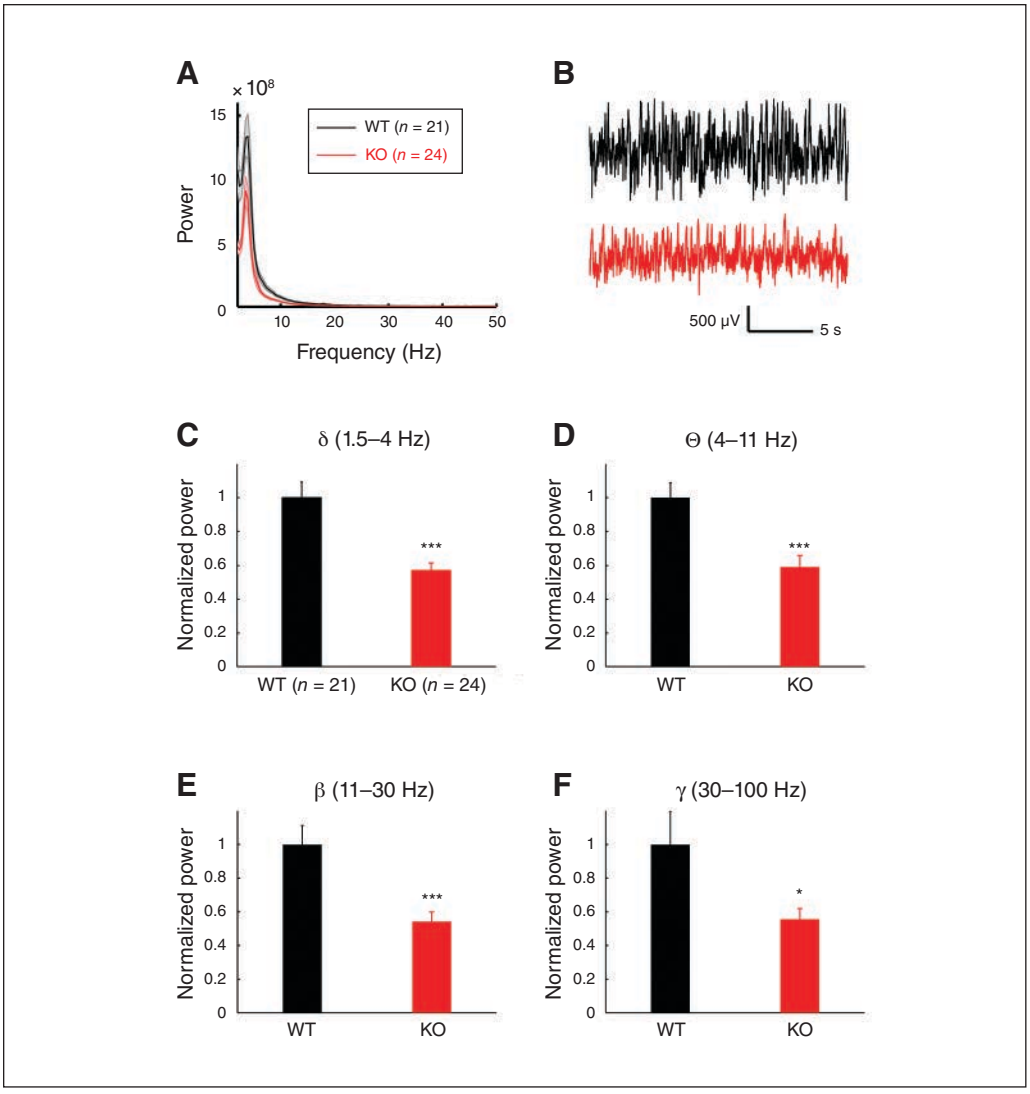

Fig. 2: Reduced lOFC LFP oscillation power in *Sapap3* KO mice. (**A**) Averaged LFP power spectrogram of WT and *Sapap3* KO mice. Shading represents standard error of the mean. (**B**) Representative LFP raw recording traces from WT mice (black) and *Sapap3* KO mice (red). Traces were from mice with an LFP power spectrogram closest to the mean values of the corresponding groups. (**C**, **D**, **E**, **F**) Comparison of lOFC LFP oscillation power in δ, θ, β and γ bands between WT and *Sapap3* KO mice, respectively. *$p < 0.05$, ***$p < 0.001$, Wilcoxon rank sum test. Error bars represent standard error of the mean. KO = knockout; LFP = local field potential; lOFC = lateral orbitofrontal cortex; WT = wild type.

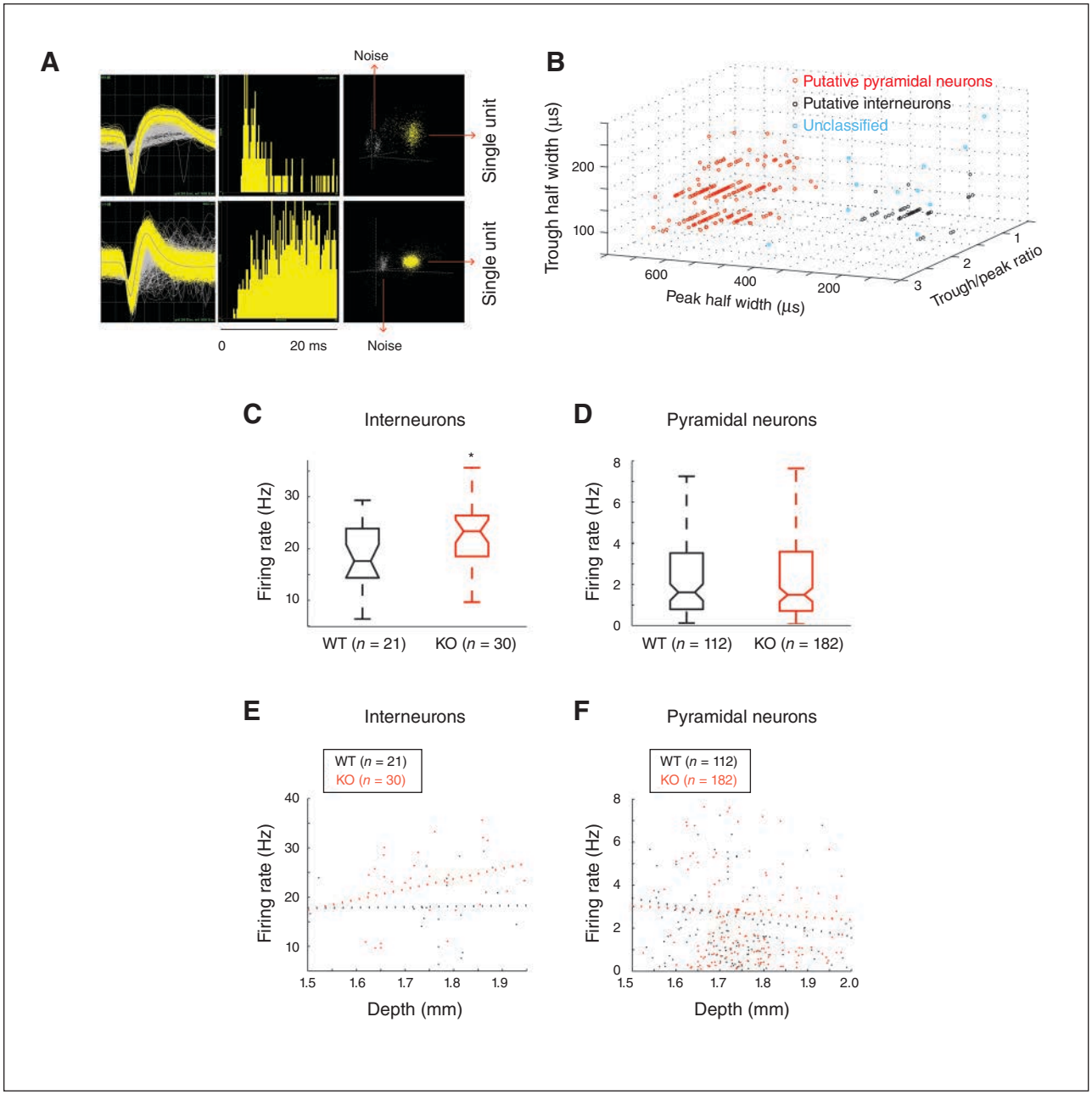

Fig. 3: The mean firing rate of lOFC putative interneurons increased in *Sapap3* KO mice, but the mean firing rate of putative pyramidal neurons did not change. (**A**, **B**) Isolation and classification of the recorded single units in lOFC. (**A**) Top panel: an example of an isolated putative pyramidal single unit in lOFC. Bottom panel: an example of an isolated putative interneuron single unit in lOFC. Left to right: overlay of the waveforms of the isolated single unit (yellow) and the noise waveforms (grey). Interspike interval histogram. Projection of the clusters correspondent to the unit and the noise (*x* axis: PC1, *y* axis: PC2, *z* axis: nonlinear energy). (**B**) Three-dimensional scatter plot illustrating spike characteristics of all 362 single units recorded in the lOFC of WT and *Sapap3* KO mice. Each unit is represented as a dot for peak width at half-peak amplitude (*x* axis), trough width at half trough amplitude (*y* axis) and ratio of trough to peak amplitude (*z* axis). We identified 2 major clusters. Putative pyramidal neurons are shown in red. Putative interneurons are shown in black. Units that did not meet the criteria for these classifications are shown in blue. (**C**) The mean firing rate of putative interneurons increased in *Sapap3* KO mice (red) compared to WT mice (black); **p* = 0.02, Wilcoxon rank sum test. (**D**) The mean firing rate of putative pyramidal neurons was similar between WT (black) and *Sapap3* KO (red) mice; *p* = 0.63, Wilcoxon rank sum test. The whiskers in the box plots cover 95% of the data. (**E**) We found no correlation between interneuron firing rate and depth. Spearman rank correlation coefficient: WT, *r* = 0.02, *p* = 0.94; KO, *r* = 0.29, *p* = 0.12. (**F**) We found no correlation between pyramidal neuron firing rate and depth. Spearman rank correlation coefficient: WT, *r* = –0.15, *p* = 0.11; KO, *r* = –0.04, *p* = 0.57. KO = knockout; lOFC = lateral orbitofrontal cortex; PC = principal component; WT = wild type.

we adopted a method that was less sensitive to firing rate fluctuation over time than the coefficient of variation of ISIs.[41] This method compared only adjacent ISIs by calculating C_{V2} for adjacent ISIs (see Methods).

Neurons cannot fire as variably at a high rate as at a low rate because of the refractory period. To avoid comparing the periods when the neuron fires quickly with periods when the neuron fires slowly, we did not compute the mean C_{V2} over the entire recording period. Instead, we computed the mean C_{V2} for different ISI values. Both lOFC putative pyramidal neurons and interneurons in *Sapap3* KO mice exhibited enhanced discharge variability for ISIs from 10–190 ms compared to WT mice ($p_{FWE} < 0.001$ for both putative pyramidal neurons and putative interneurons, Wilcoxon rank sum test for each ISI range; family-wise error rate was calculated to correct for multiple comparisons; Fig. 5). Cortical neurons typically fire action potentials with high temporal precision.[44] Change of the spike timing influences information coding in several sensory modalities, such as olfaction,[45] gustation,[46] audition[47] and vision.[48] The increased discharge variability of pyramidal neurons and interneurons interferes with normal information coding and processing in OFC and may reflect circuitry abnormalities for OCD-like behaviours.

Altered synchronization of lOFC putative pyramidal neurons and interneurons in Sapap3 *KO mice*

Temporal precision of firing and a tightly maintained balance between excitation and inhibition is critical to normal neural synchronization. Because we observed altered firing variability

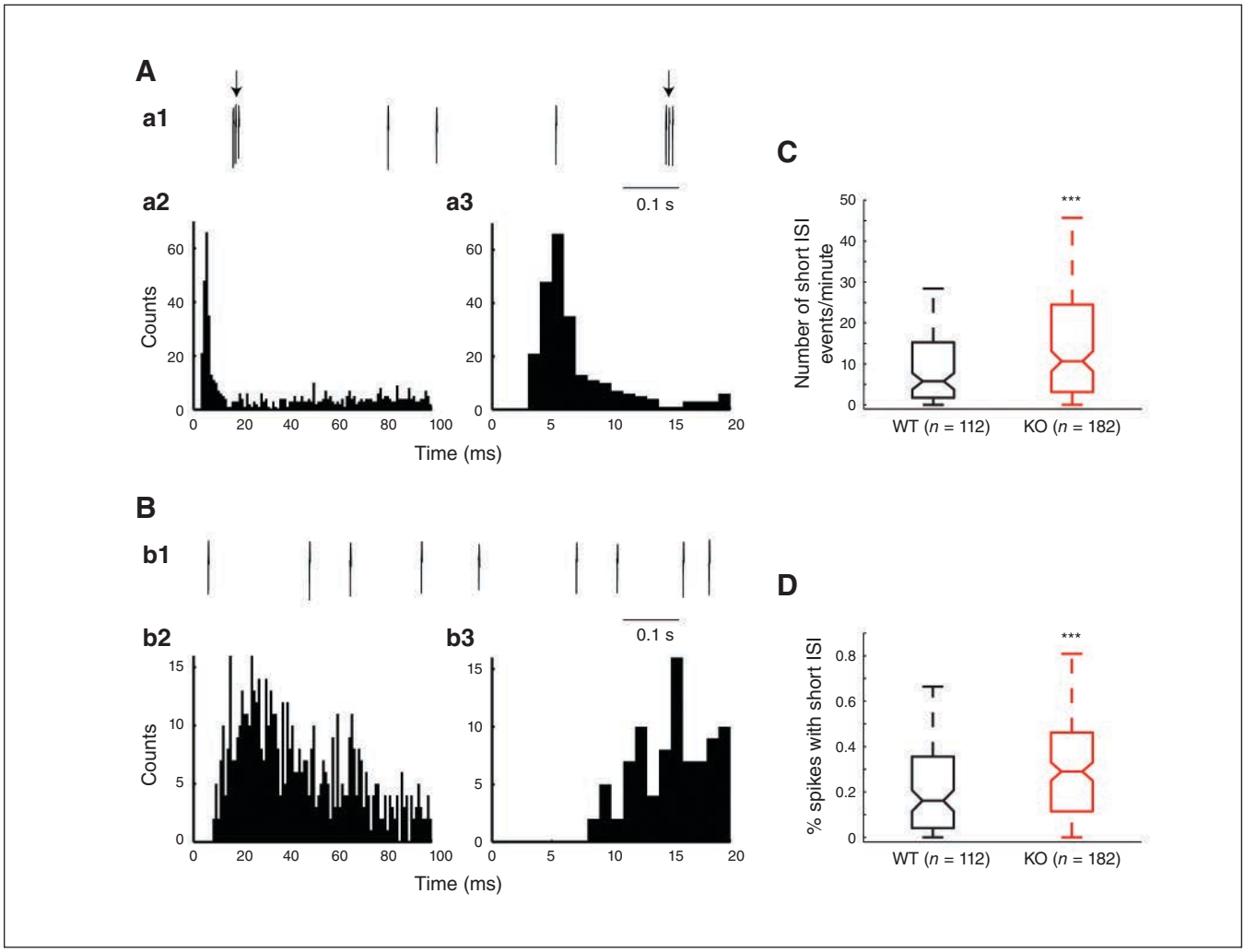

Fig. 4: The lOFC putative pyramidal neurons showed increased bursting activity in *Sapap3* KO mice. (**A**) A representative example of bursty pyramidal neurons in *Sapap3* KO mice: a1 shows the raw recording trace showing 2 bursts with short intra-burst ISI (intra-burst ISI < 10 ms, shown by arrows); a2 shows ISI distribution (bin size 1 ms); a3 shows an enlarged view of the ISI distribution from 0–20 ms to better demonstrate the short intra-burst ISI. (**B**) A representative example of non-bursty pyramidal neurons in *Sapap3* KO mice. (**C**) The number of bursts per minute per neuron increased in *Sapap3* KO mice; ***p = 0.001, Wilcoxon rank sum test. (**D**) The percentage of spikes per neuron in the bursting mode increased in *Sapap3* KO mice; ***p < 0.001; Wilcoxon rank sum test. The whiskers in the box plots cover 95% of the data. KO = knockout; ISI = interspike interval; lOFC = lateral orbitofrontal cortex; WT = wild type.

and distinct perturbations of excitatory and inhibitory neurons, we then sought to investigate whether the levels of synchronous activity in lOFC would change in *Sapap3* KO mice by calculating the STA of LFP. Because the LFP averages over many neurons, STA is more sensitive than cross-correlation in detecting local neuronal synchronization.[49] Troughs in STA of LFP correspond to depolarization of intracellularly measured membrane potential, reflecting summed excitatory events in a pool of neurons. Upward deflections in STA of LFP correspond to a drop in membrane potential.[50] In both WT and *Sapap3* KO mice, lOFC putative pyramidal neurons and interneurons all fired preferentially at the lowest point of the trough. The percentage of cells entrained to the LFP oscillations as measured by significant fluctuations in the STA around the time of spike was similar between WT and *Sapap3* KO mice (WT putative pyramidal neurons 70.6 ± 9.5% mean ± SEM, KO putative pyramidal neurons 72.0 ± 7.0%, $p = 0.9$, Wilcoxon rank sum test; WT putative interneurons 96.4 ± 3.9%, KO putative interneurons 100%, $p = 0.9$, Wilcoxon rank sum test). However, the shape of averaged STA of both putative pyramidal neurons and interneurons differed in *Sapap3* KO mice. The central trough of the STA of both putative pyramidal neurons and interneurons was reduced in *Sapap3* KO mice (Fig. 6). This reduction may have been due to the reduced power of LFP oscillation in *Sapap3* KO mice. In WT mice, the averaged STA of putative interneurons exhibited a broad second peak after the central trough (Fig. 6A). This peak was significantly reduced in *Sapap3* KO mice, indicating that interneurons experienced less synchronized inhibition after firing a spike. The peak ahead of the central trough of the STA of putative pyramidal neurons was eliminated in *Sapap3* KO mice (Fig. 6B), indicating that synchronized inhibition on membrane potential, which sculpts the time window when an action potential can occur, was reduced in *Sapap3* KO mice. As a result, in *Sapap3* KO mice, the spike timing of individual lOFC pyramidal neurons may become less accurate. This was consistent with our finding that the firing variability of lOFC putative pyramidal neurons increased in *Sapap3* KO mice. Taken together, the changes in synchrony, along with the spike activity pattern and LFP changes reported in previous sections, point to the lOFC as a malfunctioning neural substrate for behavioural phenotypes relevant to OCD.

Discussion

Cognitive and executive function requires the coordinated activity of large-scale networks. Deficits in temporal coordination in the OFC can lead to disruption of its normal function and be involved in the pathophysiology of OCD. In the present study, we have reported alterations in LFP oscillations in the lOFC of an OCD mouse model, to our knowledge, for the first time. Specifically, we found that *Sapap3* KO mice exhibited reduced power in δ, θ, β and γ oscillations at rest. The neural substrates contributing to the different frequency bands of LFP oscillations and the mechanisms by which these oscillations are generated are not well understood. Therefore, a mechanistic interpretation of how the altered activity pattern of lOFC pyramidal neurons and interneurons contributes to decreased LFP oscillations in multiple frequency bands is challenging. Nevertheless, changes in neuronal activity synchronization do contribute to LFP oscillation alterations. We found that putative interneurons experienced less synchronized inhibition after firing an action potential and putative pyramidal neurons experienced less synchronized inhibition before firing an action potential. This reduced synchronous activity in the lOFC may contribute to decreased LFP oscillation power in multiple frequency bands. Consistent with our results, animal studies have shown that deep-brain stimulation of the nucleus accumbens, which can effectively alleviate OCD symptoms, elevated spontaneous LFP oscillation power in the δ, β and γ frequency bands in the OFC in rats.[51,52] In contrast, low-frequency deep-brain stimulation of the nucleus accumbens, which is ineffective in OCD, exerted no effect on LFP in the OFC.[51,52] Given that LFP oscillation power in the OFC was decreased in an OCD mouse model and increased with deep-brain stimulation of the nucleus accumbens in rats, alterations in LFP may serve as a potential neurophysiological biomarker to be further examined in people with OCD.

Inhibitory interneurons form reciprocal connections broadly with pyramidal neurons, and so are well positioned to coordinate the timing of pyramidal cell activity, regulate information processing and gate information flow. Compromised cortical inhibitory interneurons have been implicated in multiple psychiatric and neurologic disorders, including schizophrenia,[53] autism[54] and epilepsy.[55] However, little research on interneurons has been done in people with OCD or in animal models. It has been reported that *Sapap3* KO mice have a decreased number of PV-expressing interneurons in the centromedial striatum.[37] For the first time, our work found elevated spontaneous activity and enhanced discharge variability of putative inhibitory interneurons in the lOFC of *Sapap3* KO mice. Because the lOFC directly projects to the striatum, inhibition is disrupted in both parts of the cortical–striatal circuit in this OCD mouse model. Inhibitory interneurons are critical for the normal function of the OFC. The activity of inhibitory interneurons in the OFC showed strong behaviour correlates.[56] Compromised inhibitory interneurons in the OFC altered pyramidal neuron activity correlations with decision and reward, and impaired reversal learning.[40] The activity alterations of interneurons we found may disrupt the normal function of the lOFC and help identify one aspect of malfunction in this region for behaviours relevant to OCD. Interneurons also play a fundamental role in rhythmogenesis. The elevated spontaneous activity and discharge variability of interneurons may be causally involved in the LFP alterations in lOFC, as we found in *Sapap3* KO mice. Alternatively, the increased spontaneous activity of interneurons could represent adaptive, homeostatic or unrelated processes to compensate for other primary abnormalities of the lOFC in *Sapap3* KO mice.

Although the OFC is thought to play a critical role in OCD, there are discrepancies in the directionality of findings about how the baseline activity of the OFC is altered in people with OCD or animal models. These discrepancies may be due to several factors, including the heterogeneity of the disorder,

comorbidities, medication history and the different subdivisions of OFC analyzed. Our study excluded these confounders by focusing on the lOFC in an OCD mutant mouse model, and with clear classification of different cell types. Two studies have assessed OFC activity change in OCD mouse models. One found that the baseline activity of lOFC putative pyramidal neurons measured by electrophysiological recording was similar between WT and *Sapap3* KO mice,[37] consistent with our results. The other reported upregulated baseline activity in the OFC in *Slitrk5* KO mice measured by FosB expression.[57] Because this study relied on molecular markers of cell activity, we do not know the details of activity pattern change for

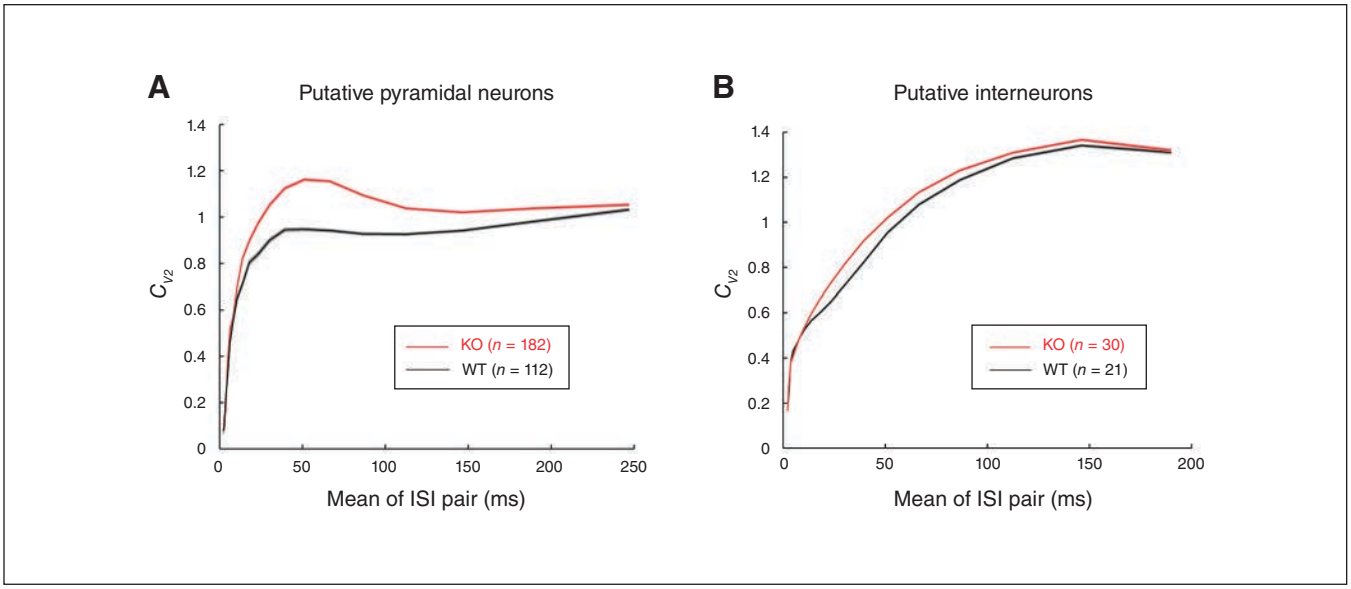

Fig. 5: The lOFC putative pyramidal neurons and interneurons exhibited enhanced discharge variability in *Sapap3* KO mice (red) compared with WT littermates (black). (**A**) Mean C_{V2} of lOFC putative pyramidal neurons plotted against the mean of the 2 adjacent ISIs used to compute C_{V2}. (**B**) Mean C_{V2} of lOFC putative interneurons plotted against the mean of the 2 adjacent ISIs used to compute C_{V2}. The *x* axis is the mean of the 2 adjacent ISIs used to compute C_{V2}. The lines are the mean C_{V2} values in logarithmically spaced bins. The ratio between bin boundaries was 1.3. We chose logarithmic binning because the upper limit of C_{V2} at shorter ISIs changes much more rapidly than at longer ISIs. Shading represents standard error of the mean. KO = knockout; ISI = interspike interval; lOFC = lateral orbitofrontal cortex; WT = wild type.

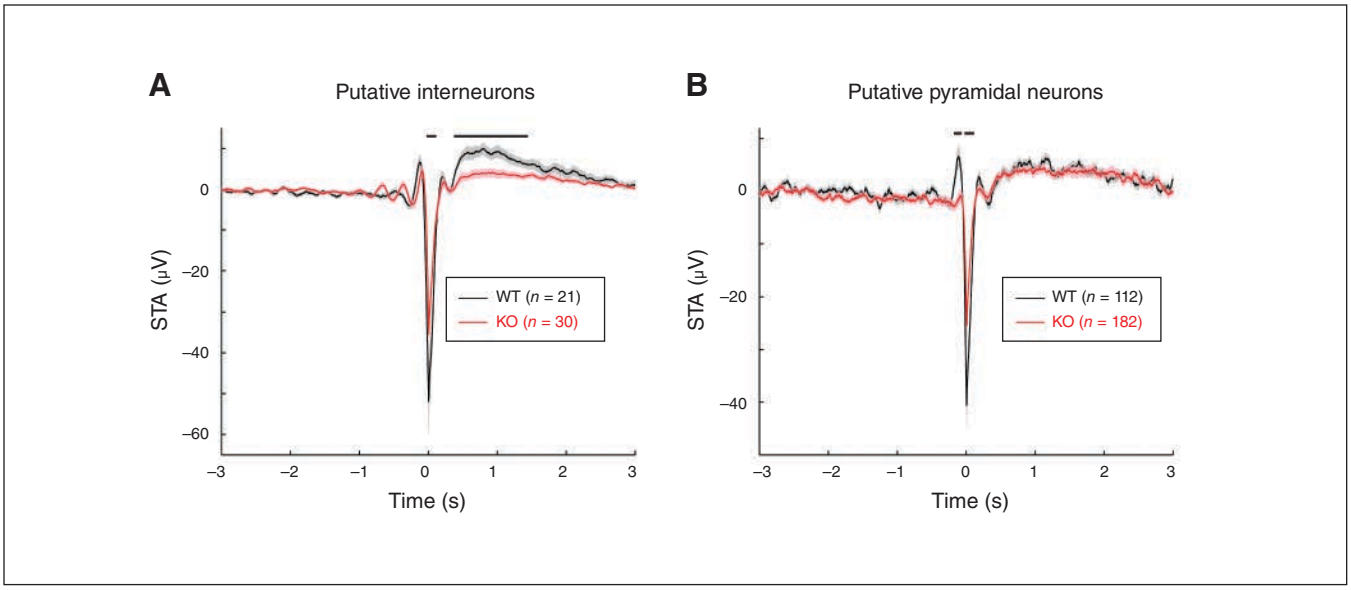

Fig. 6: Comparisons of lOFC ensemble synchronization in WT (black) and *Sapap3* KO (red) mice. (**A**) Averaged STA of LFP of lOFC putative interneurons. (**B**) Average STA of LFP of lOFC putative pyramidal neurons. Black horizontal bars indicate ranges with significant difference between WT and *Sapap3* KO mice. Shading represents standard error of the mean. KO = knockout; LFP = local field potential; lOFC = lateral orbitofrontal cortex; STA = spike-triggered average; WT = wild type.

specific neuronal types. The increased bursting activity of putative pyramidal neurons we found could cause this increase in FosB expression. The discrepancy may also result from the different OCD animal models used (*Sapap3* KO v. *Slitrk5* KO), different cell types (putative pyramidal neurons v. all cells) and different subregions of the OFC examined (lOFC v. the entire OFC). The medial and lateral OFC perform different functions, such as processing positive versus negative valence.[35,36] The activity of these 2 subregions may be differentially affected in OCD mouse models, giving rise to inconsistent results when examining the lOFC versus the entire OFC.

Although the mean firing rate of lOFC pyramidal neurons was similar between WT and *Sapap3* KO mice, their activity pattern changed dramatically in *Sapap3* KO mice. Specifically, lOFC pyramidal neurons exhibited significantly increased bursting activity with short intra-burst ISI (< 10 ms). Overall activity pattern determines neuronal function, not merely firing rate. Bursts with short intra-burst ISI have special importance in brain function. Compared with tonic firing, burst firing is more reliable for eliciting synaptic transmission, provides stronger output, enhances signal-to-noise ratio and facilitates synaptic plasticity.[43] The increased bursting activity of lOFC pyramidal neurons may provide pathologic stronger output through the OFC–striatal circuit and drive increased activity in the striatum of *Sapap3* KO mice, as reported in previous studies.[37,58] Another study suggested that sustained increase in synaptic strength from the OFC pyramidal neurons to ventral striatum synapses led to increased repetitive behaviour in mice.[59] Many clinical and animal studies have suggested that hyperactivity in the cortico–striato–thalamo–cortical circuit is associated with OCD pathology.[2,3,10,11] The enhanced bursting activity of lOFC pyramidal neurons may drive hyperactivity in the cortico–striato–thalamo–cortical circuit and contribute to OCD-like behaviours in *Sapap3* KO mice. A recent study reported that a depression-like state depended critically on a bursting mode of firing in the lateral habenula in rats and mice.[60] The bursting activity of neurons in the lateral habenula was greatly enhanced in rat and mouse models of depression, and reducing their bursting activity elicited antidepressant effects. Increasing bursting activity by optogenetics was sufficient to induce depression-like behaviours. This study suggested that abnormal bursting activity in a single nucleus could lead to symptoms relevant to a psychiatric disorder. Abnormal bursting activity has not been studied in people with OCD or in animal models. In a future study, we plan to investigate whether fluoxetine can suppress the abnormal bursting activity of lOFC pyramidal neurons, accompanied by alleviation of OCD-like behaviours in *Sapap3* KO mice. We also plan to investigate whether artificially increasing the bursting activity of lOFC pyramidal neurons can induce symptoms relevant to OCD.

Limitations

One limitation of this study was that we examined activity pattern alterations of lOFC neurons only when the mice were resting; we did not examine grooming-related activity. As an association cortex, the OFC performs complex cognitive and executive brain functions. Its neuronal activity is modulated by many behaviours, including grooming-associated movements themselves. To exclude such confounders, we compared neuronal activity between WT and *Sapap3* KO mice, recorded only when the mice were stationary. To collect enough data during stationary periods, we applied a head-fixed configuration instead of a free-behaviour configuration, because mice stayed stationary for most of the time during head-fixed recording (percent of time spent stationary, mean ± SEM: WT 90.1 ± 2.3%, KO 90.8 ± 3.5%). In contrast, mice usually moved most of the time during free-movement recording (including both locomotion and fine movement), leaving few stationary periods for effective data analysis. Comparing resting neuronal activity between WT and *Sapap3* KO mice required very high recording and spike-sorting quality. We applied very strict criteria for spike sorting and included only very well isolated single units to ensure the accuracy of our results. Specifically, the cluster of the isolated single unit had to be well separated from other clusters without any overlapping of the edge, because edge overlapping in spike sorting results in contamination by other units or loss of spikes of the isolated unit. Either situation can significantly affect the measurement of firing rate and firing variability. Another limitation was that we investigated functional abnormalities without establishing causality for these functional changes and the OCD-like behaviours. Our reasons were as follows. First, this was a pioneering in vivo electrophysiological study of OFC dysfunction in an OCD animal model; characterizing the functional abnormalities was the first step and can serve an important foundation for future work. Second, artificially generating bursts with very short intra-burst ISI without changing the mean firing rate is very challenging; we have not found an appropriate way to manipulate the oscillation power of broad frequency bands in the LFP without changing the mean firing rate of excitatory neurons. Nevertheless, causal manipulation is definitely a key future experiment that may require us to develop new manipulation techniques.

Conclusion

Here, we have provided the first direct in vivo electrophysiological evidence of detailed functional alterations in different neuronal types and local network dysfunction in the lOFC in phenotypes relevant to OCD. These findings advance our understanding of the neuropathophysiology and circuitry mechanisms that underlie OCD-like behaviours, and may help generate and refine hypotheses for further investigation. For example, the LFP alterations and increased bursting activity may be useful biomarker candidates for further examination in people with OCD.

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Competing interests: None declared.

Contributors: H. Lei, Q. Xu and G. Feng designed the study. H. Lei, J. Lai and X. Sun acquired the data, which H. Lei and J. Lai analyzed. H. Lei and G. Feng wrote the article, which all authors reviewed. All authors approved the final version to be published and can certify that no other individuals not listed as authors have made substantial contributions to the paper.

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