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Insights about Striatal Circuit Function and Schizophrenia from a Mouse Model of D2 Receptor Upregulation

Eleanor H. Simpson[1,2,*] and **Christoph Kellendonk**[3,4]

[1]Department of Psychiatry, Columbia University

[2]Neurobiology and Behavior, New York State Psychiatric Institute

[3]Department of Pharmacology, Columbia University

[4]Molecular Therapeutics, New York State Psychiatric Institute

Abstract

The dopamine hypothesis of schizophrenia is supported by a large number of imaging studies that have identified an increase in dopamine binding at the D2 receptor selectively in the striatum. Here we review a decade of work using a regionally restricted and temporally regulated transgenic mouse model to investigate the behavioral, molecular, electrophysiological, and anatomical consequences of selective D2 receptor upregulation in the striatum. These studies have identified new and potentially important biomarkers at the circuit and molecular level that can now be explored in patients with schizophrenia. They provide an example of how animal models and their detailed level of neurobiological analysis allow a deepening of our understanding of the relationship between neuronal circuit function and symptoms of schizophrenia, and as a consequence generate new hypotheses that are testable in patients.

Keywords

Schizophrenia; Dopamine; D2 Receptor; mouse model; striatal circuit function; Negative Symptoms

Classifications

Animal Models; Basic Neuroscience; Behavioral science; Schizophrenia/Psychosis; Electrophysiology

[*]Corresponding author: Eleanor H. Simpson, New York State Psychiatric Institute, 1051 Riverside Drive, Unit 87, New York, New York 10032, Es534@columbia.edu, +1-646-774-6835.

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What is known about abnormalities in the dopamine system in schizophrenia

The dopamine hypothesis of schizophrenia originally formulated by van Rossum in the 1960s postulated that “overstimulation of dopamine receptors could be part of the etiology” of schizophrenia (1). The hypothesis was supported by Philip Seeman and Solomon Snyder, and their colleagues, seminal findings in the 1970s that there is an inverse relationship between the therapeutic dose of antipsychotic medication and its binding affinity for dopamine receptors. These findings imply that efficacy of antipsychotic medication is directly proportional to the degree to which the medication engages dopamine receptors (2) (3).

In the last 20 years human imaging studies have consistently found alterations in the striatal dopamine system. At the presynaptic level increased striatal uptake of ^{18}F-fluorodopa (or L-β-^{11}C-DOPA) and increased amphetamine-induced dopamine release have been measured in patients in over 10 independent studies (4). Changes in presynaptic dopamine are thus among the most reliably replicated findings observed in patients with schizophrenia. Alterations in presynaptic dopamine appear to occur early on in the disease process as they are observed in prodromal subjects that are at high risk for conversion (5)(6). Surprisingly, high resolution imaging revealed that the largest effect size of these abnormalities is not in the limbic striatum, as has been postulated for many years, but rather in the associative striatum (4; 7). This finding has significant implications for relating dopamine dysfunction to specific symptoms of the disease because the limbic and associative areas of the striatum are involved in anatomically and functionally distinct cortico-striatal circuits. The limbic striatum receives input from the ventromedial prefrontal cortex (vmPFC) and this connection is involved in affective-emotional processing. The associative striatum receives dense input from the dorso-lateral prefrontal cortex (dlPFC) and is important for cognition (8). It is currently unknown how differential changes in dopamine function occur in different compartments of the striatum. Potential factors include presynaptic changes that are pathway specific or cellular changes that affect dopamine release locally within the striatum.

At the postsynaptic level, imaging studies have identified an increased density of D2Rs in the striatum. In 1998 Marc Laruelle performed a meta-analysis of 13 different imaging studies and calculated a 12% increase in striatal D2R density in drug-naïve or drug-free patients (9). However, a more recent meta-analysis questions whether the increase in D2R density is a result of the disorder or whether it is induced by antipsychotic treatment (4). Dopamine depletion experiments have additionally reported increased basal occupancy of striatal D2Rs in drug-free patients that not only correlates with positive symptoms but predicts their response to antipsychotic medication, thus suggesting a tight relationship between D2R occupancy in the striatum and psychosis (10; 11). In contrast to the positive correlation between increased striatal dopamine and positive symptoms, the severity of negative symptoms has been correlated with low dopamine activity in the ventral striatum (7). This finding suggests that while dopamine tone is consistently found to be increased at the level of the whole striatum, subregional analyses may be highly informative about specific symptoms of the disease.

In comparison to the *increase* in dopamine that has been identified at the level of the whole striatum in patients with schizophrenia, a *decrease* in dopamine in the cortex has long been proposed as a potential mediator of the cognitive symptoms of schizophrenia. A series of early, pioneering functional imaging studies determined that when patients performed a working memory task, no significant increase in PFC activity could be observed (12–14). This contrasted with healthy controls in which the same task increased cerebral blood flow in the PFC (12–14). The third study of this series found that the degree of dlPFC activation in patients performing a working memory task was inversely correlated with the concentration of dopamine metabolites in the cerebrospinal fluid (14). More direct evidence of a decrease in cortical dopamine comes from a recent imaging study using a newly developed high affinity PET tracer showing that amphetamine-induced dopamine release is lower in the cortex of patients compared to healthy controls (15). Because dopamine plays a critical role in several prefrontal cortical dependent cognitive functions, including working memory, associative learning, cognitive flexibility and attention (16), this finding suggests that a sub-optimal level of cortical dopamine release could be contributing to some of the cognitive deficits observed in patients with schizophrenia.

Using D2R overexpressing mice to explore the dopamine hypothesis of schizophrenia

In addition to imaging studies supporting the dopamine hypothesis, 70–80% of patients respond to dopamine D2 receptor antagonists (reviewed in (17)), further implicating D2 receptor overstimulation in the pathophysiology of schizophrenia for a majority, if not all, patients. Animal models provide a powerful tool in which invasive and terminal procedures can be used to probe possible pathophysiological mechanisms that contribute to dysregulation of the dopamine system and lead to symptoms of the disease.

To mimic the increase in density and occupancy of striatal D2Rs in patients, we previously generated mice in which D2Rs are selectively overexpressed in the striatum beginning in late embryonic development (18). Transgene expression is not only spatially restricted but also temporally controlled by using an artificial promoter system, the tetracycline transactivator system (for detailed explanation of this transgenic system, see (19). This Bi-transgenic system allows for switching off the D2R transgene by supplementing the mice's diet with the tetracycline analogue, doxycycline. *In situ* hybridization determined that transgene expression is restricted to striatal projection neurons with no expression in cholinergic interneurons and dopaminergic midbrain neurons, (18) (20). An E*x-vivo* ligand-binding assay further determined that fortuitously, the level of increase in receptor expression is comparable to that measured in patients, around 15% (Fig 1D). Single cell PCR methods determined that 33% of striatal output neurons express the transgene. Striatal projection neurons are divided into two pathways, striatopallidal and striatonigral neurons, 40% and 26% of which, respectively, express the transgene (21).

Despite its limitations that are inherent to any rodent model studying human disorders, D2R-OE mice have been very informative for schizophrenia research. Here, we will summarize the findings that have been made over the last 10 years using D2R-OE mice, with an

emphasis on understanding how striatal D2Rs regulate circuit function and behaviors that are relevant for schizophrenia.

Cognitive deficits in schizophrenia can be modeled in rodents

Patients with schizophrenia may display positive, negative and cognitive symptoms. Although the positive symptoms are the most characteristic symptoms of the disorder it is the degree of the cognitive and negative symptoms that predicts long-term prognosis (22–24). Cognitive symptoms predate the onset of psychosis, range in severity from moderate to severe and some of the cognitive deficits can be studied in rodents.

Over the last few decades, cognitive neuroscientists have generated a wealth of literature on the specificity of cognitive dysfunctions that occur in schizophrenia including attention (25), working memory (26) and executive function (27). Detailed examinations have identified the component sub-processes involved in these cognitive deficits. For example, in the case of working memory, evidence suggests that the maintenance of information is not critically disrupted in schizophrenia. Instead, the ability to manipulate information within working memory is more severely affected (28; 29) Working memory capacity (the maximum amount of information that can be held) is also significantly reduced (30). Because experimental psychologists have developed cognitive assays for rodents that selectively measure specific cognitive domains, we have been able to apply behavioural assays to D2R-OE mice that measure cognitive domains that are specifically relevant to schizophrenia (25–27).

Table 1 summarizes cognitive tests performed on D2R-OE mice, the homologous tasks used for patients, and the reported outcomes in each case. D2R-OE mice showed deficits in conditional associative learning, decreased temporal precision and a deficit in the acquisition of a spatial working memory tasks whereas performance in a spatial reference memory was unimpaired (18). The nature of the acquisition deficit in the spatial working memory task is unclear and may not represent a deficit in memory (the retention and recall of information), given that maintenance of information in working memory appeared normal in a two choice visual discrimination task. D2R-OE mice performed poorly in the conditional associative learning task due to cognitive interference from the previous trial (31), therefore, it is possible that also in the delayed non-match to sample T-maze working memory task the observed deficit was due to interference from the previous trial.

D2R-OE mice do not show a deficit in PPI (18), a clinical sign that is prevalent in several disorders, including schizophrenia (45; 46) and can be improved by some antipsychotic medications (47). That D2R-OE mice do not show PPI deficits may suggest that the model recreates an altered pathology that is downstream of enhanced pre-synaptic dopamine release. For a more detailed discussion of modeling cognitive endophenotypes of schizophrenia in mice, see (48).

Because we used the Bi-transgenic system, we were able to investigate the temporal relationship between striatal D2R overexpression and the cognitive phenotypes. We found that switching off the transgene once the mice had reached adulthood does not ameliorate

the deficit in conditional associative learning or the deficit in acquiring the spatial working memory task (18; 31), and resulted in only partial improvement in timing (20; 38). These findings suggest that an increase in striatal D2R density or occupancy may not only be important for positive symptoms but could also be linked to cognitive symptoms. It is surprising, since D2R antagonists do not reverse the cognitive deficits in patients (49). One possibility is that antipsychotic medications are ineffective at treating cognitive symptoms because they are given too late. Diagnosis typically occurs around the second decade of life, this may be long after alterations in D2 receptors has resulted in persistent brain abnormalities that can no longer be reversed by treatment with D2R blockers. Future studies must investigate the potential benefits as well as the risks of targeting D2Rs early on in individuals at high risk for schizophrenia

Negative symptoms of schizophrenia can be modeled in rodents

Negative symptoms of schizophrenia include deficits in motivation, emotional responsiveness, socialization and speech. Understanding the underlying pathophysiology of negative symptoms is a high priority because negative symptoms like cognitive deficits are highly correlated with functional outcomes. In particular, amotivation/apathy has been shown to strongly predict psychosocial functioning (24). The D2R-OE mouse model displays deficits in motivation. In the course of extensive cognitive testing, we identified a significant difference in the rate of responding for reinforcement (typically lever pressing) of D2R-OE mice compared to their control littermates. To determine if this decrease in response vigor was related to a deficit in motor abilities, sensitivity to fatigue, or an indifference to the food reinforcers being earned in the tasks, we performed a series of studies which led to the conclusion that D2R-OE mice are not impacted in any of those ways (20; 50; 51) Instead the mice, like patients, express a deficit in incentive motivation.

There are a large number of component behavioral processes involved in motivated behavior. These include evaluation and encoding of information about current, as well as future positive and negative consequences. Such consequences include both benefits (meeting physiological and psychological needs) and costs (effort expenditure, time, discomfort etc). All such information must be valued and counter-valued (in a cost-benefit analysis), and is subject to typical learning factors(52). Determining which of these processes are disrupted in schizophrenia has been the focus of much recent research (53). Many studies suggest that the motivational deficit in patients with schizophrenia is not due to an inability to experience pleasure in the moment as hedonic reaction appears intact (54). Instead, the motivation deficit represents a reduced capacity for anticipating future pleasure resulting from goal-directed action. This diminished anticipation appears to be a consequence of an inability to accurately represent the expected reward values of actions (55; 56) and also impairment in the allocation of effort in the pursuit of reward (57; 58).

A number of rodent paradigms that measure aspects of amotivation and apathy related behaviours have been developed (59–61) and the application of such assays has revealed a striking similarity between the incentive motivation phenotype in D2R-OE mice and patients. D2R-OE mice exhibit normal hedonic reactions to appetitive reinforcers and show a reduced sensitivity to the value of future outcomes (50). D2R-OE mice also show a

reduced allocation of greater effort for more highly preferred rewards, compared to their control littermates (50). Although the assays used in mice and patients to measure components of motivation differ in the sensory modalities and rewards used, the findings are convergent, suggesting that an acute increase in striatal D2 receptors may underlie the deficit in anticipatory motivation in patients (table 2).

Not only does the specific type of motivational deficit appear to be highly similar in the D2R-OE mice and patients, in both the mice and patients, systemic pharmacological ***blockade*** of D2Rs with antipsychotic medication haloperidol, does not improve motivation (51). Because ***removing*** the excess transgenic D2 receptors by switching off the transgene did improve motivation, it suggests that the mouse model provides a tool for investigating novel treatment strategies that are downstream of striatal D2 receptor as opposed to D2Rs in other areas of the brain. Indeed, the model has been used to identify a 5-HT2C receptor ligand (SB242084) that enhances goal directed action in both D2R-OE and wild-type mice (38; 51; 72). Earlier studies have suggested that this drug may increase impulsivity in some conditions (73; 74), however using a novel behavioural assay, we determined that SB242084 treatment can enhance goal-directed efficiency, even when sustained responses are required to obtain rewards (72).

Not all cognitive and negative symptoms are readily separable in patients, or disease models

There has been much debate over whether some of the negative symptoms of schizophrenia, such as decreased motivation, should really be considered a cognitive symptom, since they are due to deficits in information processing (75). It is also the case that in some tests of cognition a lack of motivation may account for a proportion of the poor performance (76).

In fact, it is the interactions between motivational and cognitive deficits that is implicated in producing functional impairments in patients (77). Because this interaction is not well understood at either the behavioral or neural level, we developed a procedure for mice in which a cognitive measure, sustained attention, is modulated by a motivationally relevant signal that predicts reward probability on a trial-by-trial basis (42). We found that whereas in control mice attention was modulated by reward-related cues, in D2R-OE mice this modulation was absent. These results indicate that deficits in motivation impair the ability to use reward-related cues to recruit attention. In a separate study, we employed a cognitive timing task that allowed us to detect changes in cognitive performance that are not influenced by general activity or arousal factors such as the speed or persistence of responding. This approach allowed us to manipulate motivation and measure the impact on cognitive performance. We found that manipulating motivation genetically, pharmacologically and psychologically (by increasing reward value), all resulted in enhanced temporal cognition (38). Together, if generalized to patients with schizophrenia these results suggest that addressing motivational impairments in patients could be critical to achieving substantive cognitive and functional gains, as recently proposed (78).

Negative symptoms of schizophrenia include deficits in social interaction that can also be modeled in rodents

Another core negative symptom is deficits in social behaviors that tend to emerge prior to the full blown onset of the disease. Specifically, by the time of adolescence, social withdrawal becomes a fairly sensitive, if not specific, marker of schizophrenia (79). To determine if the increase in striatal dopamine observed in patients with schizophrenia might play a role in the emergence of deficits in social interaction, we carried out a multimodal characterization of social behavior at different development time points (juvenile, adolescent and adult) in control and D2R-OE mice (80). This characterization included measures of passive and active physical interactions as well as ultrasonic vocalizations. D2R-OE mice show a reduction in social interaction that emerges in adolescence and becomes more pronounced in adulthood. These results suggest that striatal dopamine dysfunction plays an important role in the development of social behavior that may be relevant to schizophrenia.

Neuronal mechanism by which striatal D2R upregulation impair cognitive behaviors

The finding that up-regulation of D2Rs in the striatum would lead to acquisition deficits in spatial working memory and conditional associative learning tasks was unexpected at the time because acquisition and performance of these tasks is critically dependent on the prefrontal cortex (18; 31). Subsequently, studies in humans have shown correlations between striatal dopamine function and prefrontal activity during working memory performance (81–83). D2R-OE mice are therefore useful tools to investigate mechanisms that underlie functional interactions between striatum and cortex. In this context we observed that D2R up-regulation in the striatum led to a decrease in dopamine turnover and an increase in D1R sensitivity in the prefrontal cortex (18) (Figure 1). Disrupted cortical D1R activation may be responsible for the cognitive phenotype in D2R-OE mice as a tight relationship has been described between D1R activation in the cortex and cognition, especially working memory (84; 85), More recently, we have discovered a decrease in burst firing of dopaminergic neurons of the ventral tegmental area (VTA) in D2R-OE mice that cannot be reversed by normalizing striatal D2R expression (86). A decrease in the burst firing of meso-cortical VTA neurons is expected to reduce phasic dopamine release in the cortex. Therefore, it is possible that D2R upregulation in the ventral striatum, via polysynaptic projections to the VTA, alters cortical dopamine turnover, leading to deficits in PFC dependent functions.

The observation that both, cognitive deficits and VTA burst firing are not reversed by switching off the transgene in the adult animal again suggests that antipsychotic medication may not ameliorate cognitive deficits because they are given too late. Increased striatal D2R activity during development may have altered VTA function in a persistent, irreversible way. Our observation, if extrapolated to humans, stresses the importance of early diagnosis of the disorder and suggests that cognitive outcomes may be significantly improved with early pharmacological, as well as psychosocial interventions, a notion that has been proposed before (87).

Interestingly, the decrease in dopamine neuron burst firing in the VTA of D2R-OE mice was associated with a decrease in mRNA expression of NMDA receptor subunits NR1 and NR2B in VTA dopamine neurons (86). Because NMDA receptors are important for burst firing, downregulation of NR1/NR2B may indeed underlie the observed changes in firing patterns (88). This would suggest that pharmacological enhancement of NMDA receptor function could be an effective therapeutic strategy for enhancing cognition.(89). Indeed, enhancing NMDA receptor function has been attempted by inhibiting the Glycine transporter (90). Phase III trials of this drug did however not remediate motivational (or cognitive) deficits in patients, suggesting that a different pharmacological approach, that is either cell or receptor type specific may be required. The finding that striatal D2R upregulation affects cortical dopamine function may have implications with regard to the etiology of the disorder. The long prevailing hypothesis has been that a presumed cortical hypofunction comes first and leads to the increase in striatal dopamine release and D2R occupancy observed in schizophrenia. Alterations in striatal dopamine and cortical activity seem to coexist in patients or subjects with high risk for schizophrenia (5; 91) though see (92). However, it is unknown which area is affected first in patients, the cortex or the subcortical dopamine system. Animal models have shown that cortical hypofunction can lead to a hyperactive dopamine system (93–95). The D2R-OE mice suggest that the opposite directionality is also possible where an increased in striatal D2Rs leads to changes in cortical dopamine function.

Further indications for altered prefrontal function in D2R-OE mice comes from an electrophysiological study that showed that D2R-OE mice display decreased GABAergic transmission in the cortex. This decrease in GABAergic transmission was reversed when the transgene was switched off, suggesting that it could be related to the motivational deficits of D2R-OE mice rather than their cognitive impairments (96).

Neuronal mechanism by which D2R upregulation alters striatal circuit function

As discussed, the cognitive deficits in D2R-OE mice are due to irreversible developmental changes whereas the deficit in motivation is largely rescued by switching off the D2R transgene (20; 39; 50). Strikingly, tonic firing of dopamine VTA neurons is reduced in D2R-OE mice and unlike the decrease in burst firing, the reduction in tonic firing was rescued after switching off the D2R transgene (86). Although the dopamine neurons with altered firing rates were not anatomically traced, based on location within the VTA, they are likely to include neurons that project to the NAc. Therefore, a decrease in tonic VTA firing may change ambient dopamine concentrations in the NAc. The coexisting phenotypes of decreased motivation and reduced tonic DA firing in D2R-OE mice is consistent with the observations that local dopamine levels in the NAc modulate incentive motivation, with dopamine depletion decreasing motivation (97; 98) and increased dopamine enhancing motivation (99).

In addition to identifying changes in the activity of dopamine neurons in D2R-OE mice, we have also identified changes in striatal circuitry downstream of dopamine neuron functions.

We measured the physiological properties of striatal projection neurons in D2R-OE and control mice. We found that excitability of striatal projections neurons was enhanced in D2R-OE mice, due to a down-regulation in the expression of inward-rectifying potassium (Kir2) channels (21). Remarkably, this downregulation in Kir function had a dramatic impact on the morphology of the striatal output pathways, and as a consequence, on the function of those pathways (21).

Striatal projection neurons are organized into the direct and indirect projection pathways. The direct pathway predominantly expresses D1Rs and projects monosynaptically to the basal ganglia output nuclei, the internal segment of the globus pallidus (GPi) and the substantia nigra pars reticulata (SNr). In contrast, the indirect pathway predominantly expresses D2Rs and modulates GPi/SNr output through a polysynaptic circuit via the external segment of the globus pallidus (GPe) (100). In the classical model of basal ganglia circuitry both pathways are functionally opposing with regard to thalamo-cortical activation (101). The direct “Go” pathway dis-inhibits thalamo-cortical activity whereas this is inhibited by the indirect “NoGo” pathway. Although classical descriptions of these pathways suggest that they are anatomically segregated, this is not accurate. Several tracing studies have shown that within the dorsal striatum, the majority of direct pathway neurons that project to the midbrain also project to the GPe via axon collaterals (102–105). Since these collaterals “bridge” the direct with the indirect pathway we recently termed them bridging collaterals (106). In the ventral striatum there may be even less segregation as the functional connectivity between direct pathway and the “indirect” pallidum (here: ventral pallidum) is even stronger than it is in the dorsal striatum (107).

Surprisingly, the axon collaterals, which bridge to the GPe are extremely plastic in the adult animal (106). Moreover, their density is regulated by D2R levels in the adult animal via regulation of Kir2 channel function (106). Genetic up-regulation of striatal D2Rs (as in D2R-OE mice) enhances the density of bridging collaterals (Figure 1) whereas genetic down-regulation leads to a gene dosage-dependent decrease in their density (106). As a consequence, the functional balance between the two pathways is altered leading to an inefficient direct pathway as can be observed after optogenetic stimulation of the direct pathway. Stimulation of the direct pathway in D2R-OE mice does not result in the same level of locomotor activation as in control animals (106; 108). Switching off the D2R transgene as well as chronic treatment with haloperidol for 2 weeks reversed the anatomical changes as well as the changes in excitability, Kir2 function and direct pathway inefficiency (106).

Behavioural consequences of altered striatal circuit function in D2R-OE mice

Although we are currently lacking the much needed tools to reliably measure behavioural correlates of positive symptoms in mice, it is possible that the physiological and anatomical abnormalities in striatal circuitry observed in D2R-OE mice are relevant to the positive symptoms of schizophrenia. We hypothesize this because, as previously mentioned, striatal D2R occupancy in the striatum and amphetamine-induced dopamine release correlate with

positive symptom severity and predict antipsychotic treatment response (10; 11), indicating a tight relationship between striatal dopamine and psychosis. Full efficacy with antipsychotic medication is achieved after days to weeks of treatment (109), a duration that is comparable with haloperidol-induced retraction of bridging collaterals in mice (106). It is therefore possible that drug-naïve patients that exhibit an increase in density and occupancy of striatal D2Rs also have an increase in bridging collaterals in direct pathway striatal neurons, which contribute to the generation of positive symptoms which are relieved after chronic treatment with antipsychotic medication, treatment which normalizes bridging collateral density. Future longitudinal imaging studies of patients before and after treatment will allow for testing this hypothesis.

In addition to these changes in the anatomy and functioning of the striatal output pathways it is likely that cortico-striatal plasticity may be altered in D2R-OE mice e.g. by alterations in retrograde endocannabinoid signaling or other mechanisms (110). Such alterations may well contribute to the described behavioral deficits. The physiological and anatomical alterations observed in D2R-OE mice are summarized in table 3.

Conclusions

In summary, by modelling a single, well replicated pathophysiological abnormality observed in patients with schizophrenia in the laboratory mouse, we have been able to expand our understanding of how striatal D2 receptors impact striatal circuity and behavioral abnormalities suffered by patients. We have identified new and potentially critical biological markers that were not considered a priori, and must now be evaluated in patients. Given the serious nature of the disease and the longstanding need to discover safer and more effective treatments for patients, the use of animal models such as the one described here provide valuable tools for understanding the biological basis of schizophrenia.

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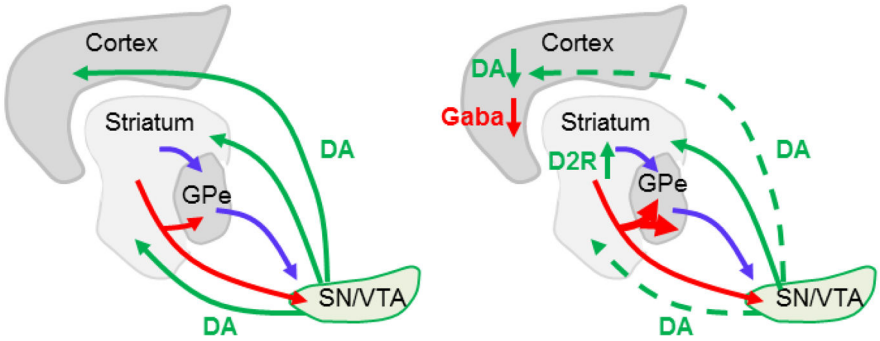

Figure 1. Circuit abnormalities induced by striatal D2R upregulation

Left: Cortico-striatal circuitry in wild-type mice. The striatum is the input area of the basal ganglia receiving projections from cortex and thalamus. Via two functional opposing pathways, the direct (red) and indirect (blue) pathways it projects to the substantia nigra (SN) and ventral tegmental area (VTA) output nuclei of the basal ganglia. Dopaminergic neurons in the SN and VTA modulate activity in cortex, dorsal and ventral striatum.

Right: Upregulation of D2Rs in the striatum led to several changes in this circuitry: 1) It enhanced the density of direct pathway collaterals in the GPe thereby affecting the functional balance between both pathways. 2) It decreases activity in dopaminergic neurons projecting to the cortex and ventral striatum but not to the dorsal striatum. 3) It decreases GABA transmission in the cortex.

Table 1

Cognitive Domains Affected in D2R-OE Mice and Patients With Schizophrenia

Cognitive Domain	**Test(s) applied in Humans**	**Outcome in patients with Schizophrenia (references)**	**Test applied in mice**	**Outcome in D2R-OE mice (reference)**
Conditional Associative Learning	Visual conditional associative learning tests	**Deficit in learning the task** (32) **and** (33)	Auditory conditional associative learning tests	**Deficit in learning the task.** (31)
Inhibitory control	Visual Go/NoGo learning task	**Reduced Response accuracy due to omitted Go trials** (34)	Auditory Go/NoGo Task	**Reduced response accuracy due to interference from prior trial** (31)
Reversal Learning	Visual discrimination task	**Deficit in simple discrimination and reversal trials** (35)	Odor/texture discrimination task	**Deficit in reversal trials**-(36)
Time perception	Auditory temporal bisection procedure	**Decreased temporal precision** (37)	Auditory temporal bisection procedure	**Decreased temporal precision** (38; 39)
Time production	Self-paced time production task	**Decreased temporal precision** (40)	Peak Interval timing procedure	**Decreased temporal precision** (20)
Spatial Working Memory	oculomotor and haptic delayed-response tasks	**Deficits in performance at 2 time delays.** (41)	Non match to sample T-maze task	**Deficit in acquisition** (18)
Maintenance of information in Working memory	A visual, color based retention task.	**Normal-**(30)	Two choice visual discrimination task	**Normal** (42)
Problem Solving/Executive Function	Spatial mazes (Selected by MATRICS)	**Poor performance** (43)	Puzzle Box digging task	**Impaired problem solving** (44)

Table 2

Motivational Deficits in D2R-OE Mice and Patients With Schizophrenia

Component of motivation	Test(s) applied in Humans	Outcome in patients with Schizophrenia (references)	Test applied in mice (Reference for test validation)	Outcome in D2R-OE mice (references)
Hedonic Reaction	Experience sampling and self-report measure of anticipatory and consummatory pleasure. Measurement of hedonic response to sucrose.	A deficit in anticipatory but not consummatory pleasure (54). Normal hedonic reaction to sucrose solutions across a range of concentrations (62).	Sucrose preference (63) and positive affective orofacial reactions to sucrose (64)	Normal sucrose preference and normal orofacial “liking” reactions to sucrose (50).
Persistence in effort expenditure	Progressive Ratio schedule of reinforcement for money	Deficit in performance (65), No group deficit but performance correlates with negative symptoms (66)	Progressive Ratio schedule of food reinforcement (67)	Deficit over several different ratios (20)(51)
Allocation of Effort for rewards	effort-based decision-making for money (EEfRT)	Less optimal decision making (a bias for easier to obtain but smaller rewards) (58) (68)	effort-related choice procedure (69)	Diminished effort allocation for preferred rewards (50)
Reward value based decision-making	Probabilistic decision-making task	Impaired value-based decision-making (70)	Concurrent choice of operant schedules (71)	reduced sensitivity to the value of future outcomes (50)

Table 3

Physiological and Anatomical Alterations in D2R-OE Mice

Brain Region	With D2R transgene ON	After D2R transgene switched OFF	Ref.
STRIATUM	15% increase in D2R membrane binding	Normalized	(18)
	Reduced dopamine stimulated adenylate cyclase activity	Not tested	(18)
	Enhanced excitability and decreased dendritic arborization of projection neurons	Normalized	(21)
	Decreased glucose metabolism *in vivo*	Normalized	(18)
	Decreased striatal volume	Partially reversed	(21)
GLOBUS PALLIDUM	Enhanced density of direct pathway collaterals (bridging collaterals)	Normalized	(106)
	Enhanced inhibition of pallidal activity after striatonigral stimulation *in vivo*	Not tested	(106)
VTA	Decreased tonic firing of VTA dopamine neurons *in vivo*	Normalized	(86)
	Decreased phasic firing of VTA dopamine neurons *in vivo*	Not reversed	(86)
	Decreased expression of NMDA receptor subunits NR1/NR2B in VTA dopamine neurons	Not tested	(86)
CORTEX	Increased D1R sensitivity in mPFC In Vivo	Reduced sensitivity (opposite phenotype)	(18)
	Increased glucose metabolism in vivo (motor and sensory cortices)	Normalized	(18)
	Increased excitatory transmission in mPFC slices	Normalized	(96)
	Reduced inhibitory transmission in mPFC slices	Normalized	(96)
	Reduced D2R sensitivity in mPFC slices	Not tested	(96)