Applications of the Neonatal Quinpirole Model to Psychosis and Convergence upon the Dopamine D_2 Receptor

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Abstract This mini review focuses on the importance of the dopamine D_2-like receptor family and its importance in psychosis. Past findings from this laboratory along with collaborators have been that neonatal quinpirole (a dopamine D_2-like receptor agonist) results in increases in dopamine D_2 receptor sensitivity that persists throughout the animal's lifetime. Findings from this model have been shown to have particular application and validity to schizophrenia, but may have broader implications toward other psychoses, which is reviewed in the present manuscript. In the present review, we also highlight other models of psychoses that have been centered on the subchronic administration of quinpirole to rats in order to model certain psychoses, which has uncovered some interesting and valid behavioral findings. This review highlights the importance of the combination of behavioral findings and neurobiological mechanisms focusing on neural plasticity in discovering underlying pathologies in these disorders that may lead to treatment discoveries, as well as the value of animal models across all psychoses.

Keywords Dopamine D_2 receptor · Neonatal · Quinpirole · D_2 receptor supersensitivity · Psychosis

Contents

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Curr Topics Behav Neurosci (2016) 29: 387–402
DOI 10.1007/7854_2015_394
Published Online: 16 October 2015

1 Introduction

Approximately 25 years ago, Dr. Richard Kostrzewa and colleagues demonstrated that neonatal treatment of rats with quinpirole, a dopamine D_2/D_3 agonist, produces an increase in dopamine D_2-like receptor sensitivity (Kostrzewa and Brus 1991), and later demonstrated this change persisted throughout the animal's lifetime (Kostrzewa 1995). This increase in dopamine D_2 receptor sensitivity is consistent with increases in D_2 receptor sensitivity in schizophrenia (Seeman et al. 2006), and over the past decade or so, our laboratory has utilized this model in studies aimed at elucidating mechanisms of substance abuse comorbidity in schizophrenia. First and foremost, however, the animal model we use must be valid. As stated by Monteiro and Feng (2015) in a recent review in *Biological Psychiatry*, 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). Findings from the neonatal quinpirole model have attained all three types of validity, in cognitive impairment and prepulse inhibition deficits (Brown et al. 2002; Maple et al. 2015), significant decreases of neurotrophic factors (Thacker et al. 2006; Brown et al. 2008) as well as decreases in expression of the regulator of G-protein signaling, RGS9 (Maple et al. 2007), and finally, olanzapine treatment alleviated cognitive impairment and decreases of neurotrophic factor protein (Thacker et al. 2006)—consistent with findings in schizophrenics (Cuesta et al. 2009; Rizos et al. 2010). This mini review will be directed toward the changes in the dopamine system that exist across several different psychoses including schizophrenia, and how these changes may have relevance to not only schizophrenia, but also other psychopathological disorders related to dysfunction in the dopamine D_2 receptor family. Finally, we will discuss animal models of each disorder and the possible applications from these findings toward the discovery of underlying neurobiological mechanisms that may lead to future treatments.

2 Schizophrenia

Patients suffering from schizophrenia exhibit an exceedingly broad behavioral syndrome that includes abnormal ideation, thought disorders, altered perception, sensory dysfunction, and often flattened affect (Picchioni and Murray 2007). A neural hallmark of the syndrome is generally proposed to be dopamine hyperactivity, specifically increases in dopamine D_2 receptor function although it is well established that serotonergic dysfunction (Selvaraj et al. 2014) and hypofunction at the glutamatergic *N*-methyl D-aspartate (NMDA) receptor (Cohen et al. 2015) are also present. The problem with modeling this disorder in rodents is that there are so many alterations in neural communication present as well as neuropathology, and there is no way to model all of these changes in one system. There have been several rodent models of schizophrenia that use acute administrations of pharmacological agents that produce robust increases in dopamine release and/or NMDA receptor hypofunction, such as amphetamine or phencyclidine (PCP; Robinson and Becker 1986; Janhunen et al. 2015). The primary issue with such a model is that there are not long-term changes in neurotransmission or plasticity that are known to be present in schizophrenia. The most prevalent rodent model of schizophrenia involves inducing neonatal hippocampal lesions to rats at postnatal day (P)7, which was developed by Barbara Lipska and Daniel Weinberger at NIMH (2002). As with many other models, this has yielded accurate and important behavioral data relative to both social and cognitive sequelae of the disorder (Sams-Dodd et al. 1997; Lyon et al. 2012). The primary weakness with the hippocampal lesion model is that there is no evidence of cell death in the hippocampus of human schizophrenics (Harrison 1999).

Regardless, increased activation of the dopamine D_2 receptor has been shown to play a major role in abnormal behaviors observed in schizophrenia (Nikam and Awasthi 2008). Additionally, all effective antipsychotic drugs are D_2-like receptor antagonists (Julien et al. 2015). Our laboratory and a collaborating laboratory have demonstrated that neonatal treatment with quinpirole, a dopamine D_2/D_3 agonist, administered to rats from postnatal days (P)1–11, 1–21, or 21–35 produces an increase in sensitivity of the D_2 receptor that is persistent through adulthood, and this is independent of a change in D_2 receptor number. Findings from our laboratory have shown that neonatal quinpirole alters the cholinergic system (ChAT), nerve growth factor (NGF), and brain-derived neurotrophic factor (BDNF) as well as genetic expression of these three proteins along with changes in expression of RGS9-2 in dopaminergic terminal areas of the brain (Maple et al. 2007). This suggests that hyperactivity of the dopamine system ultimately modulates other neurobiological systems that may also play a role in the disorder. All of these above effects are consistent with the known neuropathology of schizophrenia, which were reviewed recently in a special issue of *Developmental Neuroscience* (Brown et al. 2012, see Table 1).

Interestingly, one possible inconsistency is reflected in data from collaborators that demonstrated significant upregulation of α7 nicotinic receptors (nAChRs) in

the striatum and hippocampus in early adolescence (Tizabi et al. 1999). In this study, Tizabi and colleagues administered quinpirole HCl (1 mg/kg) or saline from (P)1–21 in male and female rats, identical to the treatment regimen used in our previous work. Animals were raised to (P)30, and brain tissue was harvested for analyses of nAChR binding. Frontal cortex, striatum, hippocampus, and cerebellum were obtained and analyzed. Regarding α4β2 nAChRs, neonatal quinpirole treatment elevated [^{3}H]cytisine binding only in cerebellum. No significant effects were detected in any other area examined. Regarding α7 nAChR binding, neonatal quinpirole treatment resulted in elevated [^{125}I]α-bungarotoxin binding in hippocampus (65 % compared to neonatal saline-treated animals) and striatum (94 % compared to neonatal saline-treated animals). No significant effect was detected in any other brain area. Critically, this finding demonstrates that neonatal quinpirole produces a significant 94 % increase in striatal α7 nAChRs without producing a change in α4β2 nAChRs in this same brain area. The striatum is a dopaminergic terminal area and is important in nicotine sensitization and the rewarding effects of nicotine (Mao and McGehee 2010).

One issue with the above findings is that the increase in hippocampal α7 nAChR is inconsistent with postmortem findings in hippocampus in schizophrenics (Freedman et al. 2000). However, it is not known whether nAChRs are changed at earlier time points of the life span in schizophrenia. What we hypothesize as particularly important is that an increase in striatal α7 nAChR availability in adolescence is especially critical to the susceptibility of smoking in schizophrenia. The striatum is known to play a role in the reinforcing and rewarding effects of addictive drugs, along with the nucleus accumbens. Based on the fact that the striatum and NAcc are both heavily innervated by the dopamine system and the inputs to both regions are primarily from dopaminergic cell bodies of the midbrain, we suspect that the α7 nAChR upregulation that is occurring in the striatum in adolescent rats treated neonatally with quinpirole is also occurring in the NAcc in these animals. However, this has not yet been analyzed. We suspect that the increase in α7 nAChR availability may play an important role in smoking behavior in schizophrenia, but may also affect dopaminergic plasticity in these brain regions, especially based on the fact the dopamine system is going through rapid development during the adolescent period (see Andersen and Teicher 2000).

Related to this issue, α7 nAChRs have been primarily identified as calcium (Ca^{+2}) channels. Calcium is known to play an important role in neurotransmitter release through its entry into presynaptic terminals due to the arrival of the action potential, its binding to calmodulin and the synaptic vesicle containing neurotransmitter, and transport of the vesicle to the terminal membrane for attachment and release. Important to brain plasticity and synaptic strength, α7 nAChRs have been shown to be localized on glutamatergic terminals in both the ventral tegmental area (VTA) and striatum. The mechanism that has been identified through which α7 nAChRs affects dopamine release in both the VTA and striatum is through its effects on glutamate. Kaiser and Wonnacott (2000) have shown that nicotine's agonist action at the α7 receptor increases glutamate release, which in turn excites dopamine terminals, stimulating dopamine release. Further support for this model

has shown glutamate stimulates the release of [^{3}H]dopamine from rat striatal slices (Jones et al. 1993) and this effect appears to be mediated by both AMPA/kainate and *N*-methyl-D-aspartate (NMDA) receptors present on dopaminergic nerve terminals (Kendrick et al. 1996; Smolders et al. 1996). Therefore, drugs acting on α7 nAChRs (e.g., nicotine) or changing glutamatergic function may influence plasticity in this region, which may have an important impact during development.

3 Plasticity Mechanisms

Developmental models always have the advantage of modeling a neurological disorder because of their long-term and persistent changes on the rewiring of the central nervous system. Important players in brain plasticity are neurotrophic factors, and one neurotrophic factor of particular interest in our work has been BDNF. BDNF is present in appreciable amounts throughout the CNS and is known to play an important role in the survival, differentiation, and maintenance of developing and mature neurons, and in the formation of synaptic circuitry in the brain (Huang and Reichardt 2001). BDNF is especially important in the modification of synaptic transmission (Binder and Scharfman 2004). Among postmortem tissue studies, BDNF levels are decreased in adult hippocampus of schizophrenics (Durany et al. 2001). We have also shown a decrease of hippocampal BDNF due to neonatal quinpirole treatment in the neonatal quinpirole model (Thacker et al. 2006). Possibly, even more important are the "downstream" changes produced by changes in BDNF. BDNF binds to the membranous tyrosine kinase B receptor and is released from both neurons and glial cells (Cowansage et al. 2010). Of interest is mammalian (or mechanistic) target of rapamycin (mTOR) and its corresponding complexes mTORC1 and mTORC2. It has been established that increases in mTOR can lead to the transcription of glutamatergic AMPA receptors (Wang et al. 2006) as well as influences on downstream targets such as ribosomal protein S6 which is directly involved in cell growth (Magnuson et al. 2012). Therefore, mTOR can have direct influence on both synaptic strength and synaptic growth. There has been interest in targeting mTOR in psychosis, and although it has yet to be established that there are changes in mTOR in different psychoses, all data appear to point to involvement of this important complex in neural plasticity.

4 The Dopamine D_2 Receptor as a Focal Point of Psychopathology

There are many disorders in which changes in dopamine D_2 receptor function have been shown, including bipolar (Salvadore et al. 2010), obsessive–compulsive disorder (OCD) (Nikolaus et al. 2010), and attention-deficit hyperactivity disorder (Ford 2014). The changes in the D_2 receptor and its function will be reviewed for

each of these disorders below. This is not to say that increases in dopamine D_2 receptor sensitivity may be relevant to all of these disorders, but it does appear that a change in dopamine D_2-like receptor functioning is a point at which psychopathology converges. Like the dopamine D_1 receptor family, dopamine D_2 receptors are metabotropic G-protein-coupled receptors. The dopamine D_2-like receptor family was first identified on the basis of its high affinity for antipsychotic drugs. Unlike the dopamine D_1 receptor family, dopamine D_2 receptors are known for their ability to inhibit adenylyl cyclase (Kebabian and Calne 1979). The highest density of D_2 receptors in the brain are in the striatum, nucleus accumbens, substantia nigra, and olfactory tubercle as well as the olfactory bulbs. In addition, unlike dopamine D_1 receptors, dopamine D_2 receptors are located both pre- and postsynaptically, with the presynaptic subtype essentially serving as an autoreceptor inhibiting dopamine release. Several drugs of abuse, including amphetamine and nicotine, have been shown to desensitize the D_2 autoreceptor in addition to increasing dopamine release (Seutin et al. 1991; Schmitz et al. 2001). This action has been hypothesized to be the basis of the reinforcing properties of these drugs.

Dr. Phillip Seeman has published several reviews over the past decade on the importance of the dopamine D_2 receptor in psychosis. Interestingly, although early work revealed that there was a significant increase of the dopamine D_2 receptor in postmortem analyses of striatum in schizophrenics, more recent work has indicated that dopamine D_2 receptors are only slightly elevated in schizophrenia. However, there have been reports that demonstrate increased dopamine responding to drugs of abuse, such as amphetamine (Laruelle et al. 1999) or enhanced psychotic responding to amphetamine (Thompson et al. 2013). Regardless, what is known is that all antipsychotic drugs block the dopamine D_2 receptor with some affinity and are especially effective at alleviating positive symptoms of the disorder (Tollefson 1996).

In addition, there have been several reports of changes in RGS in schizophrenia. RGS proteins activate the breakdown of guanosine triphosphate (GTP) that is transiently attached to the Gi and Gq subunits of G-protein and effectively act as GTPase activators to shorten or terminate the action of an agonist (Neubig and Siderovski 2002; Neubig 2002). Regulation of GTPase activity, for example, by regulation of RGS protein expression or localization, is an effective cellular strategy formulating the sensitivity of GPCRs to agonist stimulation (Hollinger and Hepler 2002). Specifically, RGS9-2 has been identified as being colocalized with dopamine D_2 class dopamine receptors located on medium spiny neurons of the striatum and accelerates the termination of D_2-triggered events (Kovoor et al. 2005). Further, this same group has shown that RGS9-2 regulates D_2 cellular functions and inhibits dopamine-mediated internalization of dopamine D_2 receptors (Celver et al. 2010). One study has shown decreases of RGS9-2 in postmortem analyses of schizophrenics (Seeman et al. 2006), although others have failed to report this change (Greenbaum et al. 2010; Okahisa et al. 2011). Importantly, the gene for RGS9 is located in the identical chromosomal region that contains at least one other marker linked to schizophrenia (Cardno et al. 2001). We have also reported that neonatal quinpirole treatment results in significant decreases of RGS9-2 expression

in the frontal cortex, striatum, and nucleus accumbens of adult male rats (Maple et al. 2007). The decreases of RGS9 were robust in all three regions, consistent with persistent dopamine D_2 receptor supersensitivity.

5 Bipolar Disorder

As mentioned, currently available antipsychotic drugs all antagonize the dopamine D_2 receptor with some affinity. Although antipsychotic drugs have been used in the treatment of schizophrenia, many typical and more recently atypical antipsychotic drugs have been utilized to treat bipolar disorder, suggesting that a neurobiological mechanism of this disorder is related to changes in the dopamine D_2 receptor. Several genetic polymorphisms in bipolar disorder are related to the dopamine system, and these include alterations in the genes that code for the dopamine D_2 receptor (Beaulieu and Gainetdinov 2011) as well as the dopamine transporter (DAT; Pinsonneault et al. 2011). However, without a defined neurobiological mechanism, bipolar disorder has traditionally been difficult to model in a rodent. Interestingly, there is a quinpirole model of bipolar disorder that has been published, in which quinpirole is administered to adult rats and the biphasic locomotor response to acute quinpirole treatment was alleviated by common treatments for bipolar disorder, including valproate and carbamazepine (Shaldubina et al. 2002). The problem with the analysis of only locomotor activity is limited, because assessment of purely locomotor activity provides only limited information regarding the etiology of a complex disorder such as bipolar disorder. Therefore, a number of manipulations have been studied in relation to mania, including sleep deprivation (Szabo et al. 2009) and social defeat stress (Einat 2007b). Such manipulations, while causing hyperactivity, also lead to other symptoms such as increased aggression and changes in sexual activity, as well as molecular alterations in systems that are affected by mood stabilizers such as the glycogen synthase kinase-3 gene (for reviews see Beaulieu et al. 2011). As with manic depressive disorder, genetic studies have been performed to assess mania (Chen et al. 2010; Einat 2007a; Malkesman et al. 2009; Saul et al. 2012), many of which take the form of assessing strain differences or disrupting circadian rhythms (Roybal et al. 2007). Ultimately, utilization of a variety of approaches will be required to gain better insight into the underlying pathophysiology of bipolar disorder.

6 Obsessive–Compulsive Disorder (OCD)

OCD is an anxiety disorder that affects approximately 2–3 % of the population and causes an impairment in social and occupational functioning (Ruscio et al. 2010). The disorder is characterized by distress- and anxiety-provoking obsessions (repetitive intrusive thoughts) and compulsions (repetitive ritualistic behavior),

which are performed to diminish anxiety (American Psychiatric Association 2013). One of the most prevalent and replicated findings in OCD is the disruption of cortico-striato-thalamocortical circuitry. Essentially, what has been discovered is that there are hyperactive circuitry communications within subregions of these anatomical areas that are manifested in the behavioral disruptions observed in OCD (for review, see Monteiro and Feng 2015). Of course, both serotonin (5-HT) and dopamine are known to play major roles in this communication (along with glutamate), and much of the research focus and treatment have centered on these neurotransmitter systems.

Treatment for OCD often involves the class of drugs known as selective serotonin reuptake inhibitors (SSRIs), which are also a common pharmacotherapy for depression (Denys et al. 2004a, b; Aouizerate et al. 2005). This treatment suggests the involvement of the serotoninergic system, and neuroimaging studies have strengthened the notion of serotonergic dysfunction in OCD by providing evidence for reduced availability of 5-HT transporters (SERTs) in the midbrain, thalamus, and brainstem; and reduced availability of 5-HT_{2A} receptors in prefrontal, parietal, and temporal brain regions (Hesse et al. 2005; Perani et al. 2008). However, an estimated 50–60 % of patients do not respond to this treatment and require additional treatment with atypical antipsychotics, most of which work on both the dopamine and serotoninergic systems (Denys et al. 2004a; Denys 2006; Fineberg et al. 2005). Abnormalities in the dopamine system have also been observed in OCD patients, such as increased DAT levels in the striatum and reduced availability of the D_1 and D_2 receptors in striatum (Kim et al. 2003; Denys et al. 2004b; van der Wee et al. 2004; Olver et al. 2009).

There are relatively few animal models that exist for OCD, but there is support for the current hypothesis that manipulations in 5-HT (Andersen et al. 2010; Schilman et al. 2010) or dopamine neurotransmission (Einat and Szechtman 1995; Hoffman and Rueda Morales 2012) are effective models with some behavioral validity. There are a number of genetic models in the mouse, including the *Sapap3* knockout. *Sapap3* is a scaffolding protein normally enriched at corticostriatal glutamatergic synapses, and deletion of this gene results in selective synaptic dysfunction in the striatum (Wan et al. 2014). This model has shown enhanced anxiety on a number of behavioral assays as well as compulsive, self-injurious grooming (Welch et al. 2007). However, in the more behaviorally adept rat, one of the more common OCD models in existence is the quinpirole sensitization model developed by Eilam, Szechtman, and colleagues (Eilam et al. 2006). This model involves behaviorally testing rats after subchronic administration of quinpirole (0.125–0.25 mg/kg) to adult rats and has shown compulsive checking behavior typically measured in an open field. This behavioral effect in rats is alleviated by 5-HT agonists (Tucci et al. 2014). The weakness with this model is primarily that increases in D_2 receptor function are not observed in OCD, but there is reduced availability in D_2 receptors. Regardless, this model appears to have some behavioral validity and suggests that increases in D_2 receptor function may be relevant to analyzing behavioral effects in an OCD rodent model.

7 Attention-Deficit Hyperactive Disorder (ADHD)

Similar to OCD at the neurobiological level, there is evidence suggesting that ADHD is the result of abnormal dopamine and 5-HT functioning (Sagvolden et al. 2005; Zeeb et al. 2009). Though the effects of dopamine on prefrontal functioning are quite complicated, the general consensus is that dopamine exerts a strong regulatory effect on prefrontal neuronal activity (Sagvolden et al. 2005). The effect of dopamine depends on the state of the prefrontal cells (e.g., hyperpolarized non-firing or depolarized firing state). Dopamine is postulated to mediate the value of delayed rewards (Wade et al. 2000). When comparing patients who have had injuries or diseases of the prefrontal cortex with individuals clinically diagnosed with ADHD, there are similarities in attention deficiencies and distractibility (Winstanley et al. 2006). Additionally, there are data from functional magnetic resonance imaging (fMRI) that show atypical fronto-striatal activity during go/no-go tasks with ADHD (Tripp and Wickens 2009). Whereas several studies have shown genetic abnormalities across the dopamine system, the role of the dopamine D_2 receptor consistently presents mixed results (Volkow et al. 2009). However, D_2 polymorphisms have been implicated in some of the behavioral deficits associated with ADHD, such as reward and motivation (Haenlein and Caul 1987: Johansen et al. 2009).

According to the American Psychiatric Association (2002), treatment for ADHD often involves the administration of stimulants including dextroamphetamine (d-AMP) or methylphenidate (MPH). These stimulants inhibit the dopamine transporter (DAT) and the norepinephrine transporter, ultimately inhibiting dopamine and norepinephrine reuptake and producing an increase of the neurotransmitters' presence at postsynaptic receptors (Russell et al. 2005; Sharma and Couture 2014). Interestingly enough, imaging studies have shown a similar neurobiology between ADHD and substance abusers, along with stimulant treatment reducing both ADHD and substance abuse symptomatology (Frodl 2010). However, it should be noted that long-term use of stimulants remains a topic of controversy. Both MPH and d-AMP are known to cause physical harm and dependence, though this does not seem to occur when taken as prescribed and may ultimately reduce the risk of substance abuse when administered at a clinically relevant dose (Nutt et al. 2007; Sharma and Couture 2014).

Currently, there are several animal models of ADHD. These rodent models range from various strains, social isolation rearing, pollutant exposure, hippocampal X-irradiation during infancy, and neurotoxic brain lesions (Sagvolden 2000). While these models are able to effectively model some of the behavioral deficits associated with ADHD, they often fail to model the genetic abnormalities or are inconsistent with the etiology of ADHD in the clinical population. Genetic models include a DAT knockout mouse, Naples High/Low Excitability rats, and the most prevalently used model, the spontaneously hypertensive rat (SHR) (Sagvolden 2000). Numerous studies have demonstrated that SHRs display behavioral characteristics analogous to the behaviors of individuals diagnosed with ADHD (Russell et al.

2005). Research assessing the validity of the SHR across measures of sustained attention (Aase and Sagvolden 2006), increased motor activity and behavioral variability (Wultz and Sagvolden 1992; Mook et al. 1993; Saldana and Neuringer 1998), as well as impulsiveness (Hand et al. 2009) has shown that SHRs demonstrate behavior analogous to that of individuals with ADHD. The dopamine system has also been shown to be disturbed in the SHR. More specifically, dopamine turnover is lower in the substantia nigra, VTA, and frontal cortex of adult SHRs which suggests that dopamine release may be decreased and impaired (Russell et al. 2005). Binding studies have also shown that D_2 receptor density increased the striatum of the SHR (Chiu et al. 1982). An analysis of the role of the D_2 receptor in psychostimulant treatment in a developmental model, as ADHD has been reclassified as a developmental disorder, will likely provide insight toward the role of dopamine in ADHD.

8 Substance Abuse

In a previous review, we discussed substance abuse comorbidity in schizophrenia and the consequences of substance abuse in this population along with the underlying neurobiological mechanisms. We focused much of this review toward nicotine, because the majority (70–90 %) of the schizophrenic population smokes cigarettes and smokes them heavily (McCreadie and Kelly 2000). However, when it comes to psychosis, increased substance abuse is not unique to the schizophrenic population, because there is a substantial increase in alcohol and psychostimulant use across many behavioral disorders (Mueser and Gingerich 2013). Not surprisingly across all disorders, symptoms are worsened when drugs are abused, with the costs of care being dramatically increased (Dixon 1999).

A more recent focus at the National Institute on Drug Abuse (NIDA) has been on the increased use of cannabis in psychotic populations. With the exception of alcohol, cannabis is the most commonly abused substance worldwide, with estimates at approximately 5 million daily users. In the USA, it was also the most commonly used illicit drug by children 12–17 years (7.9 %) in 2011(Schneider and Koch 2003). Cannabis contains more than 70 different cannabinoids, and the main psychoactive ingredient of cannabis is delta-9-tetrahydrocannabinol (THC). Substantial epidemiological evidence suggests a link between cannabis use and the risk of schizophrenia (Andréasson et al. 1987; Johnston et al. 2012), and individuals diagnosed with schizophrenia are 10 times more likely to use cannabis than the general population (Henquet et al. 2005). There is also a strong relationship between cannabis exposure and symptoms of psychosis (Iritani 2007). Risk of psychosis has been positively associated with the frequency of cannabis use (50–200 % in the most frequent users; Harrison 1999), and earlier age of onset of psychotic symptoms has been associated with earlier initiation of cannabis use.

Surprisingly, there are relatively few studies on substance abuse comorbidity in animal models of psychosis. However, it has been shown that there is enhanced sensitivity to the behavioral response to other substances. For example, the neonatal ventral hippocampal lesion (NVHL) model of schizophrenia has been shown to demonstrate enhanced nicotine and cocaine sensitization as well as enhanced sensitivity to alcohol (Conroy et al. 2007; Berg and Chambers 2008; Chambers et al. 2013). Likewise, have several reports in our model also demonstrate enhanced dopamine release to both amphetamine (Cope et al. 2010) and nicotine (Brown et al. 2012). The consequences of these changes are yet to be determined, which may lead to unique treatments of substance abuse comorbidity in psychosis.

9 Conclusions

In summary, it is clear that the dopamine D_2 receptor system plays an important role in several psychoses. Moreover, the D_2 receptor has been the target for antipsychotic drugs since the mid-1950s. As with any neurotransmitter system, changes in dopamine D_2 receptor function lead to a number of other changes in brain involving other neurotransmitter systems, brain plasticity, and genetic expression. It is in these neurobiological plasticity changes that mechanisms will likely be discovered and in the future possibly lead to pharmacological targets for the development of treatments for these devastating disorders.

References

Aase H, Sagvolden T (2006) Infrequent, but not frequent, reinforcers produce more variable responding and deficient sustained attention in young children with attention deficit/hyperactivity disorder (ADHD). J Child Psychol Psychiatry 47:457–471

American Psychiatric Association (2002) Practice guideline for the treatment of patients with bipolar disorder. American Psychiatric Pub

American Psychiatric Association (2013) Diagnostic and Statistical Manual of Mental Disorders, 5th edn. American Psychiatric Publishing, Arlington

Andersen SL, Teicher MH (2000) Sex differences in dopamine receptors and their relevance to ADHD. Neurosci Biobehav Rev 24:137–141

Andersen SL, Greene-Colozzi EA, Sonntag KC (2010) A novel, multiple symptom model of obsessive-compulsive-like behaviors in animals. Biol Psychiatry 68:741–747

Andréasson S, Engström A, Allebeck P, Rydberg U (1987) Cannabis and schizophrenia longitudinal study of Swedish conscripts. The Lancet 330:1483–1486

Aouizerate B, Guehl D, Cuny E, Rougier A, Burbaud P, Tignol J, Bioulac B (2005) Updated overview of the putative role of the serotoninergic system in obsessive-compulsive disorder. Neuropsychiatr Dis Treat 1:231–243

Beaulieu JM, Gainetdinov RR (2011) The physiology, signaling, and pharmacology of dopamine receptors. Pharmacol Rev 63:182–217

Beaulieu JM, Del'guidice T, Sotnikova TD, Lemasson M, Gainetdinov RR (2011) Beyond camp: the regulation of Akt and GSK3 by dopamine receptors. Front Mol Neurosci. 4:38

Berg SA, Chambers RA (2008) Accentuated behavioral sensitization to nicotine in the neonatal ventral hippocampal lesion model of schizophrenia. Neuropharmacology 8:1201–1207
Binder DK, Scharfman HE (2004) Brain-derived neurotrophic factor. Growth Factors 22:123–131
Brown RW, Gass JT, Kostrzewa RM (2002) Ontogenetic quinpirole treatments produce spatial memory deficits and enhance skilled reaching in adult rats. Pharmacol Biochem Behav 72:591–600
Brown RW, Perna MK, Maple AM, Wilson TD, Miller BE (2008) Adulthood olanzapine treatment fails to alleviate decreases of ChAT and BDNF RNA expression in rats quinpirole-primed as neonates. Brain Res 20:66–77
Brown RW, Maple AM, Perna MK, Sheppard AB, Cope ZA, Kostrzewa RM (2012) Schizophrenia and substance abuse comorbidity: nicotine addiction and the neonatal quinpirole model. Dev Neurosci 34(2–3):140–151
Cardno AG, Holmans PA, Rees MI, Jones LA, McCarthy GM, Hamshere ML, Williams NM, Norton N, Williams HJ, Fenton I, Murphy KC, Sanders RD, Gray MY, O'Donovan MC, McGuffin P, Owen MJ (2001) A genomewide linkage study of age at onset in schizophrenia. Am J Med Genet 105:439–45
Celver J, Sharma M, Kovoor A (2010) RGS9-2 mediates specific inhibition of agonist-induced internalization of D2-dopamine receptors. J Neurochem 114:739–749
Chambers RA, McClintick JN, Sentir AM, Berg SA, Runyan M, Choi KH, Edenberg HJ (2013) Cortical-striatal gene expression in neonatal hippocampal lesion (NVHL)-amplified cocaine sensitization. Genes Brain Behav 12:564–575
Chen G, Henter ID, Manji HK (2010) Translational research in bipolar disorder: emerging insights from genetically based models. Mol Psychiatry 15:883–895
Chiu P, Rajakumar G, Chiu S, Kwan CY, Mishra RK (1982) Enhanced [3 H] spiroperidol binding in striatum of spontaneously hypertensive rat (SHR). Eur J Pharmacol 82:243–244
Cohen SM, Tsien RW, Goff DC, Halassa MM (2015) The impact of NMDA receptor hypofunction on GABAergic neurons in the pathophysiology of schizophrenia. Schizophr Res 167:98–107
Conroy SK, Rodd Z, Chambers RA (2007) Ethanol sensitization in a neurodevelopmental lesion model of schizophrenia in rats. Pharmacol Biochem Behav 86:386–394
Cope ZA, Huggins KN, Sheppard AB, Noel DM, Roane DS, Brown RW (2010) Neonatal quinpirole treatment enhances locomotor activation and dopamine release in the nucleus accumbens core in response to amphetamine treatment in adulthood. Synapse 64:289–300
Cowansage KK, LeDoux JE, Monfils MH (2010) Brain-derived neurotrophic factor: a dynamic gatekeeper of neural plasticity. Curr Mol Pharmacol 3:12–29
Cuesta MJ, Jalón EG, Campos MS, Peralta V (2009) Cognitive effectiveness of olanzapine and risperidone in first-episode psychosis. Br J Psychiatry 194:439–445
Denys D (2006) Pharmacotherapy of obsessive-compulsive disorder and obsessive-compulsive spectrum disorders. Psychiatr Clin North Am 29:553–584
Denys D, de Geus F, van Megen HJ, Westenberg HG (2004a) A double-blind, randomized, placebo-controlled trial of quetiapine addition in patients with obsessive-compulsive disorder refractory to serotonin reuptake inhibitors. J Clin Psychiatry 65:1040–1048
Denys D, van der Wee N, Janssen J, De Geus F, Westenberg HG (2004b) Low level of dopaminergic D2 receptor binding in obsessive-compulsive disorder. Biol Psychiatry 55:1041–1045
Dixon L (1999) Dual diagnosis of substance abuse in schizophrenia: prevalence and impact on outcomes. Schizophr Res 35(Suppl):S93–S100
Durany N, Michel T, Zöchling R, Boissl KW, Cruz-Sánchez FF, Riederer P, Thome J (2001) Brain-derived neurotrophic factor and neurotrophin 3 in schizophrenic psychoses. Schizophr Res 52:79–86
Eilam D, Zor R, Szechtman H, Hermesh H (2006) Rituals, stereotypy and compulsive behavior in animals and humans. Neurosci Biobehav Rev 30:456–471

Einat H (2007a) Establishment of a battery of simple models for facets of bipolar disorder: a practical approach to achieve increased validity, better screening and possible insights into endophenotypes of disease. Behav Genet 37:244–255
Einat H (2007b) Different behaviors and different strains: potential new ways to model bipolar disorder. Neurosci Biobehav Rev 31:850–857
Einat H, Szechtman H (1995) Perseveration without hyperlocomotion in a spontaneous alternation task in rats sensitized to the dopamine agonist quinpirole. Physiol Behav 57:55–59
Fineberg NA, Sivakumaran T, Roberts A, Gale T (2005) Adding quetiapine to SRI in treatment-resistant obsessive–compulsive disorder: a randomized controlled treatment study. Int Clin Psychopharmacol 20:223–226
Ford CP (2014) The role of D2-autoreceptors in regulating dopamine neuron activity and transmission. Neuroscience 282C:13–22
Freedman R, Adams CE, Leonard S (2000) The alpha7-nicotinic acetylcholine receptor and the pathology of hippocampal interneurons in schizophrenia. Chem Neuroanat 2000(20):299–306
Frodl T (2010) Comorbidity of ADHD and substance use disorder (SUD): a neuroimaging perspective. J Attention Disord 14(2):109–120
Greenbaum L, Pelov I, Teltsh O, Lerer B, Kohn Y (2010) No association between regulator of G-protein signaling 9 (RGS9) and schizophrenia in a Jewish population. Psychiatr Genet 20:47–48
Haenlein M, Caul WF (1987) Attention deficit disorder with hyperactivity: a specific hypothesis of reward dysfunction. J Am Acad Child Adolesc Psychiatry 26:356–362
Hand DJ, Fox AT, Reilly MP (2009) Differential effects of d-amphetamine onimpulsive choice in spontaneously hypertensive and wistar-kyoto rats. Behav Pharmacol 20:549–553
Harrison PJ (1999) The neuropathology of schizophrenia. A critical review of the data and their interpretation. Brain 122:593–624
Henquet C, Murray R, Linszen D, van Os J (2005) The environment and schizophrenia: the role of cannabis use. Schizophr Bull 31:608–612
Hesse S, Muller U, Lincke T, Barthel H, Villmann T, Angermeyer MC et al (2005) Serotonin and dopamine transporter imaging in patients with obsessive-compulsive disorder. Psychiatry Res 140:63–72
Hoffman KL, Rueda Morales RI (2012) D1 and D2 dopamine receptor antagonists decrease behavioral bout duration, without altering the bout's repeated behavioral components, in a naturalistic model of repetitive and compulsive behavior. Behav Brain Res 230:1–10
Hollinger S, Hepler JR (2002) Cellular regulation of RGS proteins: modulators and integrators of G protein signaling. Pharmacol Rev 54:527–559
Iritani S (2007) Neuropathology of schizophrenia: A mini review. Neuropathology 27:604–608
Huang EJ, Reichardt LF (2001) Neurotrophins: roles in neuronal development and function. Annu Rev Neurosci 24:677–736
Janhunen SK, Svärd H, Talpos J, Kumar G, Steckler T, Plath N, Lerdrup L, Ruby T, Haman M, Wyler R, Ballard TM (2015) The subchronic phencyclidine rat model: relevance for the assessment of novel therapeutics for cognitive impairment associated with schizophrenia. Psychopharmacology
Johansen E, Killeen PR, Russell VA, Tripp G, Wickens JR, Tannock R, Sagvolden T (2009) Origins of altered reinforcement effects in ADHD. Behav Brain Functions 5:7–11
Johnston L, Bachman J, O'Malley P, Schulenberg J (2012) Monitoring the future: a continuing study of American youth (12th-Grade Survey), ICPSR34409-v2. Ann Arbor MI Inter-Univ Consort Polit Soc Res Distrib 11–20
Jones CA, Zempléni E, Davis B, Reynolds GP (1993) Glutamate stimulates dopamine release from cortical and limbic rat brain in vitro. Eur J Pharmacol 242:183–187
Julien RM, Advokat C, Comaty J (2015) A primer of drug action, 12th edn. Worth Publishers, New York
Kaiser S, Wonnacott S (2000) Alpha-bungarotoxin-sensitive nicotinic receptors indirectly modulate [(3)H]dopamine release in rat striatal slices via glutamate release. Mol Pharmacol 58:312–318

Kebabian JW, Calne DB (1979) Multiple receptors for dopamine. Nature 277:93–96
Kim CH, Koo MS, Cheon KA, Ryu YH, Lee JD, Lee HS (2003) Dopamine transporter density of basal ganglia assessed with [123I] IPT SPET in obsessive-compulsive disorder. Eur J Nucl Med Mol Imaging 30(12):1637–1643
Kostrzewa RM (1995) Dopamine receptor supersensitivity. Neurosci Biobehav Rev 19:1–17
Kostrzewa RM, Brus R (1991) Ontogenic homologous supersensitization of quinpirole-induced yawning in rats. Pharmacol Biochem Behav 39:517–519
Kovoor A, Seyffarth P, Ebert J, Barghshoon S, Chen CK, Schwarz S, Axelrod JD, Cheyette BN, Simon MI, Lester HA, Schwarz J (2005) D2 dopamine receptors colocalize regulator of G-protein signaling 9-2 (RGS9-2) via the RGS9 DEP domain, and RGS9 knock-out mice develop dyskinesias associated with dopamine pathways. J Neurosci 25:2157–2165
Laruelle M, Abi-Dargham A, Gil R, Kegeles L, Innis R (1999) Increased dopamine transmission in schizophrenia: relationship to illness phases. Biol Psychiatry 46:56–72
Lipska BK, Weinberger DR (2002) A neurodevelopmental model of schizophrenia: neonatal disconnection of the hippocampus. Neurotox Res 4:469–475
Lyon L, Saksida LM, Bussey TJ (2012) Spontaneous object recognition and its relevance to schizophrenia: a review of findings from pharmacological, genetic, lesion and developmental rodent models. Psychopharmacology 220:647–672
Magnuson B, Ekim B, Fingar DC (2012) Regulation and function of ribosomal protein S6 kinase (S6K) within mTOR signalling networks. Biochem J 441:1–21
Malkesman O, Austin DR, Chen G, Manji HK (2009) Reverse translational strategies for developing animal models of bipolar disorder. Disease Models Mechanisms. 2:238–245
Mao D, McGehee DS (2010) Nicotine and behavioral sensitization. J Mol Neurosci 40:154–163
Maple AM, Perna MK, Parlaman JP, Stanwood GD, Brown RW (2007) Ontogenetic quinpirole treatment produces long-lasting decreases in the expression of Rgs9, but increases Rgs17 in the striatum, nucleus accumbens and frontal cortex. Eur J Neurosci 26(9):2532–2538
Maple AM, Smith KJ, Perna MK, Brown RW (2015) Neonatal quinpirole treatment produces prepulse inhibition deficits in adult male and female rats. Pharmacol Biochem Behav 137:93–100
McCreadie RG, Kelly C (2000) Patients with schizophrenia who smoke. Private disaster, public resource. Br J Psychiatry 176:109–116
Monteiro P, Feng G (2015) Learning from animal models of obsessive-compulsive disorder. Biol Psychiatry
Mook DM, Jeffrey J, Neuringer A (1993) Spontaneously hypertensive rats (SHR) readily learn to vary but not repeat instrumental responses. Behav Neural Biol 59:126–135
Mueser KT, Gingerich S (2013) Treatment of co-occurring psychotic and substance use disorders. Soc Work Public Health 28:424–439
Neubig RR (2002) Regulators of G protein signaling (RGS proteins): novel central nervous system drug targets. J Pept Res 60:312–316
Neubig RR, Siderovski DP (2002) Regulators of G-protein signalling as new central nervous system drug targets. Nat Rev Drug Discov 1:187–197
Nikam SS, Awasthi AK (2008) Evolution of schizophrenia drugs: a focus on dopaminergic systems. Curr Opin Investig Drugs 9:37–46
Nikolaus S, Antke C, Beu M, Müller HW (2010) Cortical GABA, striatal dopamine and midbrain serotonin as the key players in compulsive and anxiety disorders-results from in vivo imaging studies. Rev Neurosci 21:119–139
Nutt D, King LA, Saulsbury W, Blakemore C (2007) Development of a rational scale to assess the harm of drugs of potential misuse. The Lancet 369:1047–1053
Okahisa Y, Kodama M, Takaki M, Inada T, Uchimura N, Yamada M, Iwata N, Iyo M, Sora I, Ozaki N, Ujike H (2011) Association between the regulator of G-protein signaling 9 gene and patients with methamphetamine use disorder and schizophrenia. Curr Neuropharmacol 9:190–194
Olver JS, O'Keefe G, Jones GR, Burrows GD, Tochon-Danguy HJ, Ackermann U, Norman TR (2009) Dopamine D1 receptor binding in the striatum of patients with obsessive–compulsive disorder. J Affect Disord 114:321–326

Perani D, Garibotto V, Gorini A, Moresco RM, Henin M, Panzacchi A, Fazio F (2008) In vivo PET study of 5HT 2A serotonin and D2 dopamine dysfunction in drug naive obsessive-compulsive disorder. Neuroimage 42:306–314

Picchioni MM, Murray RM (2007) Schizophrenia. BMJ 335:91–95

Pinsonneault JK, Han DD, Burdick KE, Kataki M, Bertolino A, Malhotra AK, Gu HH, Sadee W (2011) Dopamine transporter gene variant affecting expression in human brain is associated with bipolar disorder. Neuropsychopharmacology. 36:1644–1655

Rizos EN, Papadopoulou A, Laskos E, Michalopoulou PG, Kastania A, Vasilopoulos D, Katsafouros K, Lykouras L (2010) Reduced serum BDNF levels in patients with chronic schizophrenic disorder in relapse, who were treated with typical or atypical antipsychotics. World J Biol Psychiatry 11:251–255

Robinson TE, Becker JB (1986) Enduring changes in brain and behavior produced by chronic amphetamine administration: a review and evaluation of animal models of amphetamine psychosis. Brain Res 396:157–198

Roybal K, Theobold D, Graham A, DiNieri JA, Russo SJ, Krishnan V, McClung CA (2007) Mania-like behavior induced by disruption of CLOCK. Proc Natl Acad Sci 104:6406–6411

Ruscio AM, Stein DJ, Chiu WT, Kessler RC (2010) The epidemiology of obsessive-compulsive disorder in the national comorbidity survey replication. Mol Psychiatry 15:53–63

Russell V, de Villiers A, Sagvolden T, Lamm M, Taljaard J (1995) Altered dopaminergic function in the prefrontal cortex, nucleus accumbens and caudate-putamen of an animal model of attention-deficit hyperactivity disorder—the spontaneously hypertensive rat. Brain Res 676:343–351

Russell VA, Sagvolden T, Johansen EB (2005) Animal models of attention-deficit hyperactivity disorder. Behav Brain Functions 1(1):9

Sagvolden T (2000) Behavioral validation of the spontaneously hypertensive rat (SHR) as an animal model of attention-deficit/hyperactivity disorder (AD/HD). Neurosci Biobehav Rev 24:31–39

Sagvolden T, Asse H, Johansen EB, Russell VA (2005) A dynamic developmental theory of attention-deficit/hyperactivity disorder (ADHD) predominately hyperactive/impulsive and combined subtypes. Behav Brain Sci 28(397):486

Saldana L, Neuringer A (1998) Is instrumental variability abnormally high in children exhibiting ADHD and aggressive behavior? Behav Brain Res 94:51–59

Salvadore G, Quiroz JA, Machado-Vieira R, Henter ID, Manji HK, Zarate CA (2010) The neurobiology of the switch process in bipolar disorder: a review. J Clin Psychiatry 71:1488–1501

Sams-Dodd F, Lipska BK, Weinberger DR (1997) Neonatal lesions of the rat ventral hippocampus result in hyperlocomotion and deficits in social behaviour in adulthood. Psychopharmacology 132:303–310

Saul MC, Gessay GM, Gammie SC (2012) A new mouse model for mania shares genetic correlates with human bipolar disorder. PLoS ONE 7:e38128

Schilman EA, Klavir O, Winter C, Sohr R, Joel D (2010) The role of the striatum in compulsive behavior in intact and orbitofrontal-cortex-lesioned rats: possible involvement of the serotonergic system. Neuropsychopharmacology 35:1026–1039

Schmitz Y, Lee CJ, Schmauss C, Gonon F, Sulzer D (2001) Amphetamine distorts stimulation-dependent dopamine overflow: effects on D2 autoreceptors, transporters, and synaptic vesicle stores. J Neurosci 21:5916–5924

Schneider M, Koch M (2003) Chronic pubertal, but not adult chronic cannabinoid treatment impairs sensorimotor gating, recognition memory, and the performance in a progressive ratio task in adult rats. Neuropsychopharmacology 28:1760–1769

Seeman P, Schwarz J, Chen JF, Szechtman H, Perreault M, McKnight GS, Roder JC, Quirion R, Boksa P, Srivastava LK, Yanai K, Weinshenker D, Sumiyoshi T (2006) Psychosis pathways converge via D2 high dopamine receptors. Synapse 60:319–346

Selvaraj S, Arnone D, Cappai A, Howes O (2014) Alterations in the serotonin system in schizophrenia: a systematic review and meta-analysis of postmortem and molecular imaging studies. Neurosci Biobehav Rev 45:233–245

Seutin V, Verbanck P, Massotte L, Dresse A (1991) Acute amphetamine-induced subsensitivity of A10 dopamine autoreceptors in vitro. Brain Res 558:141–144

Shaldubina A, Einat H, Szechtman H, Shimon H, Belmaker RH (2002) Preliminary evaluation of oral anticonvulsant treatment in the quinpirole model of bipolar disorder. J Neural Transm 109 (3):433–440

Sharma A, Couture J (2014) A review of the pathophysiology, etiology, and treatment of attention-deficit hyperactivity disorder (ADHD). Ann Pharmacother 48(2):209–225

Smolders I, Sarre S, Vanhaesendronck C, Ebinger C, Michotte C (1996) Extracellular striatal dopamine and glutamate after decortication and kainate receptor stimulation, as measured by microdialysis. J Neurochem 66:2373–2380

Szabo ST, Machado-Vieira R, Yuan P, Wang Y, Wei Y, Falke C, Du J (2009) Glutamate receptors as targets of protein kinase C in the pathophysiology and treatment of animal models of mania. Neuropharmacology 56:47–55

Thacker SK, Perna MK, Ward JJ, Schaefer TL, Williams MT, Kostrzewa RM, Brown RW (2006) The effects of adulthood olanzapine treatment on cognitive performance and neurotrophic factor content in male and female rats neonatally treated with quinpirole. Eur J Neurosci 24:2075–2083

Thompson JL, Urban N, Slifstein M, Xu X, Kegeles LS, Girgis RR, Beckerman Y, Harkavy-Friedman JM, Gil R, Abi-Dargham A (2013) Striatal dopamine release in schizophrenia comorbid with substance dependence. Mol Psychiatry. 18:909–915

Tizabi Y, Copeland RL Jr, Brus R, Kostrzewa RM (1999) Nicotine blocks quinpirole-induced behavior in rats: psychiatric implications. Psychopharmacology 145:433–441

Tollefson GD (1996) Update on new atypical antipsychotics. J Clin Psychiatry 57:318–319

Tripp G, Wickens JR (2009) Neurobiology of ADHD. Neuropharmacology 57:579–589

Tucci MC, Dvorkin-Gheva A, Sharma R, Taji L, Cheon P, Peel J, Kirk A, Szechtman H (2014) Separate mechanisms for development and performance of compulsive checking in the quinpirole sensitization rat model of obsessive-compulsive disorder (OCD). Psychopharmacology 231:3707–3718

van der Wee NJ, Stevens H, Hardeman JA, Mandl RC, Denys DA, van Megen HJ, Westenberg HM (2004) Enhanced dopamine transporter density in psychotropic naive patients with obsessive-compulsive disorder shown by [123I] β-CIT SPECT. Am J Psychiatry 161:2201–2206

Volkow ND, Wang G-J, Kollins SH, Wigal TL, Newcorn JH, Telang F (2009) Evaluating dopamine reward pathway in ADHD: clinical implications. JAMA 302:1084–1091

Wade TR, de Wit H, Richards JB (2000) Effects of dopaminergic drugs on delayed reward as a measure of impulsive behavior in rats. Psychopharmacology 150:90–101

Wan Y, Ade KK, Caffall Z, Ilcim Ozlu M, Eroglu C, Feng G, Calakos N (2014) Circuit-selective striatal synaptic dysfunction in the Sapap3 knockout mouse model of obsessive-compulsive disorder. Biol Psychiatry 75:623–630

Wang Y, Barbaro MF, Baraban SC (2006) A role for the mTOR pathway in surface expression of AMPA receptors. Neurosci Lett 401:35–39

Welch JM, Lu J, Rodriguiz RM, Trotta NC, Peca J, Ding JD, Feliciano C, Chen M, Adams JP, Luo J, Dudek SM, Weinberg RJ, Calakos N, Wetsel WC, Feng G (2007) Cortico-striatal synaptic defects and OCD-like behaviours in Sapap3-mutant mice. Nature 448:894–900

Winstanley CA, Eagle DM, Robbins TW (2006) Behavioral models of impulsivity in relation to ADHD: translation between clinical and preclinical studies. Clin Psychol Rev 26:379–395

Wultz B, Sagvolden T (1992) The hyperactive spontaneously hypertensive rat learns to sit still, but not to stop bursts of responses with short interresponse times. Behav Genet 22:415–433

Zeeb FD, Robbins TW, Winstanley CA (2009) Serotonergic and dopaminergicmodulation of gambling behavior as assessed using a novel rat gambling task. Neuropsychopharmacology 34:1–15