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# Can antipsychotic treatment contribute to drug addiction in schizophrenia?

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ABSTRACT

Individuals with schizophrenia are at very high risk for drug abuse and addiction. Patients with a coexisting drug problem fare worse than patients who do not use drugs, and are also more difficult to treat. Current hypotheses cannot adequately account for why patients with schizophrenia so often have a co-morbid drug problem. I present here a complementary hypothesis based on evidence showing that chronic exposure to antipsychotic medications can induce supersensitivity within the brain's dopamine systems, and that this in turn can enhance the rewarding and incentive motivational effects of drugs and reward cues. At the neurobiological level, these effects of antipsychotics are potentially linked to antipsychotic-induced increases in the striatal levels of dopamine D2 receptors and D2 receptors in a high-affinity state for dopamine, particularly at postsynaptic sites. Antipsychotic-induced dopamine supersensitivity and enhanced reward function are not inevitable consequences of prolonged antipsychotic treatment. At least two parameters appear to promote these effects; the use of antipsychotics of the typical class, and continuous rather than intermittent antipsychotic exposure, such that silencing of dopaminergic neurotransmission via D2/3 receptors is unremitting. Thus, by inducing forms of neural plasticity that facilitate the ability of drugs and reward cues to gain control over behaviour, some currently used treatment strategies with typical antipsychotics might contribute to compulsive drug seeking and drug taking behaviours in vulnerable schizophrenia patients.


## 1. Introduction

It is estimated that 47% of individuals with schizophrenia symptoms will also have a co-morbid substance abuse problem in their lifetime (Kavanagh et al., 2002; Regier et al., 1990). This is significantly more than in the general population and than in most other psychiatric groups (Martins and Gorelick, 2011; Regier et al., 1990; Ziedonis et al., 2008). Schizophrenia patients with a co-morbid drug problem are more severely ill, experience more physical, psychological and social distress and represent a great challenge to treatment (Kerfoot et al., 2011; Owen et al., 1996). Although drug abuse and addiction are excessively common in schizophrenia, the reasons for this remain unknown. Two hypotheses are most often evoked to explain this phenomenon. The first is the self-medication hypothesis (Khantzian, 1985; Schneier and Siris, 1987), which proposes that individuals with schizophrenia use drugs to relieve their symptoms or the side effects of antipsychotic medication. The second is the overlapping neural substrates hypothesis (Chambers et al., 2001), which proposes that psychosis and drug addiction share a common neurobiological origin, making schizophrenic patients biologically predisposed to drug addiction. Here, I draw attention to the fact that neither hypothesis can fully account for the high rates of drug abuse and addiction in schizophrenia. I then present a complementary hypothesis based on evidence that long-term treatment with antipsychotic medications can modify brain reward circuitry in ways that enhance the rewarding and incentive motivational properties of drugs of abuse and reward-predicting cues. Finally, I draw two main conclusions. First, the evidence reviewed here could shed new light on why individuals with schizophrenia might be particularly vulnerable to compulsive drug use. Second, this work should be considered in both the planning of dosing protocols with existing medications and in the design of new treatment strategies.

## 2. Why are drug abuse and addiction so prevalent in schizophrenia?

### 2.1. The self-medication hypothesis

The most widely cited explanation for the high rates of substance abuse co-morbidity in schizophrenia is the self-medication hypothesis, which proposes that patients select specific drugs to alleviate symptoms of their illness (Khantzian, 1985) or unwanted side effects of antipsychotic medications (Schneier and Siris, 1987). However, both clinical

*Abbreviations:* D2/3, dopamine D2/3 receptor; D2 High, dopamine D2 receptor in a high-affinity state for dopamine; DAT, dopamine transporter; h, hour.

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observations and empirical data suggest that while self-medication might play some role in drug abuse co-morbidity, it does not fully account for why drug abuse and addiction are so common in schizophrenia. At its core, the self-medication hypothesis posits that drug abuse and addiction are dependent upon the subjective experience of schizophrenia and/or medication effects. If this is true, then it must also be true that patients do not choose drugs at random, but will seek and take drugs that specifically alleviate particular schizophrenia symptoms and/or antipsychotic side effects. For example, individuals with prominent negative symptoms would preferentially abuse psychostimulant drugs. However, there appears to be no consistent link between drug choice and alleviation of either disease symptoms or antipsychotic side effects. For example, while the desire to self-medicate might contribute to abuse of certain drugs in certain patients [e.g., cigarette smoking can improve some symptoms (Dalack et al., 1998; George et al., 2002)], the majority of patients say they initiated drug use for the same reasons as drug users with no co-morbid psychiatric disorders [e.g., to get high, to increase energy or emotions, to relieve boredom or anxiety (Kolliakou et al., 2011)]. Second, patients tend to choose drugs based primarily on availability and affordability rather than drug-specific pharmacology, and many believe that drug use initiated or aggravated their symptoms (Baigent et al., 1995). Indeed, the clinical reality is that only a minority of patients (3–18.5%) report that drugs help to decrease symptoms such as hallucinations, suspiciousness or the side effects of medication (Kolliakou et al., 2011). For the majority of patients, drug abuse and addiction persist in the face of increased morbidity and worsening of the motor symptoms induced by some antipsychotic medications (Pencer and Addington, 2003; Potvin et al., 2006; Potvin et al., 2009). In this regard, schizophrenic patients are no different from drug users with no psychiatric co-morbidity; as drug addiction settles, drugs are sought and consumed in spite of serious and recurrent physical, psychiatric and social consequences. Third, drug abuse is more prevalent in individuals with schizophrenia than in many other psychiatric populations with similar symptoms (Martins and Gorelick, 2011). For example, cigarette smoking can relieve anxiety, depression, and certain cognitive and neurophysiological deficits (Smith et al., 2002; Winterer, 2010). However, when comparing psychiatric populations that exhibit such symptoms, schizophrenia patients are amongst those with the highest rates of cigarette smoking (Ziedonis et al., 2008). Finally, the most commonly abused substances in schizophrenia [tobacco, cannabis, alcohol and cocaine (DeQuardo et al., 1994; Drake et al., 1990; Martins and Gorelick, 2011; Schneier and Siris, 1987; Strakowski et al., 1994; Westermeyer and Schneekloth, 1999)] have different—sometimes opposite—effects on mood, cognition and behaviour, resulting in differential abilities to modulate schizophrenia symptoms or medication side effects.

### 2.2. The overlapping neural substrates hypothesis

A second widely cited hypothesis proposes that the same neurodevelopmental pathology that increases the vulnerability to schizophrenia also increases the vulnerability to drug addiction, making the two disorders likely to co-exist in the same individual. In its most influential form, the overlapping substrates hypothesis posits that both schizophrenia and drug addiction result in great part from a form of "network dysregulation" characterized by altered integration of cortical, hippocampal and mesolimbic dopamine signals (Chambers et al., 2001). Specifically, it is thought that individuals with schizophrenia have neuroanatomical abnormalities (of likely developmental origin) in hippocampal and prefrontal cortex excitatory inputs to the nucleus accumbens, and that this in turn can lead to exaggerated cellular responses to mesoaccumbens dopamine (Weinberger and Lipska, 1995). This network dysregulation makes it such that the executive-inhibitory regulation of motivational processes is weak and the motivational response to drugs and associated stimuli is overly strong, thus laying the groundwork for both psychotic symptoms and drug addiction (Chambers et al., 2001). A strength of this hypothesis lies in the fact that there is ample scientific evidence supporting a link between hippocampal-cortical-striatal dysfunction and a facilitation of both schizophrenia symptoms (Swerdlow, 2010; Weinberger and Lipska, 1995) and drug reward (Everitt and Robbins, 2005; Kalivas and Volkow, 2005). However, there are also important limitations to this hypothesis. As put by Swerdlow (2010), "no single 'hole' or brain lesion accounts for the symptoms of this disorder, nor does one gene code for all of its aberrant neural substrates. The heterogeneity of clinical symptoms of the schizophrenias reflects abnormal activity in multiple, distributed, interacting brain circuits, with a differing involvement of these circuits across individuals." Indeed, the overlapping substrates idea might explain the incidence of co-morbid drug addiction in some patients, but the significant differences in phenotype that are often observed between patients with schizophrenia make it unlikely that a unique neurobiological signature underlies either the disease or the co-occurrence of schizophrenia and drug addiction. Second, if drug addiction and schizophrenia share overlapping neural substrates, then these two psychiatric conditions should run in the same families (Lybrand and Caroff, 2009). However, research on the prevalence of substance use disorders in relatives of individuals with schizophrenia has yielded inconclusive results (Dixon et al., 1991; Faridi et al., 2009; Gershon et al., 1988; Kendler et al., 1985; Smith et al., 2008).

## 3. The genesis of a complementary explanation: chronic antipsychotic treatment and reward

Neither the desire to self-medicate nor the overlapping substrates idea can fully account for the high rates of drug abuse and addiction in schizophrenia. A complementary and often overlooked hypothesis is that prolonged treatment with antipsychotic medications can induce changes in brain reward and motivation pathways that increase the vulnerability to drugs. The idea that antipsychotic treatment might contribute to drug use in patients was alluded to in an early review on psychostimulant drug abuse in schizophrenia (LeDuc and Mittleman, 1995). The authors of this initial report proposed, "Psychostimulant use in schizophrenics may be related to their pharmacotherapy". The proposal was based on the observation that both individuals with schizophrenia and other psychiatric patients prescribed chronic neuroleptic treatment have high rates of drug abuse. Leduc and Mittleman (LeDuc and Mittleman, 1995) did not venture to discuss how antipsychotic treatment might contribute to drug abuse. In the following paragraphs, I present findings demonstrating that chronic exposure to antipsychotic medications can induce supersensitivity to dopamine agonist stimulation, and that this in turn can enhance reward function.

### 3.1. Chronic treatment with antipsychotic medications can induce supersensitivity to dopamine

Antipsychotic-induced supersensitivity to dopamine was first described many years ago and has been linked to tardive dyskinesia (Burt et al., 1977; Tarsy and Baldessarini, 1977) and an increased vulnerability to psychosis in humans (Chouinard and Jones, 1980; Chouinard et al., 1978), and to an increased psychomotor response to psychostimulant drugs in laboratory animals (Asper et al., 1973; Clow et al., 1979; Gianutsos et al., 1974; Sayers et al., 1975). It is likely that many brain regions and neurotransmitter systems are involved in the ability of antipsychotics to produce a dopamine supersensitive state. However, several lines of evidence point to an important role of D2/3 receptors, particularly in the striatum. All currently used antipsychotic medications interact with D2/3 receptors. In human, monkey and rat brain, the density of D2/3 sites is highest in the basal ganglia, limbic regions, thalamus and cerebral cortex, with the following rank order: dorsal striatum (caudate and putamen), ventral striatum (nucleus accumbens), olfactory tubercle, ventral tegmental area, substantia nigra

(especially in pars compacta), hippocampus-amygdala and thalamus, with very low densities in cortical areas including the prefrontal cortex (Bouthenet et al., 1987; Kessler et al., 1993; Kohler and Radesater, 1986; Martres et al., 1985; Richfield et al., 1989). Antipsychotic medications could act in several of these brain nuclei to induce a dopamine supersensitive state. However, the caudate putamen and the nucleus accumbens might be preferentially involved. First, long-term haloperidol treatment produces the greatest dopamine D2 receptor up-regulation in the caudate putamen and nucleus accumbens (O'Dell et al., 1990; Wilmot and Szczepanik, 1989), with no consistent changes in D2 receptor levels in the substantia nigra (Huang et al., 1997), in striatal acetylcholine, GABA or D1 receptor sites (Marin and Chase, 1993; Muller and Seeman, 1978), or in cortical or subcortical dopamine transporter densities (Ase et al., 1999; Rivest et al., 1995). Second, antipsychotic-induced supersensitivity to dopamine is associated with increased levels of both striatal D2 receptors and striatal D2 receptors in a high-affinity state for dopamine (Ginovart et al., 2009; Samaha et al., 2007, 2008). Finally, pharmacological treatments (e.g., chronic L-DOPA) that reverse the increase in striatal D2/3 receptors induced by haloperidol also reverse the behavioural supersensitivity to dopamine agonism induced by the antipsychotic (Ezrin-Waters and Seeman, 1978; Friedhoff et al., 1977). Taken together, these findings suggest that initially, antipsychotics act in a system where levels of D2 receptors and D2 receptors in a high-affinity state are normal. With chronic antipsychotic treatment, there is an increase in both D2 receptor numbers and D2 high-affinity sites, particularly in the striatum. At this stage, striatal dopamine-mediated signalling is potentiated—likely via postsynaptic mechanisms—and this could contribute to an increased response to drugs and reward cues. This theoretical model is illustrated in Fig. 1. Importantly, the assays that have been used to assess D2 receptor densities in antipsychotic treated animals do not allow one to distinguish between pre- and postsynaptic receptors (Ginovart et al., 2009; Samaha et al., 2007, 2008). However, as will be reviewed below, converging evidence suggests that dopamine-mediated signalling is increased via postsynaptic D2-related changes.

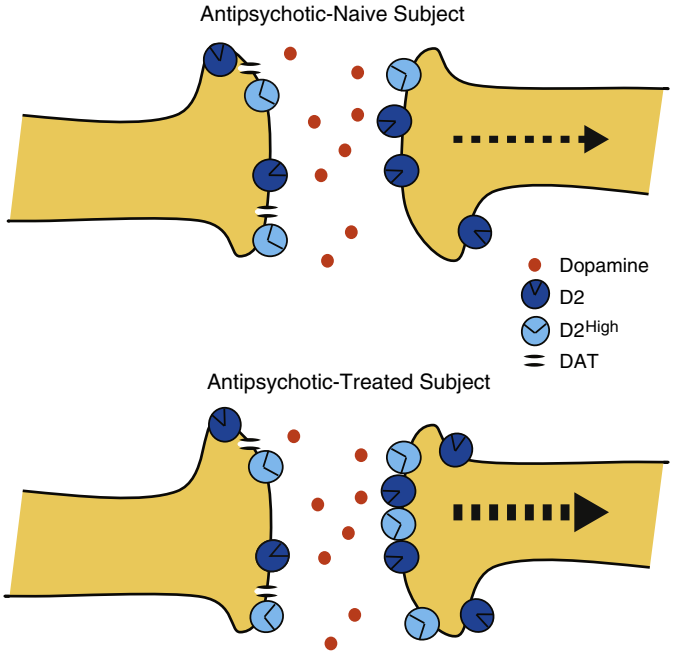


**Fig. 1.** Schematic diagram illustrating the ability of chronic antipsychotic treatment to increase the number of dopamine D2 receptors and D2 receptors in a high-affinity state for dopamine in the striatum, thereby increasing D2-mediated dopamine signalling (depicted by the arrows). Following prolonged treatment with antipsychotic medication, D2-related neuroplastic changes—particularly at postsynaptic sites (see text)—can enhance dopamine-mediated signalling, leading to a state of behavioural supersensitivity to dopamine agonist stimulation. A functional consequence of this plasticity could be an increase in the rewarding properties of drugs of abuse and reward cues. D2, dopamine D2 receptor. $D2^{High}$, D2 receptor in a high-affinity state for dopamine. DAT, dopamine transporter.

D2/3 receptors are located at both pre- and postsynaptic sites in the striatum. It remains to be determined how each receptor pool contributes to antipsychotic-induced supersensitivity to dopamine. However, several key findings suggest that the relevant plasticity is likely postsynaptic. Recent work shows that postsynaptic striatal dopamine receptors might be supersensitive in schizophrenia patients that also have a drug abuse problem. When given amphetamine, these patients release lower than normal levels of striatal dopamine (as measured by the displacement of a D2/3 radiotracer) but have increased psychotic symptoms, suggesting amplified postsynaptic D2/3 receptor function (Thompson et al., 2012). It is not known why the behavioural response to small variations in dopamine agonist stimulation might be amplified in these dual-diagnosis patients. However, the possibility that long-term antipsychotic treatment might have altered postsynaptic D2/3 receptor function must be considered. All of the patients participating in this imaging study had been chronically exposed to antipsychotic drugs (though subjects had to be medication-free for 3 weeks prior to PET scanning (Thompson et al., 2012)). Work in laboratory animals shows that chronic antipsychotic exposure can induce dopamine supersensitivity that is preferentially linked to changes in postsynaptic D2/3 receptor activity. First, chronic treatment with haloperidol—which leads to a supersensitive psychomotor response to amphetamine (Rebec et al., 1982; Samaha et al., 2007, 2008; Smith and Davis, 1975)—does not alter amphetamine-induced increases in dopamine overflow in the nucleus accumbens or in the caudate putamen (Ichikawa and Meltzer, 1992; Samaha et al., 2007). Second, chronic exposure to haloperidol leaves unchanged the ability of presynaptic D2 autoreceptors to regulate dopamine overflow (Chesi et al., 1995), suggesting no significant changes in autoreceptor number or sensitivity (as theorized in Fig. 1). Third, prolonged treatment with haloperidol enhances the locomotor response elicited by dopamine infused into the nucleus accumbens or caudate putamen (Halperin et al., 1983), suggesting altered postsynaptic dopamine receptor signalling. Finally, antipsychotic-induced supersensitivity to dopamine is accompanied by enhanced amphetamine-induced immediate early gene expression in the caudate putamen, suggesting alterations in the postsynaptic signalling events evoked by amphetamine (Bedard et al., 2011, 2012).

### *3.2. Chronic treatment with antipsychotic medications can enhance drug reward*

A dopamine supersensitive state not only enhances the psychomotor activating effects of drugs, but their rewarding properties as well. For example, animals that have been rendered supersensitive to dopamine agonist stimulation by repeated treatment with cocaine or amphetamine will subsequently learn to self-administer lower doses of psychostimulant drugs and will work harder and longer to obtain these drugs compared to controls (Horger et al., 1990; Lorrain et al., 2000; Piazza et al., 1989). Given that antipsychotic medications can induce a dopamine supersensitive state, could they potentiate the rewarding properties of drugs? A number of reports suggest that antipsychotic medications can do just that. For example, rats treated with haloperidol 1 h prior to intravenous cocaine self-administration sessions increase their rate of lever pressing for cocaine, and this effect sensitizes with repeated exposure to the antipsychotic (Roberts and Vickers, 1987). Squirrel monkeys withdrawn from chronic treatment with either spiperone or raclopride (but not SCH 23390—a D1 receptor antagonist) show a leftward shift in the dose-response curve for intravenous cocaine self-administration, suggesting enhanced sensitivity to the reinforcing effects of the drug (Howell and Byrd, 1992). Similar findings have been observed using the conditioned place paradigm. During ongoing, chronic treatment with antipsychotics such as haloperidol or flupentixol, rats develop a preference for a test cage paired with doses of cocaine (Kosten et al., 1996) or heroin (Stinus et al., 1989) that are

insufficient to produce a preference in antipsychotic-naïve rats. Similarly, mice withdrawn from chronic haloperidol show more robust conditioned place preference to cocaine (Fukushiro et al., 2007). Thus, prolonged exposure to certain antipsychotic medications can enhance the rewarding effects of drugs in laboratory animals.

### 3.3. Reward cues, drug addiction and antipsychotic treatment

In addition to enhancing the rewarding properties of drugs, a dopamine supersensitive state can also enhance the ability of drugs to potentiate the incentive motivational effects of reward cues. For example, rats submitted to a regimen of cocaine that induces dopamine supersensitivity (as indicated by an augmented locomotor response to amphetamine) will be more sensitive to the ability of an intra-accumbens infusion of amphetamine to potentiate the pursuit of a reward cue (Taylor and Horger, 1999). In drug addiction, cues predictive of drug reward can contribute in powerful ways to the initiation, maintenance and persistence of pathological drug use (O'Brien et al., 1992). Such cues can include a drug pipe or syringe for a human drug user, or a stimulus light that is illuminated each time a laboratory animal self-administers a drug injection. In both humans and laboratory animals, drug cues elicit attention and approach (Duka and Townshend, 2004; Schoenmakers et al., 2008; Uslaner et al., 2006), and generate motivational states that can elicit or invigorate drug-seeking behaviour and precipitate relapse following the cessation of drug use (Arroyo et al., 1998; de Wit and Stewart, 1981; O'Brien et al., 1992; Panlilio et al., 1996; Shaham et al., 2003).

Given the ability of a dopamine supersensitive state to augment amphetamine-induced responding for reward cues (Taylor and Horger, 1999) and the importance of reward cues in addiction, my laboratory recently undertook studies to determine whether chronic exposure to antipsychotic medications can alter the responsiveness to reward cues. To this end, rats were trained to associate a light-tone cue with the delivery of water and then treated with either haloperidol or olanzapine (Bedard et al., 2011, 2012). Antipsychotics were given at doses that produce equivalent and clinically pertinent peak levels of striatal D2 receptor occupancy [between 65 and 75%; (Farde et al., 1992; Kapur et al., 2000, 2003; Wadenberg et al., 2001)]. In addition, the antipsychotics were given either continuously (via subcutaneous osmotic minipump) or intermittently (via daily subcutaneous injection). Antipsychotic administration via minipump achieves continuously high levels of striatal D2 occupancy, whereas administration via daily subcutaneous injection achieves only transiently high occupancy that is markedly reduced 24 h post injection (Kapur et al., 2003; Samaha et al., 2007). This is because the half-life of antipsychotic medications is very short in rats. For instance, the terminal half-life of haloperidol is 24 h in humans (Bezchlibnyk-Butler and Jeffries, 1999) compared to 1.5 h in rats (Cheng and Paalzow, 1992). As such, continuous infusion of antipsychotic compounds via minipump to rats mimics the kinetics of standard antipsychotic treatment in patients, where D2 occupancy can remain high for several days following a dose (Baron et al., 1989; Farde et al., 1989; Tauscher et al., 2002). Following antipsychotic treatment cessation, we assessed lever pressing for the water cue under baseline conditions as well as following a low dose (0.5 mg/kg) amphetamine challenge. Under baseline conditions, there was no effect of prior antipsychotic treatment on responding for the cue. Following amphetamine however, rats with a history of continuous haloperidol treatment pursued the reward cue more vigorously than control animals (Bedard et al., 2011, 2012). This effect was not linked to haloperidol-induced changes in the ability to attribute predictive value to reward cues (as measured by conditioned approach behaviour), but was accompanied by the development of behavioural supersensitivity to dopaminergic stimulation (as evidenced by an exaggerated locomotor response to amphetamine), and an intensification of amphetamine-induced c-fos and Nur77 mRNA expression in striatopallidal and striatonigral cells of the caudate putamen (Bedard et al., 2011, 2012).

Thus, when given a small dose of amphetamine, rats that have previously received chronic antipsychotic treatment (particularly continuous administration of a typical antipsychotic) will pursue reward cues more vigorously (Bedard et al., 2011, 2012). This suggests that when in a hyperdopaminergic state (induced by amphetamine), rats that have been exposed to antipsychotic attribute greater incentive motivation to reward-predicting cues compared to antipsychotic-naïve animals. In these studies (Bedard et al., 2011, 2012), amphetamine was used as a pharmacological tool to acutely model the increased striatal dopamine release that has been linked to psychosis and schizophrenia (Davis et al., 1991; Howes and Kapur, 2009; Howes et al., 2012). The implication therefore is not necessarily that antipsychotic treatment promotes addiction to amphetamine, but that antipsychotic treatment can enhance the incentive motivational properties of reward cues in a subject experiencing increased striatal dopamine levels. This has potentially wide-ranging clinical implications for two primary reasons. First, increased striatal dopamine levels are the most robust and most consistently reported dopamine abnormality in schizophrenia (Howes et al., 2012). Second, an increase in the incentive motivational properties of drug cues contributes in powerful ways to many different drug addictions, including tobacco, cannabis, alcohol and cocaine addiction (Carter et al., 2009; Cousijn et al., 2012; Duka and Townshend, 2004; O'Brien et al., 1992, 1998; Schoenmakers et al., 2008; Wolfling et al., 2008).

### 3.4. Parameters that increase the likelihood of antipsychotic-induced enhancement of reward

Our work also showed that two parameters were decisive in determining the effects of antipsychotics on amphetamine-induced responding for reward cues; the use of continuous versus intermittent treatment, and administration of a typical versus atypical antipsychotic drug. Amphetamine-induced potentiation of conditioned reward, psychomotor activity and striatal immediate early gene expression were unaltered if treatment with haloperidol was intermittent (Bedard et al., 2011) or if rats were treated with olanzapine (either continuous or intermittent) instead of haloperidol (Bedard et al., 2012). These findings are consistent with evidence that relative to continuous exposure to typical antipsychotics including haloperidol and thioridazine, intermittent exposure (Ericson et al., 1996; Samaha et al., 2008) or treatment with atypical antipsychotics such as clozapine or olanzapine (Creese and Snyder, 1980; Samaha et al., 2007; Severson et al., 1984) is less likely to induce behavioural supersensitivity to dopamine. In addition, atypical antipsychotics such as ziprasidone are less likely to enhance the rewarding and psychomotor sensitizing effects of cocaine than the typical antipsychotic haloperidol (Fukushiro et al., 2007; Fukushiro et al., 2008). When typical antipsychotics are used, why might hypersensitivity to reward be more likely following continuous versus intermittent exposure? One potential explanation could be related to the fact that continuous treatment involves unremitting disruption of dopaminergic signalling. This elicits a number of compensatory changes including an increase in the density and sensitivity of striatal D2/3 receptors (Ginovart et al., 2009; Samaha et al., 2007, 2008), and alterations in the ability of amphetamine to regulate gene expression in the caudate-putamen (Bedard et al., 2011, 2012). At the behavioural level, these neurobiological changes could manifest as hypersensitivity to reward. Similarly, why might hypersensitivity to reward be more likely following treatment with typical versus atypical compounds? Several pharmacological properties distinguish these two medication classes, and any or a combination of these properties could explain the effects or lack thereof on reward function. For instance, atypical antipsychotics are more loosely bound to D2/3 receptors compared with typical medications, such that atypical compounds might allow a greater degree of endogenous dopamine to gain access to its receptors (Seeman et al., 1997). In addition, atypical antipsychotics have higher affinities at several serotonin receptor types (Meltzer et al., 1989). For example, olanzapine (but not haloperidol) has inverse agonist/antagonist effects

at the 5-$HT_{2C}$ receptor (Rauser et al., 2001; Zhang et al., 2006). Many dopamine-rich regions including the caudate-putamen, olfactory tubercle, thalamic nuclei and frontal cortex contain high densities of 5-$HT_{2C}$-like immunoreactive cells (Abramowski et al., 1995; Clemett et al., 2000). 5-$HT_{2C}$ receptors play a prominent role in regulating terminal dopamine function. These receptors are constitutively active and tonically inhibit dopamine release in both the caudate-putamen and the nucleus accumbens *in vivo* (De Deurwaerdere et al., 2004). Accordingly, 5-$HT_{2C}$ inverse agonists/antagonists can increase terminal dopamine release *in vivo* (Egerton et al., 2008). Olanzapine could therefore enhance endogenous dopamine activity in the striatum via interaction with the 5-$HT_{2C}$ receptor. This in turn would partially restore D2-mediated signalling during ongoing antipsychotic treatment, and reduce the likelihood of developing behavioural supersensitivity to dopamine and to reward.

### *3.5. The effects of antipsychotic medication on the response to reward cues: linking the animal and clinical literatures*

Schizophrenia patients treated with antipsychotic drugs—particularly of the typical class—are reported to have blunted activation of the ventral striatum when presented with cues that indicate the availability of monetary reward (Juckel et al., 2006a, 2006b; Kirsch et al., 2007; Schlagenhauf et al., 2008). This appears at odds with our findings in rats showing that treatment with either haloperidol or olanzapine does not alter the operant pursuit of reward cues under baseline conditions (Bedard et al., 2011, 2012). Typical antipsychotic medication might very well blunt certain aspects of reward function in individuals with altered dopamine systems [such as in schizophrenia, but not in the neurologically intact rats used in our studies (Bedard et al., 2011, 2012)]. However, it must also be noted that both unmedicated patients and patients treated with typical antipsychotics (but not those treated with atypical antipsychotics) show a blunted ventral striatal response during reward anticipation (Juckel et al., 2006a, 2006b; Nielsen et al., 2012; Schlagenhauf et al., 2008), suggesting that this response might not be caused by antipsychotic treatment. In addition, it is not clear what blunted activation of the ventral striatum in response to reward-indicating cues might mean. On the basis of imaging data alone, it cannot be concluded that these patients would be less sensitive to the predictive, rewarding or incentive motivational properties of either reward cues or the rewards they predict. In fact, consistent with our findings in antipsychotic-treated rats, the schizophrenic individuals in these imaging studies—whether medicated or not—perform generally like controls when asked to press a button during presentation of the reward-indicating cue to either gain or avoid losing money, and their ventral striatal activation levels in response to the monetary reward itself are also comparable to controls (Juckel et al., 2006b; Kirsch et al., 2007; Nielsen et al., 2012). In addition, some addiction-relevant effects of reward cues are actually augmented in schizophrenia patients given typical antipsychotics. For example, compared to schizophrenic individuals treated with atypical antipsychotics such as olanzapine or risperidone, patients treated with typical medications score higher on the energy subcomponent of cue-evoked craving for cocaine (Smelson et al., 2006), and on the intensity and depression dimensions of cue-elicited craving (Smelson et al., 2002).

## 4. Limitations and strengths of the animal literature on chronic antipsychotic treatment and reward

The animal literature summarized above shows that either ongoing exposure to or withdrawal from certain antipsychotic treatment regimens can potentiate the rewarding properties of drugs and the ability of drugs such as amphetamine to enhance the incentive motivational properties of reward cues. Animal models are by definition imperfect, and the animal work reviewed here has certain limitations. First, all of the animal studies above used neurologically intact animals. This has allowed researchers to establish cause-and-effect relationships between long-term antipsychotic treatment and changes in brain and behaviour. However, it is also necessary to determine the extent to which antipsychotics might interact with the underlying pathophysiology of schizophrenia to alter reward function. This can be achieved by assessing the impact of antipsychotic treatment on reward function in animal models of positive and negative schizophrenia symptoms. Second, the antipsychotic doses used were sometimes too high and unrepresentative of the clinic (Fukushiro et al., 2007; Stinus et al., 1986). One validated approach for selecting appropriate doses in animal studies involves *in vivo* levels of striatal D2 receptor occupancy by antipsychotic (Kapur et al., 2003; Wadenberg et al., 2001). At the very least, antipsychotic doses should not be chosen arbitrarily. Third, to my knowledge, there are no published studies on how antipsychotic treatment might alter the rewarding properties of cannabis, alcohol or tobacco—three of the most commonly abused substances in schizophrenia. Given the findings with other drugs of abuse, it appears warranted to investigate this issue.

In parallel, the animal work reviewed here has several strengths. Many studies showing that antipsychotic treatment can augment reward function used clinically representative doses and modes of antipsychotic treatment (Bedard et al., 2011, 2012; Roberts and Vickers, 1987). In addition, the ability of antipsychotic medications to potentiate reward behaviours has been shown both during ongoing antipsychotic treatment and after treatment cessation, using drugs of different classes, in different paradigms as well as in different species (see references above). Thus, the above limitations notwithstanding, work in animals suggests that treatment strategies with typical antipsychotics that involve long-term and continuous medication could modify brain reward substrates in ways that facilitate the ability of drugs and reward cues to influence behaviour.

## 5. Linking the animal data with clinical observations of drug use in schizophrenia

Of course, substance abuse in schizophrenia is a complex problem that is not solely explained by antipsychotic treatment. Substance abuse can antedate a diagnosis of schizophrenia and the onset of antipsychotic treatment, and not all antipsychotic-treated patients have a co-morbid drug problem. This being said, if antipsychotic treatment can indeed contribute to drug problems in schizophrenia then one would expect the likelihood and/or severity of addiction to be greater in medicated versus unmedicated patients. This issue is difficult to address because very few patients diagnosed with schizophrenia are unmedicated. In addition, many studies on the incidence of drug abuse in schizophrenia patients do not specify medication status at the time of assessment (LeDuc and Mittleman, 1995). What is known, however, is that the onset of drug abuse follows the onset of schizophrenia (and of antipsychotic treatment) in a considerable proportion of patients [38% (Hambrecht and Hafner, 1996)], and antipsychotic treatment can alter the response to drugs of abuse and reward-associated cues in patients. For example, compared to unmedicated schizophrenic patients, medicated patients are more sensitive to the psychotogenic effects of psychostimulant drugs, at doses that do not induce psychosis in non-schizophrenic individuals (Lieberman et al., 1987). In addition, individuals prescribed typical antipsychotic medications to treat either schizophrenia or other, non-schizophrenic psychiatric diseases have high rates of psychostimulant drug abuse, suggesting a potential link between neuroleptic treatment and the susceptibility to drug use (LeDuc and Mittleman, 1995). Studies also suggest that—just as is reported in animal studies—typical antipsychotics might be more likely to contribute to drug abuse and addiction than atypical compounds. Schizophrenic patients switched from a typical antipsychotic to olanzapine show a within-subject decrease in alcohol and other drug use (Noordsy et al., 2001). Compared to schizophrenic individuals treated with olanzapine, haloperidol-treated patients score

significantly higher on the energy subcomponent of cue-evoked craving for cocaine (Smelson et al., 2006). Finally, amongst cocaine-addicted schizophrenia patients, those treated with haloperidol, fluphenazine or chlorpromazine versus risperidone score higher on the intensity and depression dimensions of cue-elicited craving, and are also markedly more likely to relapse to cocaine use following abstinence [70% of patients on typicals versus 12.5% on risperidone (Smelson et al., 2002)].

## 6. Concluding remarks

Chronic treatment with antipsychotic compounds can enhance the incentive motivational and rewarding effects of drugs of abuse and reward cues. At least two parameters appear to promote such reward-related changes: the use of antipsychotics of the typical class, and the use of continuous rather than intermittent antipsychotic exposure, such that silencing of dopaminergic neurotransmission via D2/3 receptors is unremitting. Where do we go next? A challenge now is to identify the neural processes by which certain antipsychotic treatment regimens might alter reward function. As this research unfolds, it should also be considered that current treatment strategies with typical antipsychotics—which can yield continuously high levels of D2 receptor blockade for several days following a dose (Baron et al., 1989; Farde et al., 1989)—might contribute in previously unappreciated ways to drug seeking and drug taking behaviours in vulnerable patients. As we await the advent of antipsychotic treatments that might avert chronic and unrelenting blockade of dopamine receptors, the work reviewed here has important clinical implications. First, it should be explored whether schizophrenia patients vulnerable to drug addiction might be better served by treatment with atypical antipsychotics. Second, where typical antipsychotics are necessary, a dosing protocol involving regular but transiently high antipsychotic levels in the brain might be considered.

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