CHAPTER 7

Interactions of Timing and Motivational Impairments in Schizophrenia

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1 Introduction

Cognitive impairments are a hallmark of schizophrenia and include disturbances in working memory, attention, and executive function (Kerns et al., 2008). Some investigators have proposed that dysfunctional cognition is the core deficit in schizophrenia (Elvevåg and Goldberg, 2000; Heinrichs, 2005). For example, Andreason and colleagues have suggested that the primary phenotype in schizophrenia is “cognitive dysmetria” which they define as “a disruption in the fluid coordination of mental activity that is the hallmark of normal cognition” (Andreason et al., 1999). Such a dysfunction in some fundamental aspect of cognition could result in a detrimental cascade of effects, ultimately giving rise to more serious cognitive impairments, as well as contributing to the positive and negative symptoms of schizophrenia.

What crucial aspect of cognition could be responsible for such a pervasive impairment? Some have suggested that the fundamental process that may be impaired is temporal information processing (Andreason et al., 1999; Elvevag et al., 2004). Distorted timing is well documented in patients with schizophrenia. Patients have been described as being disoriented in time: not knowing the time of day, day of the week, month or even year (Lewis, 1932). Patients also report alterations in the perception of time. Sometimes time slows (even to the point of standing still) and sometimes it rushes by at high speed (Freedman, 1974; Lewis, 1932). In addition to these more anecdotal reports of temporal distortions, a growing literature has demonstrated empirically the existence of distorted temporal information processing in a variety of experimental paradigms in individuals diagnosed with schizophrenia (e.g., see Penney et al., 2005, for review). For example, patients have been reported to overestimate
interval duration when they are asked to verbally report the duration of a presented stimulus (e.g., Clausen, 1950; Densen, 1977; Johnson and Petzel, 1971; Lhamon and Goldstone, 1956; Tysk, 1983, 1984a, 1990). When asked to reproduce a standard interval of some specified duration, patients have been reported to underestimate time (e.g., Clausen, 1950; Johnson and Petzel, 1971; Tysk, 1983, 1990; Wahl and Sieg, 1980). While the specific nature of the timing deficit is different depending on the experimental paradigm employed, when all data are considered together, the most reliable finding across paradigms and studies is that patients are more variable in their timing of temporal intervals than controls (Carroll et al., 2008, 2009; Davalos et al., 2003; Elvevag et al., 2003, 2004; Todd, 2006; Yang et al., 2004). Thus, distortions in temporal information processing are reliably associated with the disease. Furthermore, interval timing deficits were evident in patients who were at risk for developing schizophrenia but not major affective disorder (Penney et al., 2005) providing additional evidence that schizophrenia and timing are deeply linked.

1.1 Dopaminergic Dysfunction in Schizophrenia

Although the specific neural underpinnings of schizophrenia are not fully described, one of the most influential hypotheses is that the disease reflects pathological changes in activity of the dopaminergic systems (e.g., Howes and Kapur, 2009). Hyperactivity of the striatal dopamine (DA) system in patients has been consistently observed through a variety of methods (see Kellendonk, 2009, for a review). For example, a number of postmortem studies have reported an increase in subcortical 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 fluorodopa 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. One of the most general and replicable findings is hyperactivity of DA D2 receptors in the striatum of patients and all effective antipsychotic drugs antagonize D2 receptors (e.g., Seeman et al., 1976). Post mortem studies report an upregulation in striatal D2 receptors in drug-free patients (Davis et al., 1991). These data have been confirmed in PET studies, which demonstrate about a 12% average increase in DA D2 receptor density in the striatum of drug-free and drug-naïve patients (Howes et al., 2009).
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 majority of evidence confirms that there is a hyperfunction of the striatal DA D2 system in schizophrenia, suggesting it is an important part of the pathophysiology of the disease. Furthermore, PFC hypactivity has also been reported (Barch, 2005; Glahn et al., 2005) and the PFC has long been a target of schizophrenia research, given the well documented reliance of working memory, which is compromised in schizophrenia, on normal PFC function (e.g., Goldman-Rakic and Selemon, 1997; Goldman-Rakic et al., 2004; Lewis et al., 1999). Abnormal PFC and striatal functioning is thought to compromise the integrity of cortico-striatal circuits, leading to functional impairments (see Simpson, Kellendonk, and Kandel, 2010, for review and discussion on how excessive striatal D2 activity could lead to PFC dysfunction).

### 1.2 Modeling Increased Striatal D2 Receptor Activity in Schizophrenia

One of the ways to examine the causal relationship between D2 receptors and the deficit in interval timing observed in patients is to utilize transgenic animal models that may mimic the endophenotypes in schizophrenia. 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 selectively overexpress DA D2 receptors in the striatum. To accomplish this, they employed the tetracycline controlled gene expression system (see Aiba and Nakao, 2007, for discussion). This system utilizes a recombinant protein, the tetracycline transactivator (tTA), which is a transcription factor 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 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 (Figure 7.1).
The upper panels show the genetic system used to generate the D2R-OE mice. In one mouse line, the human D2 receptor gene is expressed under control of the tetO promoter. In a second mouse line, the tTA element is expressed under control of the CamKIIα promoter. In a mouse in which both transgenes are present, the tTA element binds to the tetO promoter, driving expression of D2 receptors. In the D2R-OE mice, expression of excess D2 receptors is confined to the striatum and olfactory tubercule (shown via in situ hybridization in the upper right panel). Feeding the mouse doxycycline prevents tTA from binding to the tetO promoter (bottom left panel), thereby eliminating expression of the transgenic D2 receptors (bottom right panel). Figure adapted from Kellendonk (2009).

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. The overexpression can be turned off by feeding the mice...
doxycycline, which prevents tTA from binding to tetO, thus preventing expression of the D2 receptor gene.

1.3 Interaction of Timing and Motivation in D2R-OE Mice

Given that the ability of a drug to modulate timing was correlated with the affinity of the drug for the D2 receptor (Meck, 1986) as well as the dependence of timing on the striatum (Matell and Meck, 2004) we thought that it would be worthwhile to use the D2R-OE mouse to study the specific role of striatal D2 signaling on interval timing. In the first of our studies, Drew et al. (2007) found severe impairments in temporal information processing in these mice when trained on a task called the peak procedure. In this procedure, animals were first trained to press a lever in an operant chamber and to consume liquid rewards. Following this training, mice were trained to press the lever on a fixed interval (FI) schedule in which lever presses were not reinforced until after a FI had elapsed from the insertion of the lever into the chamber at the start of a trial. Mice went through training on an increasing series of FI schedules until the final target duration of 24 s was reached. When performance on the FI 24 s schedule was stable, peak interval trials were introduced. On peak trials, the lever was extended as on FI trials, but the lever remained extended for 96 s and no reward was given. In a well-trained animal, the average rate of responding generally begins low, then increases and peaks at or around the usual time of reinforcement, and then decreases (Roberts, 1981). Quantitative analysis of the distributions of lever press responses on the peak trials can be used to provide estimates of motivation to respond in the task, accuracy, and precision of interval timing. The peak height of the response rate distribution indexes 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 and Kirkpatrick, 2009; Ludvig et al., 2007; Roberts, 1981). The location of the maximal rate of responding gives an index of how accurately the mice were able to time the temporal interval, and the spread of the response rate distribution is a measure of the precision (variability) of interval timing. Figure 7.2 shows that when performance was characterized in this way, D2R-OE mice responded at overall lower rates, indicating lack of motivation.

In addition, the response rate distributions of D2R-OE mice were flatter, and peaked later than the target interval of 24 s, indicating decreased precision and accuracy of timing. Turning off the transgene with doxycycline improved motivation (increased response rate), and partially rescued the deficit in the accuracy and precision of timing. These data suggest the possibility of a motivational
component to the timing deficits, which is rescued by turning off the transgene.

Response rates in the peak procedure provided an indirect measure of motivation. To more directly assess motivation, the progressive ratio task, which measures the amount of effort a subject will expend to earn a reward, was used (Drew et al., 2007). In this task, the mouse earns reward after completing a criterion number of lever presses. The criterion was set at two lever presses for the first trial and then doubled with each successive trial. In this procedure, as shown in Figure 7.3, D2R-OE mice ceased responding significantly earlier, earned fewer rewards, and made fewer responses. These deficits were ameliorated when the transgene was turned off, indicating that the progressive ratio impairment in D2R-OE mice results from acute overexpression of the D2 receptor.

We investigated the interaction between timing and motivation in the peak procedure by reducing the probability of reward on F1 trials (Ward et al., 2009). Our reasoning was that if the timing deficits in D2R-OE mice resulted from motivational impairments, we should be able to mimic the impairment in controls by reducing motivation during the peak procedure. The peak procedure was employed exactly as described above, except that the percentage of rewarded F1 trials was decreased across conditions from 100 to 5%. Each reward percentage condition was in place for at least five sessions until the response rate data appeared stable. As shown in Figure 7.4A, manipulation of reward probability impacted performance of both control and D2R-OE mice, with poorer performance as reward probability was reduced.
Most interestingly however, when the level of motivation as indexed by peak height was similar between control and D2R-OE mice, timing accuracy and precision were also similar, strongly suggesting a motivational component to the timing deficits in D2R-OE mice.

These results are consistent with a large body of evidence implicating the DA D2 receptor in both motivation and temporal information processing. As far as motivation is concerned, DAergic signaling has been shown to be critical to the performance of motivated behavior in a number of paradigms (see...
Salamone et al., 2007, 2009, 2012, for reviews). For example, both DA antagonists and depletion of nucleus accumbens DA decrease operant responding for food, particularly when the lever press requirement becomes more effortful (e.g., Aberman and Salamone 1999; Ishiwari et al., 2004). The specific role of DA in reward motivated behavior has been clarified using a procedure in which animals are given the choice to work (lever press) for a more preferred reward, or consume a freely available less preferred reward. In this procedure, animals with intact DA signaling press the lever for the preferred reward, and consume little of the free chow. However, antagonism of DA receptors leads to a shift in

![Figure 7.4](image-url)

**A.** Peak interval performance of both control and D2R-OE mice is sensitive to manipulation of motivation. Motivation was manipulated by changing the percentage of rewarded fixed interval trials (see text for details). Circles show performance under conditions of 100% rewarded FI trials, while triangles show performance under 10% rewarded FI trials. Closed symbols show control performance, while open symbols show performance of D2R-OE mice. Decreasing motivation in control mice results in performance that is indistinguishable from that of D2OE mice. **B.** Performance of control and D2OE mice on the bisection procedure (see text for details) with anchor durations of 2 and 8 s. The figure shows the proportion of trials on which the mice chose the response lever corresponding to a “long” sample duration as a function of sample duration. There are no differences in performance between genotypes. **C.** Performance of control and D2R-OE mice on the bisection procedure with anchor durations of 6 and 24 s. D2R-OE mice are selectively impaired on longer duration sample trials, suggesting a deficit in working memory or sustained attention. Data from Ward et al. (2009).
behavior away from the more effortful lever press towards the freely available chow (Cousins and Salamone, 1994; Farrar et al., 2010; Salamone et al., 1991, 1996; Salamone and Correa, 2002). Data like these are clarifying the role of DA in motivated behavior and emphasize the importance of DA signaling in contributing to the computation of work-related response costs.

Many studies indicate that temporal information processing can be distorted by manipulations that target the DA system (Buhusi and Meck, 2005; Maricq and Church, 1983). Although theoretical accounts of the underlying mechanisms of these effects differ, administration of both DA agonists and antagonists has been shown repeatedly to produce disruption of temporal information processing in a variety of experimental protocols (see Coull et al., 2011 for review). In particular, empirical evidence indicates that temporal information processing is particularly sensitive to manipulation of D2 receptor function. For example, Meck (1986) demonstrated that the dose of a neuroleptic that was required to distort rats’ perception of a time interval by 10-15% was negatively correlated with the drugs’ affinity for DA D2 receptors. Thus, D2 receptor activity is critical in accurate temporal information processing.

1.4 Rescuing Motivation Rescues Timing in D2R-OE Mice

The data from the peak procedure in which the probability of reward was manipulated indicate that manipulation of motivation impacts timing, and strongly suggest that the timing impairment in D2R-OE mice has a motivational component. However, in the peak procedure it is not possible to separate deficits in timing from those in motivation, because the index of timing is response rate, and response rate is greatly impacted by motivation. To further examine the nature of the timing impairment, we tested the D2R-OE mice on a timing task, which is not dependent on response rate as the measure of timing (Ward et al., 2009). In the temporal bisection task (Church and Deluty, 1977) at trial onset a sample (e.g., tone) is presented for either a short (e.g., 2 s) or long (e.g., 8 s) duration. Following sample presentation, response levers are presented and responses on one lever are only rewarded following presentation of short samples while responses on the other lever are only rewarded following presentation of long samples. Once performance with these anchor durations is learned, mice can be tested on trials in which intermediate duration samples are presented. Accuracy and precision of interval timing performance can be assessed by examining the proportion of choices to the lever corresponding to a ‘long’ sample duration as a function of sample duration. Once performance is stable, the proportion of responses to the long choice option is generally an increasing sigmoidal function of sample duration (Church and Deluty, 1977). The slope of this function indicates precision of
interval timing, while the point on the function that corresponds to 50% long choices, or the point of subjective equality, gives an estimate of the accuracy of interval timing. Because only a single response is required in each trial, performance in the bisection task is not as affected by motivation to respond as the peak interval procedure.

The bottom panels of Figure 7.4 show the results of these experiments. The results indicated that D2R-OE mice have difficulty processing temporal information only at relatively long durations. With the relatively short anchor durations of 2 and 8 s (Figure 7.4B), for both control and D2R-OE mice the proportion of responses corresponding to the “long” response option increases with increasing sample duration, but there is no difference between control and D2R-OE mice, indicating that timing of these relatively short durations is intact. However, when the anchor durations were 6 and 24 s (Figure 7.4C), a difference emerged. At the longer durations, the proportion of “long” responses was significantly lower for D2R-OE mice than controls, indicating a selective impairment when required to process temporal information over longer intervals. This selective impairment in timing of relatively long durations could be due to a deficit in working memory or sustained attention, psychological processes that are critical to accurately process temporal information over longer intervals. However, when we tested the D2R-OE mice in operant paradigms, which assessed retention of information in working memory and sustained attention, we found no deficit. This suggested to us the possibility that there may be a motivational component to the timing impairment.

We had previously demonstrated that the motivational impairment could be rescued by turning off the transgene by feeding the mice doxycycline (Drew et al., 2007; Simpson et al., 2011). We next tested whether the timing impairment in the bisection procedure could also be rescued by turning off the transgene. Indeed, turning off the transgene rescued the timing impairment in the bisection procedure (Avlar et al., in preparation) suggesting a motivational basis for this deficit. The specific contribution of motivation to the timing deficits in the bisection procedure must be complex. The data from the peak procedure in which response rates of D2R-OE mice were significantly lower than controls indicates the presence of a basal motivational impairment. However, when the influence of response rates on the index of timing was removed by testing the mice in the bisection procedure, there was no general timing impairment with brief stimuli (Figure 7.4C). Only when the target duration became relatively long (>15 s) did the impairment manifest itself. On the face of it, this selective impairment in processing of longer temporal durations suggests a difficulty in working memory or attention. The fact that sustained attention and working memory maintenance are not impaired in the D2R-OE mice
when assessed separately, however, suggests the possibility that the deficit results from an interaction of these cognitive processes when they are both required to work in concert, as in processing of longer temporal delays.

If there is a motivational component to the temporal information processing impairments in D2R-OE mice, we should be able to improve performance using an experimental manipulation that improves motivation. Therefore, manipulating the reward magnitude in a temporal discrimination task is particularly beneficial, because it gives us an opportunity to assess the interval timing independent of lever pressing vigor. Preliminary results from our lab (Avlar et al., in preparation) showed that altering the levels of motivation by increasing the reward magnitude for the longer cue durations, also improved the timing of both control and D2R-OE mice, although D2R-OE mice required a longer period of exposure to the increased reward magnitude before the improvements were manifest.

2 How Does Motivation Impact Timing?

The results from our assessment of timing and motivation in D2R-OE mice indicated that motivation is critical in accurate temporal information processing. To conceptually dissect this interaction, Figure 7.5 shows the psychological processes thought to be involved in interval timing.

Although different accounts differ in the specifics, the general component processes are common across theories. In order to accurately process temporal information, an organism must perceive and attend to the passage of time, store a representation of time in memory, and then make decisions about appropriate behavioral responses based on a comparison of the currently elapsing duration with previously experienced durations. First, some environmental event must trigger a timing mechanism. Information about the duration of the currently elapsing interval is stored and continuously updated in working memory. When the stimulus event ends or another biologically significant event occurs, the duration of the interval is transferred to long term memory. On subsequent occasions when the same or similar stimulus events are encountered, the elapsing duration is compared to a stored duration in long term memory. If the comparison crosses response thresholds, an appropriate behavioral action is selected. Thus, accurate interval timing requires proper functioning of a cascade of related psychological processes, including perception, attention, working memory, long term memory, and decision processes. In addition, these processes are impacted by motivation. A large literature has demonstrated that manipulations of aspects of reward, which putatively
impact motivation during cognitive tasks, impact performance on these tasks. For example, in the peak procedure, when animals are pre-fed a large amount before the daily session, the response rate function flattened and shifted to the right, and this effect was interpreted as evidence of a change in clock speed (Roberts, 1981; see also Galtress and Kirkpatrick, 2009; Ward and Odum, 2006, 2007). Others have demonstrated similar effects with manipulations of reward magnitude. Increases and decreases of reward magnitude produce leftward, and rightward shifts in the response rate function, respectively, and these shifts have also been interpreted as changes in the speed of the clock (Grace and Nevin, 2000; Kacelnik and Brunner, 2002; Ludvig, Conover, and Shizgal, 2007; see also Bizo and White, 1995; Killeen et al., 1999; Ward and Odum, 2007). In addition to effects on clock speed, motivation has also been theorized to impact the latency to initiate the timing mechanism (Gibbon and Church, 1984; Lejueune, Macar, and Zakay, 1999), the vigilance with which the elapsing interval is attended to (Fortin and Masse, 2000; Ward and Odum, 2007; Zakay, 1989), and decision related computations (e.g., Bendiksby and Platt, 2006; Gold and Shadlen, 2001; Leon and Shadlen, 1999; Platt and Glimcher, 1999; Sugrue et al., 2004), among others. Determining the impact of motivational manipulations on specific psychological processes or their interaction is challenging, but what

**Figure 7.5** Conceptual framework showing the psychological processes which are thought to underlie temporal information processing, and their interaction with motivation (see text for details).
is clear from these types of studies is that motivation plays a critical modulatory role in cognitive processes which underlie temporal information processing.

2.1 Motivation as a Target for Improving Cognition and Timing

Our work with the D2R-OE mice indicated that both motivation and temporal information processing could be improved by switching off the transgene by feeding the mice doxycycline. These results indicate that these impairments are caused by the acute overexpression of D2 receptors, and returning D2R expression levels to normal is sufficient to rescue the performance deficits. Thus, it should be possible to perform some acute manipulation and rescue the performance. We (Simpson et al., 2011) therefore conducted a series of studies in an effort to find successful strategies for rescuing the motivational deficit. Because the most obvious effect of turning off the transgene is normalization of D2R activity, we first attempted to use a pharmacological strategy to recapitulate this normalization. We administered the D2 receptor antagonist haloperidol chronically for two weeks (via subcutaneous osmotic mini-pumps) and assessed motivation in the progressive ratio paradigm. Even with the lowest dose used, we were unable to improve performance via haloperidol. In fact, at the higher doses, haloperidol produced performance decrements. Interestingly, these results are in line with clinical reports, which indicate that haloperidol, although effective in treating positive symptoms in schizophrenia, has no efficacy for treatment of motivational deficits. In fact, as we observed and as corroborated by numerous published studies, haloperidol has been shown to decrease motivation as assessed in a number of paradigms. The lack of efficacy of haloperidol could possibly be due to the difficulty in targeting and antagonizing only the excess D2 receptors, or it could be due to haloperidol’s actions at other receptors. We, therefore, searched for an alternative strategy for modulating circuit function. We performed an unbiased gene chip assay, which determined the expression levels of thousands of genes. Because the motivational deficit was reversed when the transgene was turned off, we focused on changes in gene expression, which were also reversed when the transgene was turned off. Given the demonstrated role of the serotonin system in psychiatric diseases in which motivation is compromised, we were particularly interested in changes in this system. We surveyed the changes in the serotonin system and found increased expression of the serotonin 2C (5-HT2C) receptor in the striatum of D2R-OE mice, which was normalized when the transgene was turned off. To see if this overexpression of the 5-HT2C receptor contributed to the motivational impairment of the D2R-OE mice, we administered the selective 5-HT2C antagonist SB 242084. Systemic administration of this drug rescued performance in a progressive ratio schedule.
Not only did the 5-HT2C antagonist rescue motivation in D2R-OE mice, it also improved motivation in control mice. This suggests that the impact of the drug was not through a mechanism specific to the deficit in D2R-OE mice. Rather, the effect was likely due to a general role of 5-HT2C receptors in motivation. These results indicate that motivation in the D2R-OE mice can be rescued by 5-HT2C receptor antagonism and suggest a novel therapeutic strategy for patients.

Consistent with the idea that motivation modulates the accuracy and precision of timing, preliminary data from our lab is in line with the hypothesis that timing deficits can be ameliorated by increasing motivation via 5-HT2C antagonism. In a temporal bisection task, administration of SB242084 improved the precision and accuracy of the timing in both controls and D2R-OE mice (Avlar et al., in preparation) in the same way such improvements might be anticipated when reward factors are directly manipulated to increase motivation (Galtress and Kirkpatrick, 2010; Ward et al., 2009). Of course, improvement in timing could be due to the 5-HT2C receptor antagonist having a direct pro-cognitive effect (e.g., altered memory or attention) but the evidence so far is consistent with the hypothesis that the improvements arise from an indirect effect on cognition via modulation of motivation. We suggest that therapeutic strategies that target motivation may be a viable strategy for improving cognition in schizophrenia.

These results may also be relevant to depression. Lack of motivation is also characteristic of depression, and there are data to suggest that the 5-HT2C receptor may be altered in depression. For example, post mortem studies of suicide victims with a history of depression showed that 5-HT2C pre-mRNA editing was altered in prefrontal cortex (Gurevich et al., 2002). In addition, using a mouse model, Mombereau et al. (2010) reported that complete editing of 5-HT2C receptor mRNA resulted in an antidepressant-like phenotype as measured in a forced swimming test. There is also some evidence that temporal information processing is disrupted in depression (Bschor et al., 2004; Gil and Droit-Volet, 2009; Grinker et al., 1973; Sevigny et al., 2003; Tysk, 1984). Given the demonstrated role of the 5-HT2C receptor in motivation (Pentkowski et al., 2010; Simpson et al., 2011), perhaps targeting this receptor would be therapeutically beneficial in depression as well.

3 Conclusions

The dysmetria hypothesis of the symptoms of schizophrenia is an appealing one. It is easy to imagine how improper timing in the flow of information leads
to many of the symptoms of the disorder (see Ward et al., 2012, for discussion) including disorganized behavior, delusions, and misjudgments of causality (Andreason et al., 1999; Carroll et al., 2008; Metcalfe et al., 2012). For example, consider the case of delusions. Disruption in temporal perception could lead to failure to correctly perceive the temporal order of temporally contiguous events. This in turn could lead to a lack of attribution of causality to one’s own actions, and instead causally attributing events in one’s life to other sources (aliens, spies, etc.). Of course some of the symptoms of schizophrenia may also be directly affected by difficulties in other aspects of information processing such as memory and decision-making, or as the results of our experiments with the D2R-OE mice suggest, some of the cognitive deficits may be a consequence of a dysfunction in motivation. The developmental overexpression of striatal D2 receptors is sufficient to produce both motivational and timing impairments. Our data indicate that motivational and cognitive processes interact in producing the timing deficits. The level of motivation modulates timing accuracy and precision in both D2R-OE and control mice to such an extent that as motivation is decreased in control mice, a timing phenotype emerges that is identical to that of D2R-OE mice. Thus, it seems plausible that at least in the subset of patients who exhibit negative symptoms, the deficit in motivation contributes to their cognitive deficits including those in timing.

In recent years, there has been a renewal of research effort into the negative symptoms of schizophrenia. While positive symptoms (disordered thoughts, delusions, hallucinations) are perhaps the most prototypical symptoms of schizophrenia, severity of positive symptoms is not correlated with functional impairment in the disease. Cognitive (deficits in perception, attention, working memory, executive functioning) and negative (blunted affect, social withdrawal, lack of motivation) symptoms, on the other hand, are highly predictive of functional outcomes (Beng-Choon et al., 1998). There has been significant research effort focused on developing pharmacological interventions for the cognitive deficits in schizophrenia, but so far an effective therapeutic strategy remains elusive (Keefe et al., 2007). Aside from the general complexity of the neurobiological mechanisms of the disease, one reason that current pharmacological strategies are ineffective in producing improvements in functional outcomes may be that a critical motivational component is not being addressed. While there have been some modest successes in treating cognitive impairment, there are no efficacious therapies for treating the motivational impairments. In fact, current therapeutic strategies for treating positive symptoms based on some level of D2 receptor antagonism likely worsen motivational impairments (Salamone et al., 2009; Simpson et al., 2011). By focusing on the interaction of motivation and cognition, the work with the D2R-OE mouse
model directly points to some novel treatment strategies. The motivational impairments are rescued and there is a concomitant improvement in timing when D2 receptor expression is returned to normal levels. This suggests that targeting motivational circuits might be an effective means of improving both motivation and cognition. Consistent with this hypothesis we found that a 5-HT2C receptor antagonist improves motivation (Simpson et al., 2011) and here describe preliminary data showing that timing is also improved by this intervention.

More generally, the difficulty in finding effective treatments for psychiatric diseases with heterogeneous symptom manifestation illustrates the need for caution when trying to understand psychiatric disease as comprising distinct clusters of clinical symptoms. Of course, parsing psychiatric syndromes into symptom clusters, as in the case with the three symptom clusters in schizophrenia (positive, negative, cognitive) aids in being able to speak in a coherent way about patients and in forming a coherent clinical picture of the disease. This view, however, becomes problematic when it is treated as indicative of an actual partitioning of various psychological and biological processes that may be impaired in disease states. This mindset has perhaps been perpetuated by the advances in functional magnetic resonance imaging (fMRI) technology, which make it possible to visualize brain activity of participants while they are engaged in various experimental protocols. Many of these studies then correlate brain activity in a certain region of interest with severity of patient symptoms as indexed on a clinical scale. This practice reinforces the tendency to interpret fMRI data as a visualization of specific and distinct symptom types (or cognitive processes which underlie these symptoms) physically instantiated in the brain. These types of interpretations lead to the compartmentalization of the brain into areas based on some purported functional specificity. Although some functional selectivity has been supported empirically, in general, the notion that specific brain regions or networks subserve specific subsets of cognitive processes is the topic of considerable debate among cognitive neuroscientists (Barrett, 2012; Friston and Price, 2011; Mahon and Cantlon, 2011; Uttal, 2001, 2011).

The situation becomes even more challenging when one considers the fact that even specific symptoms are not monolithic constructs, but nuanced and complex phenomena. For example, it is easy to say that motivation is impaired in schizophrenia, but what is motivation? The outward behavioral manifestation of a lack of motivated behavior could result from impairments and interactions in numerous aspects of reward and cognitive processing (Barch and Dowd, 2010; Salamone et al., 2007; Ward et al, 2012) which would have to be dissected in order to understand the specific nature of the deficit. Thus, attempting to treat
certain symptoms while failing to consider their interactions with other symptoms is not likely to lead to the most efficacious therapeutic strategies.

In closing, we suggest that it is important to consider the inseparability of motivation, cognition, emotion, perception, decision-making, and action selection. All these features of behavioral regulation evolved to produce a reasonably successful behavioral output in the right place and at the right time. We identify psychiatric disorders because the output of these systems becomes dangerous or disruptive. Consequently, it seems foundational to understand that behavioral outputs are simultaneously regulated by this entire set of interacting processes. In this context, we should not expect to find a single cause for complex psychiatric disorders, nor perhaps a single cure. Although this approach increases the complexity of the search to understand causes of psychiatric disease, it also holds a promise for contributing to significant advances in helping patients deal with their difficulties.

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