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Dopamine and Incentive Learning: a Framework for Considering Antipsychotic Medication Effects

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Hyperfunction of brain dopamine (DA) systems is associated with psychosis in schizophrenia and the medications used to treat schizophrenia are DA receptor blockers. DA also plays a critical role in incentive learning produced by rewarding stimuli. Using DA as the link, these results suggest that psychosis in schizophrenia can be understood from the point of view of excessive incentive learning. Incentive learning is mediated through the non-declarative memory system and may rely on the striatum or medial prefrontal cortex depending on the task. Typical and atypical antipsychotics differentially affect expression of the immediate early gene *c-fos*, producing greater activity in the striatum and medial prefrontal cortex, respectively. This led to the hypothesis that performance of schizophrenic patients on tasks that depend on the striatum or medial prefrontal cortex will be differentially affected by their antipsychotic medication. Results from a number of published papers supported this dissociation. Furthermore, the effects of two atypical drugs, clozapine and olanzapine, on *c-fos* expression were different from another atypical, risperidone that resembles the typical antipsychotics. Similarly, in tests of incentive learning, risperidone acted like the typical antipsychotics. Thus, typical and atypical antipsychotic drugs differed in the types of cognitive performance they affected and, furthermore, members of the atypical class differed in their effects on cognition. It remains the task of researchers and clinicians to sort out the symptoms associated with the endogenous illness from possible iatrogenic symptoms resulting from the antipsychotic medications used to treat schizophrenia.

Keywords: Antipsychotic; Clozapine; Dopamine; Haloperidol; Incentive Learning; Nondeclarative memory; Olanzapine; Risperidone; Prefrontal cortex; Schizophrenia

INTRODUCTION

For fifty years schizophrenia and related disorders have been treated with antipsychotic medications that all share an ability to block dopamine (DA) receptors in the brain. Indeed, this observation forms one of the pillars of the DA hypothesis of psychosis, stating that DA system hyperfunction is associated with the positive symptoms of schizophrenia. In parallel research with non-human animals it has become clear that DA plays a central role in incentive learning mediated by rewarding stimuli. Many of the critical experiments utilized DA receptor blocking drugs as tools. These were often the selfsame drugs that are used to treat schizophrenia. This suggested the hypothesis that there may be a link between schizophrenia and incentive learning. It also suggested that antipsy-

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chotic drugs may affect reward-related learning in schizophrenic patients; if they do, researchers and clinicians face the challenge of sorting out the symptoms associated with the endogenous illness from possible iatrogenic symptoms resulting from the antipsychotic medications used to treat the illness.

The issue became more complex with the development of a newer class of antipsychotic medications, the *atypicals*. In contrast to the more traditional *typicals*, atypicals produce fewer extrapyramidal side effects, attributed to their differential impact on striatal versus prefrontal cortical regions of the brain. Neuropsychological studies have shown that different regions of the brain mediate different aspects of cognition; for example, performance on some forms of learning and memory tasks is mediated by the striatum and performance on others by the medial prefrontal cortex. Different classes of antipsychotics, therefore, may affect different aspects of cognition. The same may be true of drugs *within* a class of antipsychotics (*i.e.*, typical or atypical) if these affect different brain regions. Here too, researchers and clinicians are faced with the challenge of sorting out disease-related endogenous symptoms from possible iatrogenic symptoms in schizophrenic patients.

In the following, I will briefly review the DA hypothesis of psychosis, the role of DA in incentive learning and, using DA as the link, how some of the positive symptoms of schizophrenia can be understood as resulting from excessive incentive learning. This will lead to a discussion of different forms of learning and memory and how incentive learning fits into this overall classification. A consideration of i) the brain regions implicated in these different forms of learning and memory; ii) incentive leaning tasks that appear to rely on different brain regions; and iii) evidence that different classes of antipsychotic medications affect different regions of the brain will follow. This will segue into experimental results showing differential performance of schizophrenic patients treated with typical versus atypical antipsychotics on tasks that rely on the striatum versus medial prefrontal cortex. Possible differences among groups of schizophrenic patients treated with individual atypical antipsychotic medications on the same tasks will follow. Results suggest that antipsychotic medications have important effects on cognition in schizophrenic patients.

SCHIZOPHRENIA, DOPAMINE AND INCENTIVE LEARNING

The DA hypothesis of psychosis associated with schizophrenia is built on three pillars: i) antipsychotic medications are all DA receptor blocking agents; ii) psychostimulant drugs that increase DA neurotransmission in the brain are psychotogenic; and iii) postmortem and imaging studies show evidence of enhanced DA neurotransmission in the brains of schizophrenic people. The evidence for the first pillar can be traced back to the classical paper of Seeman and colleagues (1975) showing a high positive correlation between the concentration of antipsychotic drugs required to bind fifty percent of striatal DA D_2-like receptors and the average daily clinical dose. The efficacy of the newer atypical antipsychotics similarly can be attributed to their action at DA D_2 receptors (Kapur, 2000). The second pillar was supported by the finding that amphetamine and cocaine, drugs that enhance DA neurotransmission, produced psychoses (Connell, 1958; Snyder, 1972; Angrist, 1983). Postmortem data seemed to support the third pillar although there has been continuing controversy concerning the possibility that, in many cases, observed changes were iatrogenic consequences of the use of antipsychotic medications (Crow and Johnstone, 1986). Abi-Dargham *et al.* (2000) used single photon emission computerized tomography to assess D_2-like receptors and reported that by depleting endogenous DA they were able to observe significantly more DA receptors in schizophrenic patients, and recent studies continue to support these findings (*e.g.*, Yang *et al.*, 2004, Hirvonen *et al.*, 2005). Thus, the DA hypothesis of psychosis in schizophrenia remains one of the foundation stones of biological psychiatry.

Incentive learning refers to the acquisition by neutral stimuli of an increased ability to elicit approach and other responses and takes place when an animal encounters a biologically important (rewarding) stimulus (Bolles, 1972; Bindra, 1978). DA plays a critical role in incentive learning (Beninger, 1983; 1988; Robbins and Everitt, 1996; Beninger and Miller, 1998; Berridge and Robinson, 1998; Di Chiara, 1999). For example, rats trained to lever press for food showed an extinction-like decline in responding when treated with an antipsychotic drug, suggesting that the ability of food reward-

related incentive stimuli to maintain responding was gradually lost when DA receptors were blocked (Wise *et al.*, 1978). Rats showed a DA-dependent preference for a place associated with injections of amphetamine (Spyraki *et al.*, 1982) and they self-administered amphetamine when given the opportunity (Pickens and Harris, 1968). Amphetamine increases synaptic DA by reversing the transporter (Sulzer *et al.*, 2005). Thus, stimuli associated with increased synaptic DA acquired incentive properties. DA and its metabolites were increased in the nucleus accumbens following exposure to rewarding stimuli (Radakishun *et al.*, 1988), suggesting that rewarding stimuli activated the DA system. Similarly, electrophysiological studies showed that rewarding stimuli increased phasic firing of DA neurons in the ventral tegmental area (Schultz *et al.*, 1992). More recently functional magnetic resonance imaging (fMRI) studies showed increases in blood oxygenation levels in DA terminal regions following exposure to rewarding financial stimuli in humans (Elliott *et al.*, 2000), and positron emission tomographic studies showed increased DA release following food stimuli in humans (Small *et al.*, 2003). Findings support a role of DA in incentive learning.

The role of DA in incentive learning may be conceptualized as follows: when animals encounter rewarding stimuli, those stimuli produce phasic activation of DA neurons. This activity may alter the ability of the *most recently encountered* stimuli to influence behaviour in the future. If those stimuli were a lever and the patch of wall upon which the lever was mounted in a Skinner box, then the lever and lever-related stimuli may have an enhanced ability to elicit approach and other responses in the future. By definition, such stimuli are conditioned incentive stimuli. If the trained animal is placed back into the Skinner box in the future it will approach and press the lever because of this learning. If instead, one side of an apparatus with two distinct chambers is paired with activation of the DA system, by amphetamine for example, the stimuli from that side may acquire an enhanced ability to elicit approach and other responses. If, after several such pairings, the rat is placed back into the two-chambered apparatus with free access to both sides it will spend more time in the side associated with the drug possibly because the stimuli on that side have become incentive stimuli, attracting the animal. The mechanisms underlying incentive learning are thought to involve DA-mediated plasticity at glutamatergic synapses in the striatum (Beninger, 1983; Wickens, 1988; 1990; 1993; Miller *et al.*, 1990; Beninger and Gerdjikov, 2004).

Given that DA plays a critical role in incentive learning, and hyperfunctioning of the DA system is associated with psychosis, it follows that psychosis might result from excessive incentive learning. What would happen if the incentive learning mechanism began to hyperfunction? One answer to this question is that environmental stimuli that normally do not elicit approach and other responses would acquire the ability to do so. An individual suffering from excessive incentive learning would find herself attracted to stimuli that normally would be regarded as neutral. This prediction is supported by numerous reports that schizophrenic people show a heightened distractibility. McGhie (1977) postulated an attentional filter defect but the apparent distractibility of schizophrenic patients could also result from excessive incentive learning.

DA neurons may also play a role in incentive learning about social stimuli, a topic that has received limited research attention. In a recent paper, Rilling *et al.* (2004) had participants play a version of the Prisoner's Dilemma game while being scanned for blood oxygen level-dependent contrast in a fMRI imager. When participants encountered reciprocal altruists ventral striatum activition was increased, whereas interactions with individuals who did not reciprocate altruism decreased ventral striatal activation. These results suggest that the people (social stimuli) who co-operated with the person being imaged increased DA inputs to the ventral striatum. As activation of DA neurons produces incentive learning about the most recently encountered stimuli, those people (co-operators) associated with activation of the DA system would become conditioned incentive stimuli, acquiring a greater ability to elicit approach and other responses from the person being imaged in the future. As the authors put it, the signal in the DA neurons "…may teach us to seek out reciprocaters and avoid nonreciprocaters as social partners" (p. 2543).

Within the context of excessive incentive learning, this finding may be used to understand how people with psychosis inappropriately attribute importance to some other individuals. One of the positive symptoms of psychosis associated with schizo-

phrenia is delusional thinking. If a brain abnormality (hyperdopaminergia) is causing environmental stimuli, including other people, to appear important or attractive, the afflicted individual might construct an interpretation of those stimuli that is consistent with their apparent incentive value; for example, they might form delusions of grandeur or paranoia, in either case attributing importance to people or things that should be neutral. As will be discussed below, different brain systems mediate incentive learning versus the type of associative learning that might underlie the formation of delusions. Thus, an abnormality in the system mediating incentive learning might lead to the formation of erroneous conclusions by another system that is functioning relatively normally.

In summary, the DA hyperfunctioning hypothesis of psychosis remains a foundation stone of biological psychiatry. Neuroscience research supports a role for DA in incentive learning about environment stimuli associated with reward, and recent evidence suggests that DA-mediated incentive learning may also extend to social stimuli, *i.e.*, other people. By using DA as the link it follows that the positive symptoms of distractibility and delusions seen in schizophrenia may result from excessive incentive learning.

MULTIPLE MEMORY SYSTEMS

Over 40 years ago Brenda Milner (1962) made the startling discovery that patients with temporal lobe amnesia, characterized by an apparent inability to remember any new recent information, showed evidence of learning on some tasks. For example, they improved from day to day in their ability to trace between parallel lines while seeing their hand reflected in a mirror in spite of remaining severely impaired in their ability to remember having done the task from day to day (*cf*., Milner *et al.*, 1998). This pioneering work ushered in the concept of multiple memory systems that is now widely accepted.

Squire and co-workers (Squire, 1986; Milner *et al.*, 1998; Squire and Knowlton, 2000) described one system of classifying different types of memory; they specified two large categories: declarative and non-declarative. The content of declarative memory is facts and events, it is explicit, and this information is recalled consciously. Declarative memory appears to depend on the integrity of the medial temporal lobes, including the hippocampus, and medial diencephalic nuclei. By contrast, the content of non-declarative memory includes a collection of abilities such as memory for skills and habits, simple forms of conditioning and priming. Non-declarative memory is implicit and it is not recalled consciously but is manifested as improved performance in the tasks where it is used. Different brain regions have been implicated in different forms of non-declarative memory. Thus, classical conditioning relies upon the cerebellum or amygdala, priming and perceptual learning upon the neocortex, and the learning of skills and habits upon the striatum. These relationships are summarized nicely in a figure that appears in both Milner *et al.* (1998; Fig. 3) and Squire and Knowlton (2000; Fig. 53.11).

Incentive learning does not appear in the classification system of Squire and his co-workers, although they refer to habit learning and its reliance on the striatum. The term "habit learning" is frequently used to describe learning mediated by reward, suggesting that habit learning and incentive learning may refer to the same thing. For example, the probabilistic classification learning (PCL) task uses habit learning that relies on striatal DA (Knowlton *et al.*, 1990; 1996). This task involved prediction of one of two outcomes (rain or shine) on a number of trials, given the particular cues provided on each trial. There were four cues and up to three appeared on each trial; each cue was probabilistically associated with either outcome. Normal control participants gradually learned this task, improving over five blocks of ten trials (Knowlton *et al.*, 1996). A group of amnesic patients with medial temporal lobe or medial diencephalic damage also showed learning and did not differ significantly from the controls. These amnesic patients showed significantly impaired ability to recall details of the task, confirming that they suffered from a loss of declarative memory. This result provided an example of the dissociation of declarative and non-declarative memory. Importantly, a group of participants with Parkinson's disease, known to suffer from a loss of striatal DA, failed to learn the PCL task in spite of showing intact declarative memory for details of the task. We have recently replicated this finding in advanced Parkinson's disease participants and shown further that a group of early Parkinson's disease participants with milder symptoms was

not impaired (Perretta *et al.*, 2005). Together, these results indicate that people with impaired striatal DA function had impaired non-declarative habit learning.

The PCL can be viewed as an incentive learning task in that reward is provided as feedback on each trial about whether or not the weather prediction is correct. Normally, the effects of reward would be to activate the DA system and increase the incentive value of the stimuli associated with reward. In Parkinson's patients with reduced striatal DA, this incentive learning would be impaired. We verified this prediction in a study testing Parkinson's patients, arthritic patients with a comparable level of disability, and normal controls on a point-loss avoidance task and on a declarative learning paired-associates task (Charbonneau *et al.*, 1996). There were no group differences in learning the declarative memory task but the Parkinson's group was significantly impaired on the point-loss avoidance task compared to the other two groups. This finding, like that of Knowlton *et al.* (1996), showed the dissociation of declarative and non-declarative memory in Parkinson's patients, with deficits specific to non-declarative memory in this group. Thus, the PCL task fits the description of an incentive learning task and is sensitive to reductions in striatal DA.

The Iowa gambling task (IGT) is another task that relies on non-declarative memory (Bechara *et al.*, 1997). This task involves choosing cards from four decks that have different payoffs and penalties; choices from two decks result in making money and the other two in losing money. Importantly, normal controls shift to choosing from the good decks before they are aware of the differential payoffs, suggesting that learning in this task is non-declarative. One difference between the PCL and IGT is that the latter provides cumulative feedback in the form of net dollars earned or lost over trials. In functional imaging studies IGT learning activated the medial frontal gyrus (Fukui *et al.*, 2005), and learning of the task was impaired by damage to the ventromedial prefrontal cortex (Bechara *et al.*, 1994; 1997) although the subregion(s) of the prefrontal cortex that are critical for IGT learning remain the topic of debate (Bechara *et al.*, 1994; 1996; 1997; 1998; Manes *et al.*, 2002; Clark *et al.*, 2003). The IGT is another example of an incentive learning task with behavior being (unconsciously) shaped by reward but the cumulative aspect of the IGT and the additional penalty contingencies may require the use of planning. This may explain why the prefrontal cortex and not the striatum mediate the IGT. In the scheme of Squire and his coworkers, the IGT would define another subtype of non-declarative memory and the involvement of another brain region, the medial prefrontal cortex.

In summary, within the multiple memory systems model, two broad categories of declarative and non-declarative memory have been defined and a number of subtypes of non-declarative memory have been described. Incentive learning or habit learning is one type of non-declarative memory. Striatal DA plays a critical role in incentive learning and studies of the IGT suggest further that the medial prefrontal cortex may be involved in incentive learning in some tasks. Whether medial prefrontal cortical DA contributes to the putative role of this structure in incentive learning remains an open question.

TYPICAL AND ATYPICAL ANTIPSYCHOTICS: REGIONAL EFFECTS IN THE BRAIN

The prototypical typical antipsychotic drug is chlorpromazine (Delay and Deniker, 1952), the drug that ushered in the modern era of biological psychiatry. Many similarly acting compounds have since been developed including haloperidol, pimozide and flupenthixol to name a few (see Baldessarini, 1996). Typical antipsychotics continue to be used widely although they are being replaced in many areas with the newer atypical antipsychotics of which clozapine (see Tamminga and Gerlach, 1987) is the prototype. Among the other atypicals are olanzapine and risperidone. The defining border between typical and atypical antipsychotics is fuzzy (see Meltzer, 1995; Lidow, 2000). One of the major distinguishing features is the difference in extrapyramidal side effect liability, typicals being higher in this characteristic than atypicals. The two classes of antipsychotics may also differ in their effects on prolactin levels, with typicals but not atypicals producing an increase; however, even some atypicals (*viz*., risperidone) produce increased prolactin levels (Markowitz *et al.*, 1999). It may be that the typical/atypical distinction will have to be modified or abandoned as the differential actions of individual agents within

each class are further delineated.

Animal studies of immediate early gene expression in various brain regions have identified differences between typical and atypical antipsychotics by using an exemplar from each class. Studies of activation of the immediate early gene *c-fos* in rodents indicated that typical antipsychotics represented by haloperidol preferentially increased expression in the striatum; in contrast, atypical antipsychotics represented by clozapine preferentially increased expression in the medial prefrontal cortex. Both typicals and atypicals increased expression in the nucleus accumbens (Robertson and Fibiger, 1992; Wan *et al.*, 1995; Deutsch and Duman, 1996; Fujimura *et al.*, 2000; Kovacs *et al.*, 2001). Wan *et al.* (1995) also tested the typical antipsychotic chlorpromazine and observed a profile like that of haloperidol. One study has examined the effects of haloperidol and clozapine on *c-fos* expression in monkeys and similarly found differential effects in the striatum (Wirtshafter and Asin, 2003). These studies suggest that typical antipsychotics represented by haloperidol or chlorpromazine and atypicals represented by clozapine may act in different regions of the brain.

The effects of clozapine on *c-fos* expression in the medial prefrontal cortex appear to generalize to the atypical olanzapine. Thus, Ohashi *et al.* (2000) showed that olanzapine, like clozapine, increased *c-fos* expression in the medial prefrontal cortex. They showed further that this effect of olanzapine or clozapine was blocked by propranolol, implicating norepinephrine in this action. The implications of this observation will have to await further study. Heidbreder *et al.* (2001) observed increased extracellular DA release in the prefrontal cortex of rats following clozapine or olanzapine, but not haloperidol administration, again suggesting that the neural actions of haloperidol and clozapine differ. The findings complement those of Ohashi *et al.* (2000) showing that the effects of olanzapine appear to be similar to those of clozapine.

Few studies have compared the effects on *c-fos* expression of risperidone to those of clozapine and results have not been entirely consistent. Risperidone, clozapine and haloperidol increased *c-fos* expression in the nucleus accumbens but only risperidone and haloperidol increased expression in the striatum (Wan *et al.*, 1995; Fujimura *et al.*, 2000). One study (Fujimura *et al.*, 2000) reported that risperidone increased *c-fos* expression in the medial prefrontal cortex, whereas another (Wan *et al.*, 1995) found no effect using the same dose (3.0 mg/kg). Despite the contrary findings, it is clear that the effects of risperidone on expression of the immediate early gene *c-fos* are different from those of clozapine and olanzapine. Specifically, rispereidone activated *c-fos* in the striatum, an effect normally seen with typical antipsychotics.

In conclusion, typical and atypical antipsychotics differ in their effects in different brain regions. Typicals, represented by haloperidol or chlorpromazine, appear to affect the nucleus accumbens and striatum but not the medial prefrontal cortex whereas atypicals, represented by clozapine or olanzapine, appear to affect the nucleus accumbens and the medial prefrontal cortex but not the striatum. There are also differences within the class of atypicals: the effects of olanzapine parallel those of clozapine; risperidone, unlike clozapine and olanzapine, appears to act in the striatum; and the effects of risperidone in the medial prefrontal cortex remain to be resolved.

TYPICAL AND ATYPICAL ANTIPSYCHOTICS AND INCENTIVE LEARNING

Memory resulting from reward-related incentive learning is non-declarative in the classification system of Squire and Knowlton (2000) where incentive learning tasks are often termed "skill or habit learning" tasks. The effects of acutely administered antipsychotic drugs have been evaluated on skill or habit learning in healthy participants. Chloropromazine suppressed avoidance, but not escape, responding in a task in which humans pressed a lever to avoid mild shock or point loss, the points being exchangeable for money (Fishman *et al.*, 1976; Fishman and Schuster, 1979). This finding is comparable to the effects of acutely administered DA receptor antagonists in avoidance responding in animals and is consistent with a role for DA in incentive learning.

The effects of chronic antipsychotic medication on cognitive tasks have been assessed in schizophrenic patients medicated either with typical or

atypical antipsychotics. In many cases observed deficits were attributed to schizophrenia. However, as DA receptor-blocking antipsychotic medications clearly affect some forms of learning and memory, it is often difficult to dissociate the impact of drug actions on neuronal function from the contribution of disease-related neuro-dysfunction. The possible confounding of these two variables dogs the interpretation of cognitive deficits in schizophrenia.

We have sought ways to dissociate possible effects of antipsychotic drugs from those of the illness when testing cognition in schizophrenic patients by asking: Do neuroleptics impair learning in schizophrenia patients? Cutmore and Beninger (1990) evaluated schizophrenic patients treated with the typicals haloperidol or flupenthixol and matched healthy controls on an incentive learning points-loss avoidance task and on paired-associates learning, a declarative memory task. Schizophrenic patients were impaired on both tasks although performance on the declarative memory task correlated significantly with schizophrenic symptoms (measured by the Brief Psychiatric Rating Scale) while performance on the incentive learning task did not. These results suggested that deficits in incentive learning might be related to antipsychotic drug effects rather than the illness. To examine this hypothesis, an independent group of schizophrenic patients receiving a variety of typical antipsychotics (doses were converted to chlorpromazine equivalents) was tested on the same tasks. As expected, prolactin was significantly elevated in the schizophrenic group compared to healthy controls. Multiple regression analysis revealed that incentive learning on the conditioned avoidance task was significantly predicted by chlorpromazine equivalents or by prolactin, two highly correlated indices of dose of typical antipsychotic; performance on the paired-associates declarative memory task was not predicted by these variables. Results provided some support for the hypothesis that non-declarative incentive learning but not declarative paired-associates learning was related to the use of typical antipsychotic medication in schizophrenic patients.

In a more recent study, Beninger *et al.* (2003) examined groups of schizophrenic patients treated with typicals (chlorpromazine, fluphenazine, perphenazine, flupenthixol, haloperidol or loxapine) or atypicals (clozapine, olanzapine, risperidone or quetiapine) on the PCL and IGT tasks. Recall that performance on the PCL was impaired in Parkinson's disease patients suffering from a decrease in striatal DA (Knowlton *et al.*, 1996; Perretta *et al.*, 2005) and that performance on the IGT was impaired in patients suffering from damage to the ventral medial prefrontal cortex (Bechara *et al.*, 1997). Recall further that immediate early gene studies of *c-fos* expression showed that typical antipsychotics activated *c-fos* in the striatum but not the medial prefrontal cortex while atypicals activated *c-fos* in the medial prefrontal cortex but not in the dorsal striatum (Robertson and Fibiger, 1992; Wan *et al.*, 1995; Deutsch and Duman, 1996; Fujimura *et al.*, 2000; Kovacs *et al.*, 2001). As hypothesized, schizophrenic patients treated with typicals were impaired on the PCL but not on the IGT while those treated with atypicals showed the opposite pattern (FIG. 1). Participants were also tested on declarative memory questionnaires and schizophrenic symptoms were assessed with the Brief Psychiatric Rating Scale; medication groups did not differ significantly on these assessments. Results suggested that typical and atypical antipsychotics differentially affected non-declarative incentive learning mediated respectively by the striatum and medial prefrontal cortex.

In our latest study, Beninger, Wasserman and Delva (in preparation) compared the effects of different atypical antipsychotics (clozapine, olanzapine and risperidone) on performance of the two non-declarative memory tasks. In particular, we examined the hypothesis that the effects of risperidone would be more like those of typicals and would differ from the effects of the atypicals clozapine and olanzapine. We based this hypothesis on the observation that risperidone, like typicals such as chlorpromazine and haloperidol and unlike the atypicals clozapine and olanzapine, activated *c-fos* in the dorsal striatum (Wan *et al.*, 1995; Fujimura *et al.*, 2000). On the PCL significant improvement over blocks was seen in the clozapine group but not in the olanzapine or risperidone groups. On the IGT, significant improvement over blocks was seen in the risperidone but not the clozapine or olanzapine groups. Thus, the performance of the risperidone group on the PCL and IGT resembled that of the typical antipsychotic group. Results converge with those from animal studies showing that the effect of risperidone on expression of the early immediate gene *c-fos* was more like the effect

of the typical antipsychotics chlorpromazine and haloperidol than like the effects of other atypicals including clozapine and olanzapine.

Paquet *et al.* (2004) recently reported poorer procedural learning in schizopharenic patients treated with haloperidol compared to those treated with olanzapine. Using single photon emission computed tomography, they further found a significant correlation between learning and DA D_2-like receptor occupancy in the striatum for the haloperidol but not the olanzapine group. In related studies, Bedard *et al.* (2000) showed more variable learning of a procedural task in schizophrenic patients treated with typical versus atypical antipsychotics. Scherer *et al.* (2004) used a mirror drawing procedural learning task like that employed by Milner (1962) in her studies showing that some forms of learning were intact in amnesic patients. They found decreased learning in haloperidol-treated patients compared to the olanzapine and clozapine groups and decreased overall performance in the haloperidol and risperidone groups. These studies showed that procedural learning in schizophrenic patients may be affected differently by typical and atypical antipsychotics. Although it is unclear whether the tasks used in these studies have a strong incentive learning component, results agree with the present findings showing that the class and specific type of antipsychotic used to treat schizophrenic patients affects their cognitive functioning.

In summary, antipsychotic medications appear to affect non-declarative incentive learning in schizophrenic patients. Both the class of antipsychotic and the nature of the incentive learning task influence the results; in the case of atypical antipsychotics, the specific member of the class that is used also influences the results. Studies have shown that schizophrenic patients treated with typicals are impaired on striatum-dependent PCL but not on medial prefrontal cortex-dependent IGT learning and vice versa for those treated with atypicals, revealing a double dissociation. Within the atypicals class, results suggest that the effects of risperidone on incentive learning in schizophrenic patients resemble more those of typicals than those of other atypicals including clozapine and olanzapine. Results converge with findings from immediate early gene studies of *c-fos* expression, showing that different antipsychotics appear to affect different regions of the brain. These findings challenge researchers and clinicians to sort out the symptoms associated with the endogenous illness of schizophrenia from possible iatrogenic symptoms resulting from the antipsychotic medications used to treat the illness.

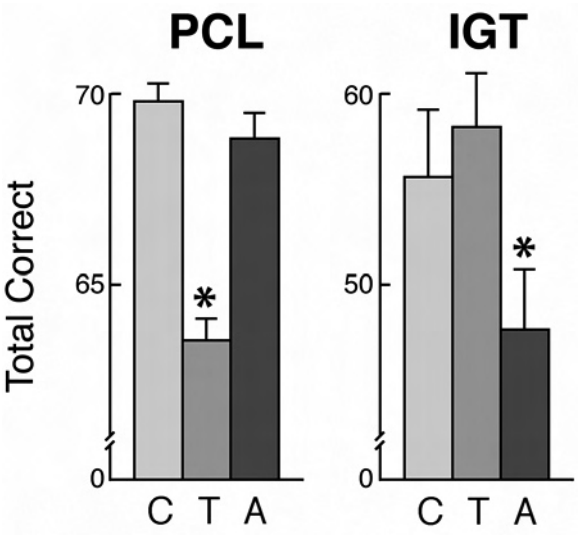

FIGURE 1 Double dissociation of the effects of typical and atypical antipsychotic medications on two non-declarative memory tasks in schizophrenic patients: Mean (±SEM) total correct on the probabilistic classification learning (PCL) and Iowa gambling tasks (IGT) are shown for healthy control (C) groups and groups of schizophrenic participants treated with typical (T) or atypical (A) antipsychotic medications. For the PCL, the T group was significantly (*) lower than the other two groups by analysis of variance (ANOVA) followed by paired comparisons. For the GAT, the group effect approached significance ($0.05 < p < 0.06$) but ANOVA of groups by block of 20 trials revealed a significant interaction and simple effects ANOVA revealed significant learning in the C and T groups but not in the A group (*). Adapted from Beninger *et al.* (2003).

SUMMARY AND CONCLUSIONS

Schizophrenia is a debilitating disease affecting about one percent of the world's population, often with devastating consequences for the affected individual and his or her family. The discovery of chlorpromazine in the middle of the last century marked a significant advance in the treatment of schizophrenia, allowing many patients some relief from their hallucinations, delusions and other positive symptoms. The newer generation of antipsychotic medications offered a further

advance, at least reducing the risk of extrapyramidal symptoms, one of the most serious side effects of the older medications. These were momentous scientific and clinical advances that have improved the lot of millions of people and their loved ones. At the same time antipsychotics may affect brain processes associated with normal functioning in intact individuals. If they do, it is important to understand these iatrogenic effects so that they can be considered as part of the decision to prescribe antipsychotic medications and so that scientists can undertake to minimize them.

This paper has used its focus on DA as playing a critical role in both schizophrenia and incentive learning to link the two. Schizophrenia might be understood as a disorder of excessive incentive learning resulting from hyperfunctioning of the DA system. Insofar as the antipsychotic drugs used to treat schizophrenia are DA receptor blockers and many studies with animals have shown that these agents block incentive learning, it follows that incentive learning may be affected in schizophrenia.

Different classes or individual members of a single class of antipsychotic medications differentially affect expression of the immediate early gene *c-fos* in several forebrain regions including the striatum and medial prefrontal cortex. Neurocognitive studies have shown that different learning and memory tasks rely differentially on these various brain regions. This suggested the hypothesis that treatment with different antipsychotic medications may differentially affect performance of different learning and memory tasks. The results reviewed support this hypothesis by showing that learning of a striatum-sensitive task is affected by typical antipsychotics and that learning of a medial prefrontal cortex-sensitive task is affected by atypical antipsychotics in schizophrenic patients. The atypicals class was best represented by clozapine and olanzapine with risperidone appearing to be more similar to typicals such as haloperidol in some studies.

DA neurotransmission appears to be overactive in schizophrenia and drugs that block DA receptors reduce the positive symptoms. If overactive DA function leads to excessive incentive learning and this contributes to the symptoms of schizophrenia, then treatments that decrease symptoms might be expected to normalize incentive learning. If this is the case, incentive learning should be intact in medicated schizophrenic patients. Why, then, do antipsychotics that target the striatum seem to *impair* performance on tasks that depend on the striatum and those that target the medial prefrontal cortex seem to *impair* tasks that depend on that structure? One possibility is that normal incentive learning requires phasic activations of the DA system in synchrony with the appearance in the environment of a rewarding stimulus. Perhaps antipsychotic drugs reduce DA neurotransmission thereby leading to the extinction of previous excessive incentive learning and mitigation of new excessive incentive learning but, at the same time, dull the impact of the phasic signals in the DA system that are needed for normal incentive learning. Thus, antipsychotic agents could be simultaneously therapeutically effective and detrimental to normal learning processes. It will be the task of future studies to refine understanding of the effects of antipsychotic medications on incentive learning and other cognitive functions.

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