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Modeling Motivational Deficits in Mouse Models of Schizophrenia: Behavior Analysis as a Guide for Neuroscience

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Abstract

In recent years it has become possible to develop animal models of psychiatric disease in genetically modified mice. While great strides have been made in the development of genetic and neurobiological tools with which to model psychiatric disease, elucidation of neural and molecular mechanisms thought to underlie behavioral phenotypes has been hindered by an inadequate analysis of behavior. This is unfortunate given the fact that the experimental analysis of behavior has created powerful methods for isolating and describing the functional properties of behavioral mechanisms that are capable of providing deep understanding of behavioral phenotypes. A better understanding of the biological basis of normal behavior and its disturbance in psychiatric disease will require the application of these rigorous behavior analytic tools to animal models. In this review we provide an example of a merging of genetic and behavioral methods and illustrate its utility in the analysis of a mouse model of the motivational deficits in schizophrenia. The synergy between basic behavior analysis, neuroscience, and animal models of psychiatric disease has great potential for achieving a deeper understanding of behavior and its neurobiological mechanisms as well as for leading to improvements in diagnosis and treatment in clinical settings.

Keywords

motivation; schizophrenia; animal models; dopamine D2 receptors; transgenic mice

Psychiatry and behavior analysis have had a tenuous relationship. With the advent of psychoanalysis followed by the cognitive revolution of the 1960s, psychiatry adopted a language for understanding disorders that focused on underlying mental causes. Because behavior analysts have subscribed to an explanation of behavior focused on the role of the

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environment in selecting behavior and eschewed mental events as having a causal role in behavior (Skinner, 1953; 1974; Watson, 1913), behavior analysts and the psychiatric community adopted different and at times oppositional views of abnormal behavior (Skinner, 1977; 1985). This separation has been a self-sustaining one in that researchers in both fields rarely expose themselves or their students to work outside their original training. This is evident in the dearth of references to psychiatric journals in both the *Journal of the Experimental Analysis of Behavior* and the *Journal of Applied Behavior Analysis* as well as the miniscule number of citations of these two journals in the psychiatric literature. Research in clinical psychiatry has particularly suffered from this separation of intellectual progress, likely due to its foundations in the medical model of disease and its earlier strong association with psychoanalysis.

One consequence of behavior analysts' lack of interaction with clinical psychiatry is that their methods and analyses have not informed the development and validation of animal models of psychiatric disease. As a result, the sophistication of the genetic and biological tools available for the study of the mechanisms of psychiatric diseases has surpassed, by far, the sophistication of the behavioral analysis conducted on the animal models generated by such tools. We suggest that the methodological and theoretical tools generated by the more than 70 years of research on the functional relationships between environment and behavior are foundational to a more complete understanding of these animal models of psychiatric disease.

It is our contention that the time for the schism between clinical psychiatry and behavior analysis to end is overdue. We suggest that collaborative efforts between behavior analysts and neuroscientists, guided by current clinical research and theory, can lead to powerful new approaches in the development and validation of animal models of psychiatric disease. In the present paper, we review recent work on the characterization of aspects of the negative symptoms of schizophrenia using transgenic models. We begin with a brief introduction to schizophrenia, as well as a brief discussion of strategies for modeling aspects of this disease in rodents. We then review our work characterizing the motivational deficit in a particular transgenic model of one aspect of the pathophysiology of the disease (increased striatal dopamine D2 receptor activity), and show how this might lead to the identification of novel molecular targets for treating this deficit. As we will illustrate, the synergy between behavior analysis and neuroscience offers great promise in understanding and treating psychiatric disease.

Negative symptoms in Schizophrenia

Schizophrenia is a debilitating psychiatric disease that afflicts about 1% of the population worldwide (Lewis & Lieberman et al., 2000). It is generally characterized by a decline in functioning during adolescence (see Corcoran et al., 2003; Neindam et al., 2009, for discussions of the prodromal phase), followed by a psychotic episode in late adolescence or early adulthood, followed by a progressive decline in functioning with periods of recovery. The final phase is a chronic and severe deficit in functioning which persists throughout the life of the patient (e.g., Lieberman et al., 2001). The disease is characterized by three sets of symptoms: Positive, negative, and cognitive. Positive symptoms are the classical "psychotic" manifestations such as delusions and hallucinations. Negative symptoms include social withdrawal, blunted affect, and lack of motivation. The cognitive symptoms include deficits in attention, working memory, and executive control (e.g., Lewis & Lieberman, 2000).

Since the days when Kraepelin (1919) first described the motivational aspect of the syndrome as a "weakening of volitional impulses", it has been noted that motivational

deficits are a core component of the negative symptoms in schizophrenia (Bleuler, 1950; see Kirkpatrick et al., 2006, for a statement on the current conceptualization of negative symptoms in schizophrenia). While current pharmaco-therapeutic approaches are effective in treating the positive symptoms, there are currently no effective treatments for the negative symptoms, a significant problem given that the severity of the negative symptoms is much more predictive of functional outcome in patients than is the severity of positive symptoms (e.g., Beng-Choon et al., 1998). Thus, the need to identify treatments for the negative symptoms is great, and animal models provide a means of achieving this goal.

Modeling Schizophrenia in animals

Although there are a variety of approaches to modeling schizophrenia in animals, with the remarkable advances made in recent decades in molecular biology, the focus of animal models has shifted toward a genetic approach (see Powell & Miyakawa, 2006, for discussion). Current genetic approaches make it possible to selectively delete, modify, or introduce target genes at virtually any stage of development (e.g., Aiba & Nakao, 2007; Morozov et al., 2003; Saur, 1998; Tanaka et al., 2010). With these tools available the question becomes which manipulation to make? Unfortunately, unlike disorders such as Huntington's disease, Fragile X, or Rett's syndrome, in which a single specific genetic defect produces the disease, schizophrenia is a complex genetic disease. Some have suggested that it is produced by the interaction of many common genetic risk factors, each with a small impact on disease risk (see Allen et al., 2008), interacting with environmental events which engage epigenetic mechanisms, leading to developmental pathophysiology, and finally culminating in the onset of the disease (e.g., Roth et al., 2009, Tsuang, 2000). Others have suggested that schizophrenia is produced by a large number of extremely rare single genetic mutations that have a profound deleterious impact on brain development and function (e.g., McClellan et al., 2007). In either case, many genes are implicated which could contribute to a variety of dysfunctions in various brain systems. Moreover, the clinical manifestations of schizophrenia are heterogeneous (e.g., Kremen et al., 2000; Taylor, 1992), making animal researchers uncertain about what the most important behavioral and biological phenotypes are to model. Finally, it is impossible to recapitulate all symptoms of interest in animal models of schizophrenia (see Powell & Miyakawa, 2006). Thus, animal researchers face a challenging task in developing valid and informative models of the disease (see Arguello & Gogos, 2006, O'Tuathaigh et al., 2010, for reviews).

Because it is impossible to simultaneously model every aspect of schizophrenia, researchers generally rely on a more modest approach. They focus on the relation between a single manipulation which produces a change in brain structure or function implicated in schizophrenia and a behavioral phenotype (i.e., impaired cognitive performance, decreased motivation) that is relevant to the disease (Arguello & Gogos, 2006; Kellendonk, Simpson, & Kandel, 2009). A large literature has documented "schizophrenia like" behaviors as a result of particular genetic manipulations (see Kellendonk et al., 2009, for review). For example, a recent study reported that mice which model a microdeletion on human chromosome 22 (22q11.2), which confers a 25–30 fold increase in the risk for developing schizophrenia (Karayiorgou et al., 2010), were slower to acquire accurate performance in a working memory task (Sigurdsson et al., 2010). Furthermore, these mice displayed impaired functional connectivity between the hippocampus and the prefrontal cortex, a result consistent with imaging studies in patients diagnosed with schizophrenia (e.g., Meyer-Lindenberg et al., 2005). Thus, genetically modeling specific phenotypic aspects of the disease in animals is a useful strategy for understanding the neural and molecular underpinnings of the functional deficits in schizophrenia.

Modeling negative symptoms in animals is particularly challenging because these symptoms are, by definition, a deficit in a normally present behavior. Although some insights have been gained from modeling social interaction deficits, interpretation of these results is complicated, particularly when a genetic manipulation may affect the olfactory system, a critical determinant of social interaction in rodents (O'Tuathaigh et al., 2010). Development of models of other aspects of negative symptoms, such as avolition (lack of motivation) and anhedonia has been slow due to the difficulty in adapting methods optimized with rats for use with mice (Powell & Miyakawa, 2006), and due to an incomplete characterization and dissection of behavioral processes. We show in the present review that careful behavioral characterization of the motivational phenotype in mice is critical for understanding and validating transgenic mouse models of phenotypic aspects of schizophrenia.

Striatal dopaminergic dysfunction in Schizophrenia

Although the underlying neurophysiological mechanisms of schizophrenia are not fully known, one of the most influential hypotheses is that the disease reflects pathological changes in activity of the dopaminergic systems (e.g., Howes & Kapur, 2009). Hyperactivity of the striatal dopamine system in patients has been consistently observed through a variety of methods (see Kellendonk, 2009, for review). For example, a number of postmortem studies have reported an increase in subcortical dopamine (DA) in patients (e.g., Davis et al., 1991). In addition, studies using positron emission tomography (PET) to assess dopaminergic neurotransmission have reported increased uptake of the radioligand Flouro-Dopa in the striatum of patients with schizophrenia (e.g., Frankle, 2007) as well as in individuals in the prodromal phase of the disease (Howes et al., 2009), indicating increased DA synthesis. Other PET studies have shown increased DA neurotransmission in schizophrenia, as evidenced by increased amphetamine-induced displacement of D2 binding in patients (see Frankle, 2007, for review).

In addition to increased DA synthesis and neurotransmission, other studies have shown that striatal D2 receptors are also altered in schizophrenia. All effective antipsychotic drugs have been found to antagonize D2 receptors and their clinical efficacy correlates directly with their occupancy of D2 receptors (e.g., Seeman et al., 1976). In addition, post mortem studies have also reported an upregulation in striatal D2 receptors in drug-free patients (Davis et al., 1991). These data were confirmed in later PET studies, which demonstrate about a 12% increase in DA D2 receptor density in the striatum of patients (see Laruelle, 1998, for meta-analysis and review). Patients also display increased occupancy of striatal D2 receptors by DA (e.g., Abi-Dargham et al., 2000). Thus, the preponderance of evidence points to a hyperfunction of the striatal DA D2 system in schizophrenia as being a core aspect of the pathophysiology of the disease.

Modeling increased striatal D2 activity

In an effort to model the increased occupancy and density of striatal DA D2 receptors in patients, Kellendonk et al. (2006) generated transgenic mice which overexpress DA D2 receptors in the striatum. To accomplish this, they employed the tetracycline controlled gene expression system (see Aiba & Nakao, 2007, for discussion). This system utilizes a recombinant protein, the tetracycline transactivator (tTA), which is a transcription factor (protein that binds to DNA and controls the transformation of genetic information from DNA to mRNA) that binds to a specific DNA sequence, the tetracycline response element (tetO). The transgene is linked downstream of tetO in this system, so that transcription of the transgene only occurs upon binding of tTA to tetO. The antibiotic tetracycline as well as the tetracycline derivative doxycycline bind tTA and render it incapable of binding to tetO, thus

preventing expression of target genes. This allows for temporal control of transgene expression; by supplementing the animals diet with doxycycline the transgene is silenced.

Kellendonk et al. (2006) used a line of transgenic mice in which the expression of tTA is directed by a region and cell type specific promoter (segment of DNA which acts as a controlling element in the expression of a gene, in this case a portion of the promoter for the CamKIIα gene) to a particular brain area and cell type of interest (Mayford et al, 1996). They generated a second line of transgenic mice, in which the DNA coding sequence for the human dopamine D2 receptor was downstream of the tetO promoter. When mice from each of these lines are bred together, mice carrying both transgenes are produced, in which the transgenic D2 receptor gene is expressed when tTA binds to its tetO promoter, thus resulting in region and cell specific expression of transgenic D2 receptors (D2OE; Figure 1). While the endogenous expression pattern of the CamKIIα gene is in neurons of the entire forebrain, this promoter, in combination with the tetO-D2R transgene, resulted in transgenic D2 receptor expression restricted to the striatum and olfactory tubercule. This model system has a 15% increase in overall striatal D2 receptors, fortuitously mimicking the level of increase found in patients.

Characterization of the motivational deficit

Initial characterization suggested that D2OE mice model some of the core deficits in schizophrenia, including deficits in working memory and behavioral flexibility (Kellendonk et al., 2006). Given the importance of motivational impairments in schizophrenia, we assessed motivation in the D2OE mouse (Drew et al., 2007). The first evidence of a motivational deficit was obtained from assessing interval timing performance with a peak procedure. Distortions in timing are observed in many patients with schizophrenia (e.g., Clausen, 1950; Densen, 1977; Johnson & Petzel, 1971; Lhamon & Goldstone, 1956; Tysk, 1983, 1984, 1990; Davalos et al., 2003; Elvevag et al., 2004; Elvevag et al., 2003; Todd, 2006; Yang et al., 2004) and we wished to see if this characteristic might be traced to overexpression of striatal D2 receptors. In the peak procedure, on some trials, called fixed interval (FI) trials, mice are rewarded for the first response that occurs after a fixed interval (e.g., 24 s) has elapsed since the onset of the cue that signals the beginning of the trial. This contingency produces a low response rate at the beginning of the trial, followed by an increasing rate of response as the target time is approached. On some trials, the reward is omitted and the trial stimulus continues for much longer than usual. On these peak trials, the rate of responding across the trial gives an indication of how accurately the mouse is able to time the latency to reinforcement on FI trials. Generally, the average rate of responding increases up to a peak at or around the usual time of reinforcement, and then decreases (e.g., Roberts, 1981). The rate of responding has been taken as an index of motivation, and is affected by manipulations that target motivational states, such as feeding the animal prior to the session, changing the magnitude of the reward, or devaluing the reward via pairings with lithium chloride (Galtress & Kirkpatrick, 2009; Ludvig et al., 2007; Roberts, 1981). In this procedure, like animals with lower motivation, D2OE mice display significantly lower response rates than controls (Figure 2; Drew et al., 2007; Ward et al., 2009). In addition, reducing the motivation in control mice by decreasing the probability of reward on FI trials produced peak interval performance that was indistinguishable from that of D2OE mice trained with reward on all FI trials (Figure 2; Ward et al., 2009). These results suggested to us that the pattern of timing and the reduced rate of responding by D2OE mice in the peak interval procedure might have a motivational origin (see Drew et al., 2007, Ward et al., 2009, for further characterization and discussion of the timing impairment and its relation to motivation in D2OE mice).

We then assessed motivation more directly in the progressive ratio schedule (Hodos, 1961), a task that measures an animal's willingness to continue working for a reward as the effort requirement increases. In this schedule, the number of lever presses required for each reward increases after each reward. For the first experiment (Drew et al., 2007), the response requirement doubled after each reward (PRx2). Sessions lasted for two hours or until 3 min had elapsed without a response, whichever came first. The performance of control and D2OE mice on this task is depicted in the survival functions in Figure 3A. The functions show the percentage of mice that were still working on the progressive ratio schedule as a function of time in the session. As the session progresses and the work requirement increases, both control and D2OE mice quit working on the schedule. However, D2OE mice quit working on the schedule significantly sooner than control mice. This deficit in motivation is also evidenced by the decreased number of rewards earned, and the decreased number of lever presses emitted by D2OE mice. The motivational deficit was ameliorated by turning off the transgene, as D2OE-DOX mice displayed similar performance to controls on most behavioral measures.

To assess motivation across a range of work requirements, we tested the D2OE mice on progressive ratio schedules in which the work requirement was varied from PR+1 to PR+10 (Simpson et al., in press). As a way of summarizing performance across schedule requirements, Figure 4 shows the number of rewards earned as a function of increasing work requirement. Both control and D2OE mice earned fewer rewards as the work requirement increased, but D2OE mice worked less than controls at all work requirements. This deficit was reversed for all schedule values when the transgene is turned off. Importantly, these parametric data rule out several alternative interpretations of the progressive ratio deficit, namely that D2OE mice satiate or fatigue earlier than controls. For example, on the PR+10 schedule, D2OE mice made fewer responses, and earned fewer rewards, than on the PR+1 schedule. This result indicates that they did not drop out of the costlier schedule earlier as a result of reaching a ceiling in terms of responses or rewards.

Although the data from the progressive ratio schedule are consistent with a motivational deficit in D2OE mice, there are a number of alternative interpretations of the progressive ratio performance. One critical alternative interpretation is that the D2OE mice suffer from a motor impairment, which makes them unable to respond as quickly or to sustain effort as long as controls. This is especially important given the fact that DA has long been known to affect motor function (see Vallone et al., 2000, for review). The results from a number of experiments argue against this interpretation. D2OE mice do not differ in open field locomotion (although there was a nonsignificant trend toward less activity), latencies to perform radial arm and T-maze tasks, or in performance of the motorically demanding Morris water maze task (Kellendonk et al., 2006). Furthermore, there is no difference in the ease with which these mice learn to press a lever for reward (Bach et al., 2008; Ward et al., 2009). Finally, we analyzed the duration of the minimum interresponse time under the most effortful progressive ratio schedule we have tested (PRx2). We reasoned that gross motor impairments in D2OE mice would likely produce differences in the minimum interresponse time between them and controls. The minimum interresponse time (standard error in parentheses) for control and D2OE mice was .40 (.25) and .66 (.45), respectively. These values did not differ statistically [$t(13)=.51$]. Together, the available data suggest that the deficits we have found in the D2OE mice are not likely due to a gross motor impairment.

Another alternative interpretation of the progressive ratio performance has to do with the fact that as the work requirement is increased, the schedule becomes progressively more and more like extinction. Perhaps D2OE mice simply extinguish more quickly than controls. This interpretation can be ruled out by examining the response rate data over the course of the progressive ratio schedule sessions. Figure 5 shows response rates of control and D2OE

mice as a function of successive rewards earned on the progressive ratio in which the response requirement doubled after each successive reward. The data show response rates beginning after the 3rd reward. We truncated the analysis because response rates during the initial rewards increased but we wanted to assess the rate of decline in responding over the course of the session as the number of non-reinforced responses increases.

The data in the left panel of Figure 5 show that response rates for both control and D2OE mice decrease with successive rewards. In addition, response rates of D2OE mice are consistently lower than response rates of control mice. To assess possible differences in the rate of decline in response rates over the course of the session, we fit the response rate data of individual mice with negative exponential functions of the form $y = a * \exp(-bx)$ where a is the y intercept of the function and b is the rate of decay. As would be expected given the lower response rates, estimates of the intercept parameter (a) were lower for D2OE mice. However, comparison of the decay rates (right panel) between D2OE and control mice indicated no significant differences. Thus, D2OE mice do not quit sooner in the progressive ratio schedule because they extinguish at a faster rate than controls.

Increased work requirement in the progressive ratio schedule is confounded with increasing intervals between rewards (e.g., Lattal, Reilly, & Kohn, 1998). Another interpretation of the deficit in this schedule is that D2OE mice are less tolerant of longer times between rewards than controls, and so stop responding sooner. To test this possibility, we exposed the D2OE mice to a schedule in which the interreward intervals doubled after each reward (2s, 4s, 8s…), but the reward was delivered if the mouse emitted at least one response during the interval. This schedule preserves the increased time between rewards experienced in the PR schedule, but limits the work requirement so as to isolate the specific contribution of the changing reward times. As in the progressive ratio schedule, sessions terminated after two hours or after 3 min had elapsed without a response, whichever came first. As is clear from the data depicted in Figure 6, there was no difference in number of rewards earned, session duration, or latency to retrieve rewards between D2OE and control mice on this schedule, indicating that D2OE mice do not display decreased tolerance for delays between rewards.

There is one other interpretation of the motivational deficit in need of consideration. Perhaps overexpression of D2 receptors impacts the hedonic response in D2OE mice such that they enjoy the reward less than controls. If the rewards themselves were less enjoyable, the D2OE mice might quit working sooner than controls. Although we do not have direct data on hedonic response to rewards in D2OE mice vs. controls (they are currently being collected), we have data from a number of related measures which suggest that the enthusiasm for the reward is intact in D2OE mice. First, in all of the paradigms we have tested, there is no difference in the latency to consume rewards once they are presented (e.g., Drew et al., 2007; Ward et al., 2009; Simpson et al., in press). In addition, in Drew et al. there was no difference in the number of earned rewards that were consumed, and in Simpson et al. D2OE mice actually consumed more earned rewards than controls. Finally, there is no difference in preference for sucrose during a two bottle choice test between D2OE mice and controls (Drew et al., 2007). Together, these data suggest that the motivational deficit in D2OE mice is not due to decreased hedonic response to reward. This dissociation is consistent with evidence indicating that the dopaminergic system is not involved in “liking” of rewards (the hedonic aspect of motivation), but is critical in “wanting”, the energizing of behavior in pursuit of a goal (see Berridge & Robinson, 2003). Furthermore, if intact hedonic response to reward is confirmed in D2OE mice, these results would parallel those from patients indicating that the motivational deficit is not due to decreased hedonic response to rewards, but rather is a deficit in anticipatory motivation (Gard et al., 2007; Heerey & Gold, 2007; see Barch & Dowd, 2010 for review). Such results would also suggest that increased striatal D2 activity may be responsible for this deficit. The

fact that motivational impairments are not improved by D2 antagonists in patients, however, suggests that increased D2 activity alone is not sufficient to produce the deficit, and that other mechanisms (perhaps compensatory changes which occur as a result of striatal D2 overexpression) are involved.

In the present series of experiments we have demonstrated that D2OE mice work less than controls in progressive ratio schedules. We have interpreted this as evidence of a motivational deficit and have ruled out several alternative interpretations. Motivated performance has been characterized by Salamone and colleagues (Salamone et al., 2007Salamone et al., 2009) by assessing the tradeoff between responding on a lever to earn a preferred reward vs. consuming freely available homecage chow (Salamone et al., 1991). In this assay of effort related choice, rats responding on relatively easy schedules of reinforcement (Fixed ratio (FR) 1 or FR5) usually work for the more preferred reward, and eat little of the chow. Increasing the work requirement shifts behavior away from the lever and towards the freely available rat chow (Salamone et al., 1997). Thus, under more demanding work requirements, rats appear less “willing to work” for the preferred reward. Particularly relevant to the current discussion is the fact that willingness to work in this paradigm is sensitive to manipulations of the nucleus accumbens dopamine system (e.g., Salamone et al., 1991; 1996; Salamone & Correa, 2002). Our data thus far from the progressive ratio schedule are consistent with an interpretation of the motivational deficit in D2OE mice as resulting from decreased willingness to work. Nevertheless, testing the D2OE mice in this behavioral paradigm would help to further clarify the specific nature of the motivational deficit.

The search for a therapeutic target

The sophistication of the genetic technologies used in the development of many transgenic models allows for specification of neural systems underlying behavioral phenotypes with a degree of precision not heretofore possible. For example, the use of the tetracycline controlled gene expression system allows for the target gene to be switched off by application of doxycycline, making possible the dissociation of behavioral phenotypes that are the result of the current brain state versus those that result from irreversible changes in structure or function that occur over the course of development. In the D2OE mice, switching off the transgene in the adult animal rescued most aspects of the motivational deficit in the progressive ratio schedule (Figures 3 and 4). This result indicates that the motivational phenotype is largely influenced by the acute overexpression of D2 receptors (or other acute compensatory mechanisms), and is not produced by changes in brain structure or function that result from D2 overexpression during development. Thus, the search for pharmacologic rescue should focus on brain changes produced by D2 overexpression that are normalized when the transgene is turned off.

The most obvious change that results from turning off the transgene is the normalization of striatal D2 receptor levels. However, antagonism of D2 receptors was ineffective in rescuing the progressive ratio deficit (Simpson et al., in press) suggesting that although turning off the transgene restores striatal D2 receptors to normal levels, decreased D2 activity alone is not sufficient to rescue the motivational deficit. Thus, the motivational deficit is likely caused by other brain changes which result from D2 overexpression and are normalized when overexpression is turned off. Because of its implicated function in depression, another psychiatric disorder characterized by motivational deficits, we were particularly interested in serotonin function in D2OE mice. Subsequent experiments showed differences between D2OE and controls in the expression of the gene regulating the expression of the serotonin 5HT-2C receptor. The receptor was overexpressed in striatum in D2OE mice and this overexpression was normalized when the transgene was turned off, suggesting a possible

role for normalization of 5HT-2C receptor levels in the motivational rescue. In support of this, we found that selective antagonism of this receptor rescued the motivational deficit in the progressive ratio schedule (Simpson et al., in press), thus pointing to a potential new treatment for the motivational impairments in SCZ.

Conclusions

Although the present studies have ruled out a number of alternative explanations for the deficit in motivation in the D2OE mice and identified a therapeutic target, the particular psychological mechanism(s) underlying the deficit still need to be specified. Recent studies have suggested that motivational impairments in patients diagnosed with schizophrenia may arise from impaired ability to represent the value of future outcomes or in using this information to functionally guide goal directed behavior (see Barch & Dowd, 2010, for review). Based on preliminary data we have collected with the D2OE mice, we have reason to believe that these mice may also have difficulty in forming or maintaining outcome representations (Richards et al., 2009). In this experiment, two distinct operant responses (left or right lever press) produced two different outcomes (different flavors of Kool-Aid) in separate daily sessions. Only one response option and outcome were available per session. During devaluation tests, mice were given free access to one of the outcomes for 1 hr and then tested in a choice situation in which both levers were presented in extinction. Control mice responded less on the lever associated with the devalued outcome, but D2OE mice responded non-differentially on both levers (data not shown). Although these results suggest failure by D2OE mice to represent distinctive outcomes, they are only preliminary and are subject to multiple interpretations (e.g., failure to discriminate between the two flavors). More experiments are needed to verify this initial finding and to determine whether rescue of this psychological mechanism underlies the rescue observed when the transgene is turned off and under 5HT-2C antagonism. Nevertheless, this line of experimentation illustrates how it is useful to allow the interaction between behavior analysis and psychiatry to be bidirectional. This latter example illustrates the importance of letting research in clinical populations focus and guide programs of research in the study of animal models of psychiatric diseases.

In conclusion, although considerable research effort has been directed towards understanding negative symptoms in schizophrenia, this effort has been unsuccessful in identifying successful therapeutic targets (Kirkpatrick et al., 2006). We suggest that this failure is due in part to the lack of rigorous behavior analysis of animal models of psychiatric disorders. As we have shown with our characterization of the motivational deficit in D2OE mice, careful experimental analysis of behavioral and cognitive processes is critical for understanding the mechanisms underlying the behavioral phenotypes in model systems and to mapping them on to the human condition. A synthesis of behavior analysis and neuroscience promises to lead to important advances in uncovering the causes of and possible treatments for psychiatric disease.

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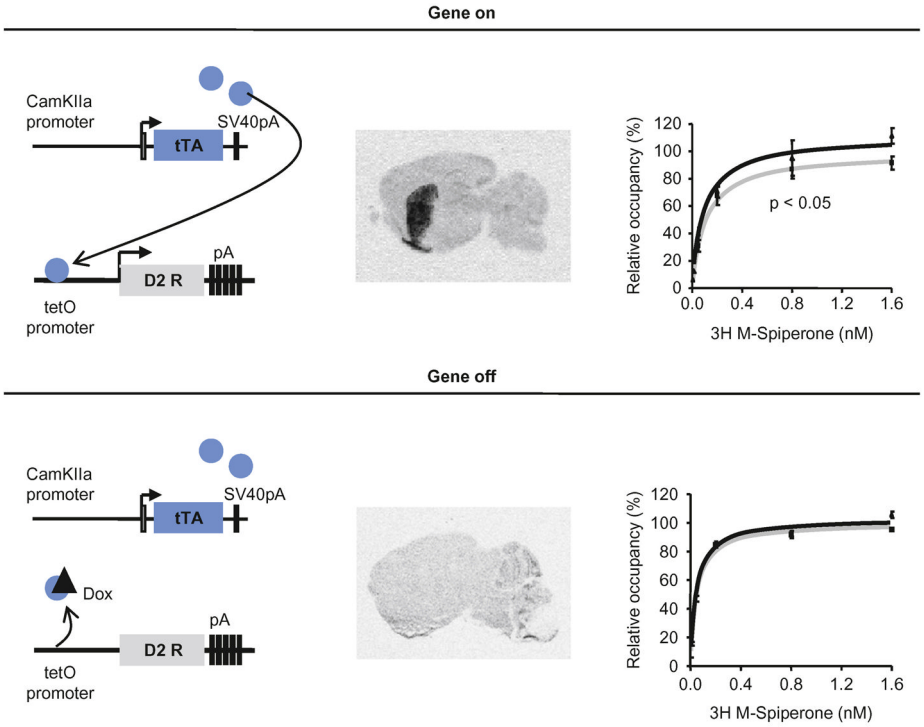

Figure 1.

The top left panel diagrams the genetic construct used to generate the D2OE mice. The CamKIIα promoter was used to target expression of the tetracycline transactivator tTA. The D2 receptor was expressed under the tetracycline responsive element tetO. In a double transgenic mouse, overexpression of D2 receptor mRNA is restricted to the striatum (shown with in situ hybridization; top middle panel). The extra D2 receptors are functional, as shown by ligand binding studies (top right panel). Feeding doxycycline for 14 days reverses the transgenic overexpression of D2 receptors (bottom panels). From Kellendonk (2009).

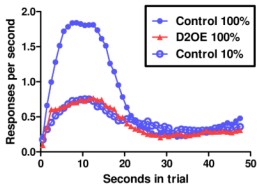

Figure 2.
Average responses per second as a function of time in the peak trial for both control and D2OE mice. Data are shown from conditions in which the probability of a reward on FI trials was varied. Adapted from Ward et al. (2009).

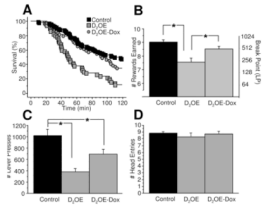

Figure 3.

A. Kaplan-Meier survival function plotting the percentage of mice continuing to respond on the progressive ratio schedule as a function of session time. **B.** Number of rewards earned and breakpoint (last ratio completed). **C.** Total number of lever presses. **D.** Number of head entries after a reward delivery. From Drew et al. (2007).

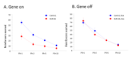

Figure 4.
Reinforcers earned during the progressive ratio schedule as a function of work requirement (see text for details) for control and D2OE mice. Data are shown from mice in which the transgene was on (panel A) and in which the transgene was turned off by application of doxycycline (panel B). From Simpson et al. (in press).

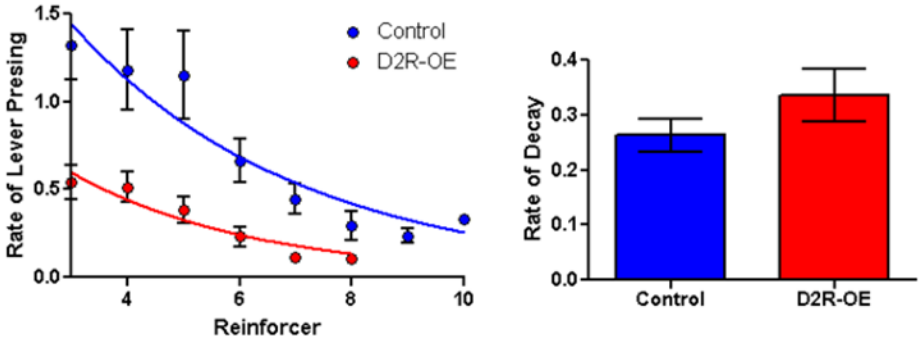

Figure 5.

The left panel shows the average rate of lever pressing as a function of successive rewards in the progressive ratio schedule for control and D2OE mice. The smooth curves through the data are the best fitting negative exponential functions (see text for details). The right panel shows the average rate of decay (b parameter from the exponential equation) for both groups of mice. From Simpson et al. (in press).

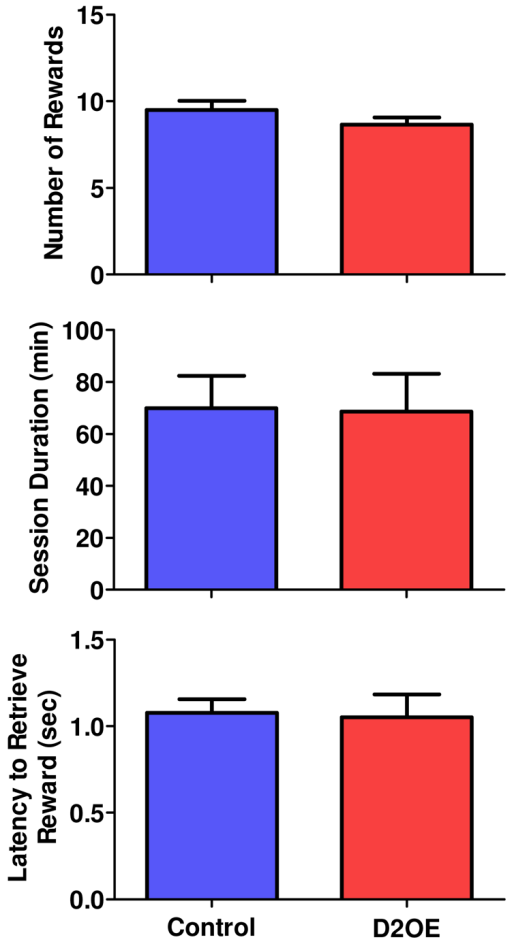

Figure 6.
Performance on the progressive delay schedule for control and D2OE mice. The top panel shows the number of rewards earned, the middle panel shows the session duration, and the bottom panel shows the latency to retrieve the reward. After Simpson et al. (in press).