Cognition and Control in Schizophrenia: A Computational Model of Dopamine and Prefrontal Function

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Behavioral deficits suffered by patients with schizophrenia in a wide array of cognitive domains can be conceptualized as failures of cognitive control, due to an impaired ability to internally represent, maintain, and update context information. A theory is described that postulates a single neurobiological mechanism for these disturbances, involving dysfunctional interactions between the dopamine neurotransmitter system and the prefrontal cortex. Specifically, it is hypothesized that in schizophrenia, there is increased noise in the activity of the dopamine system, leading to abnormal "gating" of information into prefrontal cortex. The theory is implemented as an explicit connectionist computational model that incorporates the roles of both dopamine and prefrontal cortex in cognitive control. A simulation is presented of behavioral performance in a version of the Continuous Performance Test specifically adapted to measure critical aspects of cognitive control function. Schizophrenia patients exhibit clear behavioral deficits on this task that reflect impairments in both the maintenance and updating of context information. The simulation results suggest that the model can successfully account for these impairments in terms of abnormal dopamine activity. This theory provides a potential point of contact between research on the neurobiological and psychological aspects of schizophrenia, by illustrating how a particular physiological disturbance might lead to precise and quantifiable consequences for behavior.
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Introduction

Some of the most prominent clinical symptoms exhibited by patients with schizophrenia include: distractibility, loosening of associations, and disorganized or socially inappropriate behavior. A number of investigators have postulated that these symptoms might relate to core cognitive deficits in a number of domains, such as attention (Cornblatt and Keilp 1994; Kornetsky and Orzack 1978; Nuechterlein 1991), working memory (Park and Holzman 1992; Weinberger et al 1986), episodic memory (Gold et al 1992; Goldberg et al 1993) and inhibition (Abramczyk et al 1983; Barch et al in press a; Carter et al 1993; Chapman et al 1964). However, the underlying mechanisms that contribute to both clinical symptomatology and cognitive impairments in schizophrenia are still not well understood, at either the psychological or neurobiological level.

In previous work, we have argued that many cognitive deficits in schizophrenia (and the clinical symptoms stemming from them) can be interpreted as reflecting a failure to exert *control* over thoughts and actions, and that a central feature of cognitive control is the ability to properly maintain and update internal representations of task-relevant context information (Cohen and Servan-Schreiber 1992). This theory has been made explicit in the form of connectionist computational models of behavioral tasks in which patients with schizophrenia exhibit specific cognitive deficits. Furthermore, these models have provided a conceptual mapping between the psychological processes thought to be impaired in schizophrenia and their neurobiological underpinnings. Specifically, they have shown how: a) cognitive control can emerge from the biasing influence of representations of goal-related, or context, information actively maintained in PFC on more posterior pathways responsible for task performance; b) dopamine (DA) can exert a neuromodulatory influence on this function of PFC; and c) disturbances in this neuromodulatory function can produce disturbances in cognitive performance that closely match those observed in patients with schizophrenia.

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In our initial modeling work, the role of DA was treated in a relatively abstract form, as influencing the responsivity of processing units to their afferent input—the "gain" hypothesis (Cohen and Servan-Schreiber 1993; Servan-Schreiber et al 1990). In recent work we have begun to refine our model of DA function, driven simultaneously by the pressure to conform more closely to accumulating neurobiological evidence, and to arrive at a more powerful and complete theory of the computational mechanisms underlying cognitive control. This has led us to a new hypothesis: that DA serves a "gating" function in PFC, regulating access of context representations into active memory (Braver and Cohen in press a). This gives DA an important control function, responsible for the flexible updating of active memory in PFC, while retaining protection against interference. Here, we suggest an important component of the pathophysiology of schizophrenia may be an increase in the noise in the DA system, and that this increased variability leads to disturbances in both the updating and maintenance of context information within working memory. Below, we briefly review the literature on cognitive deficits in schizophrenia, our theory of cognitive control, and its ability to account for empirical findings in the schizophrenia literature. Finally, we present the results from a new set of computer simulation modeling studies, that implement our new theory of DA function, and use it to address empirical data regarding the behavioral deficits observed in patients with schizophrenia during performance of a specific cognitive control task.

Cognitive Deficits in Schizophrenia

A large literature on cognitive function in schizophrenia suggests that patients with this illness display deficits in several different cognitive domains. In particular, much recent work has focused on deficits in attention, working memory, episodic memory, and executive functions. In the attentional domain, the research to date suggests that the most reliable impairments exhibited by schizophrenia occur when attention must be exerted in a selective and controlled manner to both facilitate the processing of task-relevant information or inhibit the processing of task-irrelevant information. In the cognitive psychology literature, researchers often use the Stroop (Stroop 1935) color naming task as a paradigmatic measure of selective/controlled attention (MacLeod 1991). In this task, participants are presented with words printed in colors, and are told to either: 1) read the word and ignore the print color; or 2) name the print color, and ignore the word. When asked to read the word, participants can effectively ignore the print color, as evidenced by the fact that print color has little influence on reading time. When participants are asked to name the print color, they have difficulty suppressing the effects of the word. In particular, when the word and its color conflict (such as RED displayed in blue print) participants are slower than when there is no such conflict. This effect is called Stroop *interference*, and is thought to result from the obligatory nature of word reading disrupting color naming performance (MacLeod 1991). A similar, but smaller effect can be observed in improved performance for congruent stimuli (e.g., RED displayed in red print), referred to as Stroop *facilitation*.

A large number of studies have used the Stroop task to test patients with schizophrenia, employing both the traditional card-based method (Abramczyk et al 1983; Everett et al 1989; Golden 1976; Wapner and Krus 1960; Wysocki and Sweet 1985), as well as more modern methods using tachistoscopic presentation and the on-line monitoring of response times and accuracy (Barch et al in press a, in press b; Carter et al 1992; Cohen et al 1999; Schooler et al 1997; Taylor et al 1996). These have consistently produced reliable evidence of enhanced Stroop interference or facilitation among patients, indicative of an impairment in selective/controlled attention in schizophrenia. Deficits in selective/controlled attention have also been observed using other tasks, such as the anti-saccade task in which subjects must inhibit the prepotent response to make a saccade to the location of visual stimulus, and instead saccade to a location in the opposite visual field (Clementz et al 1994; Katsanis et al 1997; McDowell and Clementz 1997; Radant et al 1997).

Working memory (WM) has also been shown to be impaired in schizophrenia. WM is commonly defined as the collection of processes responsible for the on-line maintenance and manipulation of information necessary to perform a cognitive task (Baddeley and Hitch 1994). A growing number of studies suggest that patients with schizophrenia show deficits on tasks designed to measure WM (Cohen et al 1999; Gold et al 1997; Goldberg et al 1998; Park and Holzman 1992; Park and Holzman 1993; Stone et al 1998; Wexler et al 1998). For example, several recent studies have shown impairments in spatial WM among schizophrenia patients (Keefe et al 1997; Park and Holzman 1992; Stone et al 1998). Studies have also shown deficits in verbal WM (Servan-Schreiber et al 1996; Wexler et al 1998), although there is some suggestion that deficits of verbal WM may be most evident when patients are challenged with a high information load (Carter et al 1998), when they have to deal with distraction (Keefe et al 1997), or when they are required to manipulate maintained information in WM (Cohen et al 1999; Gold et al 1997). Based on such findings, several researchers have suggested that a deficit in WM may be a fundamental cognitive defect present in schizophrenia (Cohen and Servan-Schreiber 1992; Goldman-Rakic 1991; Weinberger and Gallhofer 1997).

A third type of deficit that has been implicated in

schizophrenia is in episodic memory (Duffy and O'Carrol 1994; Gold et al 1992; Goldberg et al 1993; Hutton et al 1998). Episodic memory refers to the ability to encode or retrieve newly learned information. Some research suggests that this function is more seriously disturbed in schizophrenia than general intellectual ability (McKenna et al 1990; Tamlyn et al 1992) or other cognitive functions (Saykin et al 1991; Saykin et al 1994). Based on such findings, some investigators have argued that episodic memory deficits are a core cognitive deficit in schizophrenia, either in addition to or instead of WM deficits (Clare et al 1993; McKay et al 1996). One possible interpretation of episodic memory deficits in schizophrenia is that they reflect an inability to use contextual cues to organize information at either encoding or retrieval, rather than a fundamental inability to encode new information (O'Reilly et al 1999). For example, some studies have shown that schizophrenia patients are more impaired on recall than recognition memory tasks (Calev 1984; Goldberg et al 1989; Koh 1978; Paulsen et al 1995; Rizzo et al 1996; Rushe et al 1998), consistent with the hypothesis that patients' performance improves with the addition of cue information. In addition, among patients with schizophrenia, recall performance benefits from the addition of explicit cues to organize the information at encoding (Koh 1978), as well as from additional cues at retrieval (Sengel and Lovallo 1983).

A fourth area that schizophrenia patients show deficits is the domain of executive functioning. This includes functions such as set switching, planning, and dual-task coordination. Patients with schizophrenia show consistent deficits in each of these domains. For example, two classic tasks associated with the measurement of set switching ability are the Wisconsin Cart Sorting Task and the Trails B task. It has long been known that schizophrenia patients show deficits on both of the tasks, and many researchers consider deficits on these tasks to be a hallmark sign of schizophrenia (Berman et al 1986; Gold et al 1997; Goldberg et al 1988; Weinberger et al 1986). Patients also display disturbances on tasks that measure planning ability, such as the Tower of London task (Andreasen et al 1992). In addition, recent research utilizing dual-task paradigms has also provided evidence that patients are impaired when required to perform two tasks simultaneously (Granholm et al 1996), or to alternate between two different tasks (Smith et al 1998). In all of the tasks involving executive function, a central feature is the requirement that goal-related information must be both represented and updated at appropriate junctures.

As the above review suggests, the literature on cognitive function in schizophrenia points to impairments in a set of basic cognitive functions including: 1) attentionally-mediated selection of task-relevant information, and suppression of task-irrelevant information; 2) maintenance and manipulation of information in WM; 3) context-based organization of cues for memory encoding and retrieval; and 4) updating and switching of internally represented goal-related information These findings could be interpreted as evidence that patients with schizophrenia suffer cognitive dysfunction in a variety of qualitatively distinct domains. However, we have argued that all of the cognitive functions considered above may rely on a common process: the internal representation and use of context information in the service of exerting control over behavior. Thus, it is possible that deficits in attention, memory, and executive function all reflect the disturbance of a single underlying processing mechanism that is central to cognitive control. Below, we review our arguments in support of this hypothesis.

Cognitive Control

The need for a control mechanism in cognition has been long noted within psychology. Virtually all theorists agree that some mechanism is needed to guide, coordinate, and update behavior in a flexible fashion—particularly in novel or complex tasks (e.g., Norman and Shallice 1986). More specifically, control over processing requires that information related to behavioral goals be actively represented and maintained, such that these representations can bias behavior in favor of goal-directed activities over temporally-extended periods. Moreover, goal-related information must be: 1) appropriately selected for maintenance; 2) maintained for arbitrary lengths of time; 3) protected against interference; and 4) updated at appropriate junctures. The recognition that active representation and maintenance of goal-related information are central components of cognitive control can be seen in many theories. The best known of these is Baddeley's working memory executive model (Baddeley 1986), that includes a specific sub-component, "the central executive," responsible for utilizing goal-related information in the service of control. The postulation of a cognitive system involved in executive control closely parallels theorizing regarding the nature of frontal lobe function (Bianchi 1922; Damasio 1985; Luria 1969), based on the clinical observation that patients with frontal lesions often exhibit impairments in tasks requiring control over behavior—the so-called "dysexecutive syndrome." Traditional theories have not specified the mechanisms that the executive operates.

Theories aimed at providing a more explicit computational account of human behavior have also included goal representations as a central component. For example, in production system models, goal states represented in declarative memory are used to coordinate the sequences of production firings involved in complex behaviors

(Anderson 1983). One critical feature of goal representations in production systems is that they are actively represented and maintained throughout a sequence of behaviors. Shallice (Norman and Shallice 1986; Shallice 1982; Shallice 1988) has relied upon the production system framework to put forth his Supervisory Attentional System (SAS) as a mechanism by which complex cognitive processes are coordinated and non-routine actions are selected.

In our own work, we have suggested that the active maintenance of context information is critical for cognitive control (Braver et al 1999; Cohen et al 1996; Cohen and Servan-Schreiber 1992). We have defined context as any task-relevant information that is internally represented in such a form that it can bias processing in the pathways responsible for task performance. Goal representations are one form of such information, that have their influence on planning and overt behavior. We use the more general term context to include representations that may have their effect earlier in the processing stream, on interpretive or attentional processes. For example, in the sentence "To keep his chickens, the farmer needed a pen," the words "chicken" and "farmer" may elicit a context representation that is used to constrain the interpretation of the word pen to its weaker, but relevant meaning (i.e., "fenced enclosure"). Thus, context representations may include a specific prior stimulus, or the result of processing a sequence of stimuli, as well as task instructions or a particular intended action. Because context representations are maintained on-line, in an active state, they are continually accessible and available to influence processing. Consequently, context can be thought of as one component of WM. Specifically, context can be viewed as the subset of representations within WM that govern how other representations are used. Representations of context are particularly important for situations where there is strong competition for response selection. These situations may arise when the appropriate response is one that is relatively infrequent, or when the inappropriate response is prepotent (such as in the Stroop task). In this respect, context representations are closely related to goal representations within production system architectures. Maintenance of internal goal representations, or goal-related knowledge, is critical for initiating the selection of "weak" behaviors, and for coordinating their execution over temporally extended periods, while at the same time suppressing competing, possibly more compelling behaviors. Next, we discuss evidence that context information is actively maintained within PFC.

PFC and Active Memory

NEUROBIOLOGICAL PERSPECTIVES. Over a hundred years of neuropsychological studies on patients with PFC lesions have provided strong evidence of the involvement of this brain region in the regulation of behavior. In recent years, a large body of converging evidence from neurophysiology and neuroimaging studies have suggested a more specific role for PFC in the active maintenance of task-relevant information. Single-cell recording studies in nonhuman primates have typically examined the active maintenance properties of PFC through the use of delayed-response paradigms, in which the animal must maintain a representation of a cue stimulus over some delay, to respond appropriately at a later point. It is now well-established that during performance of these tasks, populations of neurons in monkey PFC exhibit sustained, stimulus-specific activity during the delay period (Fuster and Alexander 1971; Kubota and Niki 1971). The mnemonic properties of these neurons have been demonstrated by showing both that: 1) local and reversible lesions to PFC impair task performance; and 2) performance errors in intact animals are correlated with reduced delay-period activity (Bauer and Fuster 1976; Fuster 1973). Neuroimaging studies have confirmed and extended these findings in humans. For example, in humans, PFC activity has been shown to: 1) increase as delay interval increases (Barch et al 1997); 2) increase as memory load increases (Braver et al 1997b); and 3) be sustained over the entire delay interval (Cohen et al 1997; Courtney et al 1997).

In addition to these other properties, PFC also seems to be particularly specialized to maintain information in the face of interference, whereas still allowing for flexible updating of stored information. Recently, Miller and colleagues (Miller et al 1996) have provided direct evidence for this hypothesis. They trained monkeys to respond to repeats of a prespecified cue (e.g., A) when presented with sequences such as A–B–B–A. This task clearly required the ability to identify the cue on each trial, and maintain it across intervening distractors. They observed cue-specific delay period activity for units in both inferotemporal cortex (IT) and PFC after initial presentation. Subsequent stimuli obliterated this activity in IT, whereas it was preserved in PFC until a match occurred. The crucial role of PFC in updating and interference-protection can also clearly be seen in studies of PFC pathology. Increased distractibility and perseveration are hallmarks of PFC damage (Damasio 1985; Engle et al 1999; Milner 1963; Owen et al 1991; Stuss and Benson 1986), as well as a classic symptom of schizophrenia (Malmo 1974; Nuechterlein and Dawson 1984). Together, these findings support the idea that there are specialized mechanisms within PFC for active memory, as well as for protecting maintained information from both perseveration and interference. More specifically, we hypothesize that representations of context are housed within PFC and actively maintained there.

COMPUTATIONAL PERSPECTIVES. From a computational viewpoint there are a number of different processing mechanisms that could support short-term maintenance of information. The most commonly employed and well-understood of these are fixed-point attractor networks (Hopfield 1982; Zipser 1991). Such networks possess recurrent connections, that "recirculate" activation among units, and are thus capable of supporting sustained activity. The state of such networks typically settles into "attractors," defined as stable states in that a particular pattern of activity is maintained. Thus, attractors can be used to actively store information. Indeed, a number of computational models of simple maintenance tasks have demonstrated that both physiological and behavioral data regarding PFC function can be captured using an attractor-based scheme (Braver et al 1995; Dehaene and Changeux 1989; Moody et al 1998; Zipser et al 1993).

Simple attractor systems have a number of limitations that create problems in more complex maintenance tasks. These limitations can be traced to the fact that the state of an attractor system is determined by its inputs, so that presentation of a new input will drive the system into a new attractor state, thereby overwriting previously maintained information (Bengio et al 1993; Mozer 1993). Although attractor networks can be configured to display resistance to disruption from input (i.e., hysteresis), this impairs their ability to be updated in a precise and flexible manner. One way that attractor networks can overcome these difficulties is through the addition of a gating mechanism. Such systems only respond to inputs, and change their attractor state, when the "gate" is opened. Computational analyses suggest that gating mechanisms provide the most effective way to stably maintain information in an active state, protect this information from interference, and still retain the ability of flexible updating. For example, Hochreiter and Schmidhuber (1997) compared gated recurrent neural networks with other types of attractor systems, and concluded that networks with a gating mechanism were able to learn and perform complex short-term memory tasks better than simple attractor networks, especially when the tasks involved noisy environments, frequent updating, and relatively long periods of storage. Thus, computational studies suggest that a gated attractor system is the optimal one for active memory. Moreover, the physiological evidence reviewed above is consistent with the hypothesis that PFC implements such a gated system. Indeed, in previous work, Zipser and colleagues (Moody et al 1998; Zipser 1991; Zipser et al 1993) have proposed a gated attractor model and have used it to successfully simulate the pattern of delay period activity observed for PFC neurons. However, the Zipser model has not specified the source of the gating signal. In the following section, we suggest that phasic increases in DA activity serve as a gating signal within PFC.

DA Modulation of Behavior

MOTOR FUNCTIONS. The DA system has been implicated in a wide range of effects on behavior. The most prominent of these is the linkage of DA with motor function. It is well-established that disturbances to the subcortical DA system cause severe movement-related disorders such as Parkinson's disease. Further, stimulants such as amphetamine and apomorphine (that are thought to act by stimulating DA release; Kelly et al 1975) have clear effects on motor behavior. For example, in animals, these drugs produce consistent changes in both locomotor activity (Segal 1975), and the repertoire of behaviors exhibited (Norton 1973), with high doses inducing species-specific stereotypies (Randrup and Munkvad 1970). There are also many studies documenting the effect of DA activity on response activity in goal-directed tasks, such as operant conditioning paradigms (Heffner and Seiden 1980; Louilot et al 1987). A number of investigators have hypothesized that, together, these findings suggest a function for DA in selecting or initiating new motor response patterns (Iversen 1984; Oades 1985).

REWARD FUNCTIONS. Another commonly postulated function of DA is that this neurotransmitter mediates the processing of reward information. This reward-based account of DA activity is supported by findings that suggest that DA facilitates a number of primary motivation behaviors, such as feeding, drinking and sexual activity (Willner and Scheel-Kruger 1991). Conversely, spontaneous engagement in these behaviors has been shown to result in increased DA transmission (Heffner et al 1980). In addition, innumerable studies have shown that the electrical self-stimulation paradigm is primarily dependent on stimulation of DA pathways (Mora and Cobo 1990; Phillips and Fibiger 1989). This finding is consistent with the pharmacological evidence that many drugs of addiction act through the DA system (Koob and Bloom 1988). Taken together, these findings have led some researchers to postulate a crucial role for DA in conveying information regarding the rewarding or reinforcing properties of specific behaviors (Wise and Rompre 1989).

COGNITIVE FUNCTIONS. The literature on the behavioral effects of DA is not limited to studies of motor and reward-related behaviors. There have also been a number of reports of DA effects on cognitive function. In humans, systemic administration of DA agonists have been associated with improvements on various cognitive tasks (Callaway et al 1994; Klorman et al 1984). In particular, the most consistent effects of DA on cognition have been in tasks relying on WM. DA effects in WM have been seen systemically in humans (Luciana et al 1995; Luciana et al

1992), and through local manipulations in nonhuman primates (Brozoski et al 1979; Sawaguchi and Goldman-Rakic 1994). These local effects in primates have focused on DA activity selective to PFC. For example, Goldman-Rakic and colleagues have found that pharmacologically blocking DA receptors in circumscribed areas of PFC produced reversible deficits in task performance (Sawaguchi and Goldman-Rakic 1991). Moreover, microiontophoresis of DA agonists and antagonists, and even DA itself has been found to directly affect the activity patterns of PFC neurons (Sawaguchi and Goldman-Rakic 1991; Sawaguchi et al 1990). Goldman-Rakic and others have concluded from these findings that DA activity serves to modulate the cognitive functions mediated by PFC (Cohen and Servan-Schreiber 1992; Goldman-Rakic 1991).

A UNITARY FUNCTION? The literature on DA involvement in motor, reward and cognitive functions reveals the wide-spread influence of this neural system on behavior. Further, the disparate nature of these three domains suggests that DA may perform multiple, unrelated behavioral functions. A more parsimonious explanation is also possible: DA activity plays a unitary function in the central nervous system that is expressed in different domains as a result of its interaction with the different brain systems that the DA system projects (i.e., striatal, limbic, and cortical). Specifically, we propose that the function of the DA system is to provide a means for the organism to learn about, predict, and respond appropriately to events that lead to reward. The DA system serves this function through simple neuromodulatory effects in the neural populations that it targets. One effect modulates the responsivity of the target neurons to other inputs, and the other effect modulates the synaptic strength between the target neuron and its other inputs. The DA effects on synaptic strength serve to drive the learning of predictors of reinforcement, whereas the effects on responsivity serve to transiently bias on-going processing. Most importantly, we propose that through its projection to PFC, the responsivity effect of DA serves to gate access to active memory, whereas its coincident learning effect allows the system to discover what information must be actively maintained for performance of a given task. In previous reviews of the literature (Braver and Cohen in press a, in press b; Cohen et al 1996), we have discussed a number of lines of research supporting this hypothesis, including evidence that argues that: 1) DA exerts a modulatory effect on target neurons; 2) This effect is of a type that could be exploited to perform a gating function in PFC; and 3) The role of the DA system in reward-prediction learning provides it with particular activation dynamics and timing that are required of a gating signal.

A Theory of Dopaminergic Regulation of Active Memory

Taken together, the properties of DA and PFC reviewed above suggest the outlines of a theory regarding the neural and computational mechanisms of cognitive control. In particular, we refine our previous work on active maintenance in PFC by integrating it with the work of Montague et al (1996) on reward-based learning. This integration provides a means of accounting for the relevant data regarding DA activity dynamics and reward functions as well as the modulatory role of DA in active memory. Specifically, the following refinements are made to our original theory (Cohen and Servan-Schreiber 1992):

- DA gates access to active memory in PFC to provide flexible updating while retaining interference protection.
- Phasic changes in DA activity mediate gating *and* learning effects in PFC.
- Both effects occur locally at the synapse, and rely on similar neuromodulatory mechanisms (possibly through different receptor subtypes).
- The gating effect occurs through the transient potentiation of both excitatory afferent and local inhibitory input.
- The learning effect occurs through Hebbian-type modulation of synaptic weights, and is driven by errors between predicted and received rewards.
- The temporal coincidence of the gating and learning signals produces cortical associations between the information being gated, and a triggering of the gating signal in the future.

The power of this new theory is that it provides a framework that may be able to account for specific patterns of normal behavioral performance across a wide-range of tasks requiring cognitive control. At the same time, by making close contact with the known physiological properties of both the DA system and PFC, it allows for more detailed and biologically realistic investigations of the neural basis of control. In the following section we discuss the relationship of DA and PFC function to the pathophysiology of schizophrenia.

Disturbances of PFC and DA in Schizophrenia

PFC. The centrality of PFC function to schizophrenic cognitive deficits is a common theme in recent research. Structural abnormalities have been observed in PFC of schizophrenic patients (Andreasen et al 1986; Weinberger et al 1980), and these have been linked to reductions in resting PFC metabolism (Andreasen et al 1986; Buchsbaum et al 1982; Farkas et al 1984; Franzen and Ingvar 1975; Ingvar and Franzen 1974; Morihisa and McAnulty

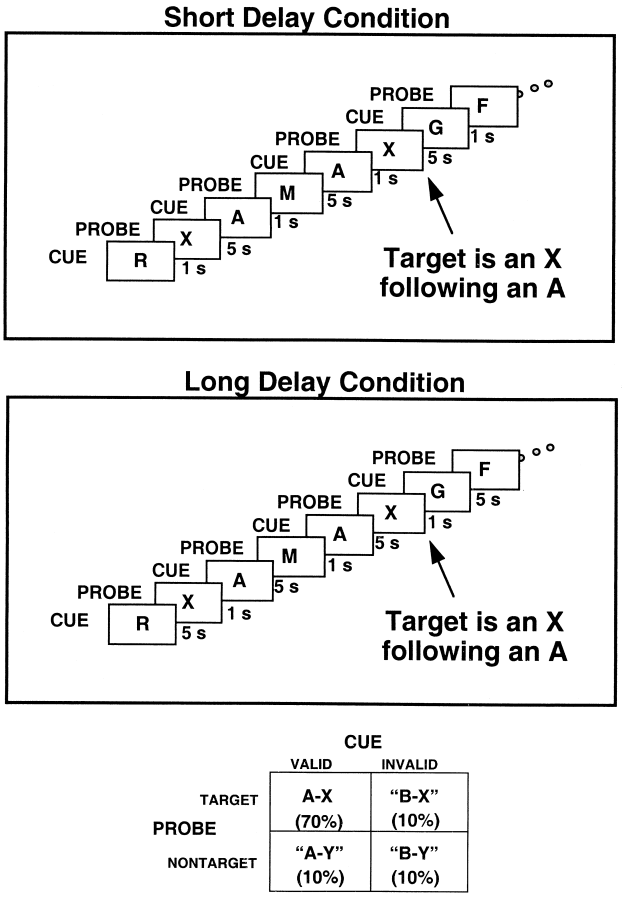
1985; Weinberger et al 1980). These findings have been supported by two reviews (Andreasen et al 1992; Buchsbaum 1990) that suggest that decreased metabolic activity or diminished cerebral blood flow in PFC is reliably present in schizophrenia. Despite this seemingly impressive literature, the presence of hypofrontality in schizophrenia remains somewhat controversial. For example, Gur and Gur (Gur and Gur 1995) cited several recent studies that did not find decreased frontal metabolism or rCBF in schizophrenia patients. These authors strongly questioned the presence of resting hypofrontality in schizophrenia, but did acknowledge that *functional* hypofrontality, defined as a failure to activate frontal cortex during cognitive activity, "may still merit further investigation." Indeed, studies using functional neuroimaging techniques have greater sensitivity for detecting PFC disturbances in schizophrenic subjects, and relating these to cognitive disturbances. In particular, a number of recent functional neuroimaging studies in schizophrenia have linked disturbance in PFC function to impaired performance on tasks measuring WM (Carter et al 1998; Stevens et al 1998), controlled/selective attention (Carter et al 1996), planning (Andreasen et al 1992), and set switching (Berman et al 1986; Weinberger et al 1986).

DA. Disturbances to the DA system have also long been regarded as a fundamental pathophysiological component of schizophrenia. Most of the support for this viewpoint comes from observations regarding the therapeutic efficacy of neuroleptics. The finding that the clinical potency of traditional neuroleptics is highly correlated with its affinity for DA receptors (Creese et al 1976) strongly implicates this neurotransmitter in schizophrenic symptomatology. In addition, long-term usage of drugs that stimulate DA activity in the CNS can lead to schizophreniform psychoses (Snyder 1972). Although the view that dopamine plays a role in schizophrenia is a long-standing one, it is clear that not all data on the pathophysiological disturbances present in schizophrenia are consistent with this hypothesis. The DA projection to PFC in particular has been a recent focus of attention in schizophrenia research. Specifically, a common current viewpoint is that schizophrenia is not simply caused by a hyperactive dopamine system. Rather, it has been postulated that many of the cognitive impairments seen in schizophrenia are related to *reduced* DA activity in PFC (Davis et al 1991; Goldman-Rakic 1991).

Simulating Behavioral Impairments in Schizophrenia

Because our theory of DA and PFC function is conceptualized in terms of explicit computational mechanisms, it can be explored through simulation studies. In recent work, we have conducted simulations that tested the computational validity of the theory and that investigated the influence of different gating parameters on updating, maintenance, and interference protection (Braver and Cohen in press b). We also provided support for the hypothesis that DA implements both gating and learning effects, and that these can work synergistically to provide a mechanism for how cognitive control might be learned through experience (Braver and Cohen in press a). Specifically, in these simulations, the timing of the gating signal developed as a function of reward-prediction errors using in a temporal difference algorithm (Sutton 1988). This algorithm enabled the network to chain backward in time to find the earliest predictor of reward, that was a cue stimulus that also had to be maintained in active memory to receive the reward. Because this cue triggered a phasic response in the gating/reward-prediction unit, the information provided by the cue was allowed access to active memory.

In addition to providing an account of the neural mechanisms underlying normal cognitive control, our theory provides an explicit framework for testing ideas regarding the particular neurobiological disturbances that may underlie schizophrenia and their consequences for behavior. Most importantly for understanding schizophrenia, our prior work provided useful insights into the relationship between gating unit activity and active maintenance (Braver and Cohen in press b). In particular, previous simulations have demonstrated three significant effects: 1) Reduced phasic activity during the presentation of "task-relevant" stimuli leads to perseveratory behavior, by decreasing the probability that the previous context will be replaced by the current context; 2) Increased phasic activity during the presentation of "irrelevant" stimuli produces interference effects, by increasing the probability that these stimuli will disrupt the currently maintained context; and 3) Increased tonic activity during delay periods produces a delay-related decay of active memory, by increasing the probability that the current context will deactivate over time. Together, these three effects may provide a model of how DA impairment influences cognitive control. Indeed, perseverations, poor interference control, and maintenance deficits are three symptoms commonly associated with schizophrenia (Malmo 1974; Nuechterlein and Dawson 1984). Our theory provides an explicit mechanism that can explain how these cognitive deficits arise in schizophrenia. In the remainder of this article, we report a study that tests this idea directly, by incorporating the gating mechanism into a model of performance on a simple cognitive control task and examining whether disturbances to this mechanism can account for the patterns of behavioral impairments observed in schizophrenia patients.



		CUE: VALID	CUE: INVALID
PROBE	TARGET	A-X (70%)	"B-X" (10%)
	NONTARGET	"A-Y" (10%)	"B-Y" (10%)

Figure 1. The AX-CPT task. Trials consist of single letters occurring as sequences of cue-probe pairs. In the short delay condition, the delay period is 1 s, intertrial interval is 5 s. In the long delay conditions, the delay period is 5 s, intertrial interval is 1 s. A target is defined to be an X immediately following an A. Targets occur with 70% frequency, and the three other trial types (AY, BX, BY) each occur with 10% frequency.

The model suggests that the pattern of deficits observed in patients is consistent with a decrease in phasic and increase in tonic DA activity. The gating hypothesis predicts that tonically increased DA activity should produce deficits in active or WM, whereas decreased phasic DA activity should produce perseveration and interference-effects. Here, we directly test these predictions by conducting simulations of behavioral performance on a simple cognitive control task that requires both active maintenance and frequent updating of context information. The task is an "AX" variant of the Continuous Performance Test (CPT, Rosvold et al 1956). We have collected extensive behavioral data regarding the performance of both healthy subjects and patients with schizophrenia on this task (Barch et al 1998; Braver et al 1999; Cohen et al 1999; Servan-Schreiber et al 1996). Simulations of behavioral data were conducted by adding a gating mechanism to an existing computational model of the task (Braver et al 1995, 1999; Cohen et al 1996).

Methods and Materials

Task

In the AX-CPT, single letters are visually presented as a sequence of cue-probe pairs (Figure 1). A target response is required to a specific probe letter (X), but only when it follows a designated cue (A). A manipulation of the delay interval between cue and probe (1 sec short delay vs 5 sec long delay) enables an examination of active memory demands. In addition, target trials occur with high frequency (70%), that allows us to examine the role of context in biasing response competition and inhibiting response prepotencies. Specifically, control over processing via context representations can be examined in the three types of non-target trials, that occur with 10% frequency each (BX, AY, and BY, where "B" corresponds to any non-A stimulus, and "Y" to any non-X). Context information must be used on BX trials to inhibit the prepotent tendency to make a target response to the X. In contrast, context acts to bias incorrect responding on AY trials, because the presence of the A sets up a strong expectancy to make a target response to the probe. BY trials provide an index of performance in the absence of response competition.

Behavioral Data

The data for this simulation were taken from a study first presented in Braver et al (1999). Participants in the study were 16 DSM-IV schizophrenia patients and 16 matched controls. Patients were neuroleptic-naive and experiencing their first hospitalization for psychotic symptoms. Consequently, they formed a select subgroup of participants who are free of many of the confounds and complications associated with studying schizophrenia patients (e.g., medication, chronicity, or institutionalization effects). Both groups performed 200 trials of the AX-CPT evenly divided between short and long delay conditions. Intertrial interval was counterbalanced so that total trial duration was equated across delay conditions. Participants pressed one button of a response box for target probes and a separate button for nontargets. Both accuracy and reaction time data were collected. There were two primary behavioral measures of interest. The first, context sensitivity, indexed the ability to respond correctly to an X probe based on its prior context. Context sensitivity was computed by comparing AX hits to BX false alarms, using the d′ function. The second measure, context cost, indexed the degree of response slowing on non-target trials due to the presence of an A cue. Context cost was computed by calculating the difference in reaction time in AY trials relative to BY trials. These two measures were calculated separately for the long and short conditions in each group.

Computational Model

The simulations described in this paper were conducted using a computer model developed within the connectionist framework.

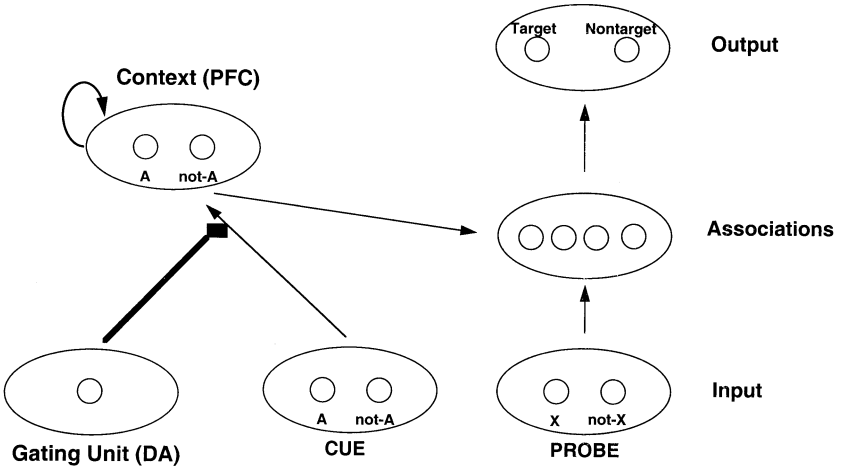


Figure 2. Diagram of Gating Model. Architecture of model used to simulate the AX-CPT task. Units in the context layer have self-excitatory connections, that provide a mechanism for active maintenance. The gating unit makes a multiplicative connection with both afferent excitatory and local inhibitory (not shown) inputs to the context layer.

Space limitations preclude a detailed introduction to the methods and principles of this modeling framework (but see Rumelhart and McClelland 1986 for a comprehensive introduction). Briefly, the connectionist or "neural network" framework enables simulation of human performance in cognitive tasks using principles of processing that are similar to those believed to apply in the brain. Thus, information is represented as graded patterns of activity over populations of simple units, processing takes place as the flow of activity from one set of units to another, and learning occurs through the modification of the connection strengths between these. From one perspective, such models are highly simplified, capturing brain-*style* computation, without necessarily committing to the details of any particular neural system or sub-system. With appropriate refinement, such models offer the opportunity to build bridges between our understanding of the low-level properties of neural systems, and their participation in higher level (system) behavior.

For the simulations below, we incorporated a gating mechanism into an existing computational model of the AX-CPT. The original model was found to successfully capture many aspects of both normal and schizophrenic performance in the task (Braver et al 1995, 1999; Cohen et al 1996). The addition of a gating mechanism provided a means to check whether the new model could also account for performance by incorporating a more refined model of DA activity. The architecture of the model is shown in Figure 2. The model consisted of a direct pathway composed of feed-forward connections between a pool of input units, representing the four stimulus conditions (A, B, X, or Y), a pool of four associative units (representing the two possible associations—target or nontarget—activated for each probe stimulus), and a pool of two output units. In addition, the cue inputs also projected to a layer of two context units. The context layer then projected back to the pool of associative units in the direct pathway. Units within the context layer had strong (nonmodifiable) self-excitatory connections (+6.0 weight) that provided a mechanism for active maintenance. Additionally, within each pool of units, there were lateral inhibitory connections that produced competition for representations. Finally, each unit was associated with a local inhibitory unit that provided a tonic negative bias (−2.5 weight) on baseline activity states.

Processing evolved continuously over time in the model according to a temporal difference equation described previously (Braver and Cohen in press a). The duration of relevant events within the simulation (e.g., cue and probe presentation, delay periods) were scaled to approximate the temporal relationships used in the actual task. Thus, the cue and probe were each presented for 2 time steps, the short delay lasted 7 time steps, and the long delay lasted 33 time steps. The presentation of each stimulus was simulated by adding an external source of activation (i.e., soft-clamping) to units in the input layer for a short duration. Input activation states were then allowed to evolve in response to this external input. All input units were provided this external source of activation during presentation of every stimulus, to approximate the effects of distributed representations, and lateral competition at the sensory stage of processing. Network weights were developed through a back propagation training procedure consisting of repeated presentations of each of the 8 different trial types of the AX-CPT (AX, AY, BX and BY at both short and long delays), with the presentation frequency of each type matching that of the behavioral task. This learning approach enabled optimization of weight strengths based on both the constraints of task performance and the relative frequencies of task events. Gating was added to the trained model by including an additional unit that had modulatory effects on the local inhibitory and afferent excitatory connections to the context layer that were identical to those in the normal model (Braver and Cohen in press a). In previous work, we have shown how these connections could develop appropriate weights through a learning mechanism based on predictions of future reward (Braver and Cohen in press a). In the current simulations, these connections were not trained, but were assumed to already have been learned. The only other addition to the model was that the input-to-context connections were adjusted so that the presence of external input alone was strong enough to activate the context module when it was in a resting state (i.e., when no other units

in the pool were active), but not strong enough to update it from an active state (i.e., when a competing unit in the pool was already activated).

Simulations

One thousand trials of each of the 8 stimulus conditions (4 trial types × 2 delays) were simulated in both the intact and impaired models. Trials were presented to the model as a continuous sequence of events occurring in the following order: cue, delay, probe, ITI. The gating unit became transiently activated during presentation of the cue and probe stimuli. Simulations of performance on each condition were conducted by determining which of the output units was the first to surpass a prespecified threshold value, and then collecting accuracy and RT statistics across each trial. Noise was added to each unit's activation state on each time step to simulate variability in processing. Both the noise and threshold parameters were fixed at the levels derived for the original model (noise = 0.95; threshold = 0.65). To simulate disturbances in the mesocortical DA system thought to be present in schizophrenia, we increased noise in the activity of the gating unit in the model (to a value 5 times that of the rest of the units). This pattern of disturbance causes changes to both tonic and phasic activity levels, as a result of the function that relates gating unit activity to its multiplicative effects on synaptic strength. Specifically, because the function is bounded and monotonic (i.e., a logistic), increases in noise will raise the mean value of gain for baseline (low) levels of gating unit activity (i.e., tonic gating) and decrease the mean value of gain for high levels of gating unit activity (i.e., phasic gating).

Results

Behavioral Data

The behavioral data are shown in Figure 3. For healthy controls, sensitivity to context was relatively high ($d' > 3$). Moreover, there were no significant effects of delay on sensitivity. Conversely, the cost of maintaining context was also relatively high in terms of RT slowing (~140 ms), and also did not decrease much with delay. In contrast, in patients with schizophrenia both context sensitivity and context cost were significantly reduced. These effects further interacted with delay, so that the difference between patients and controls was greatest at the long delay. Thus, the performance data suggest patients showed impairments in both the representation and maintenance of context information. Furthermore, the pattern of performance elicited by patients in this task also provides evidence that patients suffer from a specific impairment in cognitive control, rather than a more general deficit pattern (Chapman and Chapman 1978). This pattern can be observed by noting that the context disturbance exhibited by patients actually results in a relative benefit in performance, because they show *less* of a context cost, manifest as less response slowing to AY trials relative to BY trials.

Simulation Data

The simulations were able to successfully capture the qualitative pattern of the behavioral data (see Figure 3). Context sensitivity and context cost were both high in the intact model but decreased in the noisy gating model. Further, these effects also replicated the interaction with delay observed empirically. In particular, the difference between the two models (intact and noisy gating) was greatest at the long delay for both measures. Despite an overall qualitative fit, there was a discrepancy between the simulation and empirical data. In the model, context cost increased with delay in the intact condition, and decreased only slightly in the noisy gating condition. In the empirical data, context cost decreased slightly with delay for controls, and decreased substantially for schizophrenia patients. This discrepancy could reflect an overall improvement in reaction time that both groups of subjects exhibited at the long delay—an effect that is well-recognized in the literature (Parasuraman 1979), but that was not captured by the model. This improvement at the long delay might provide extra benefit to AY trials relative to BY trials (that would be required to produce a reduction in context cost, as this is measured by the difference between AY and BY RT), because BY RT is already close to ceiling. This discrepancy reflects the incompleteness of our current models. It seems to involve components of information processing that do not seem to be directly related to the updating of context.

An examination of the dynamics of activity in the context layer during the delay interval revealed two related mechanisms underlying the delay-related impairments in performance observed in the noisy gating model. First, it was found that in the noisy gating model, there was an increased failure for the context representation to update appropriately after presentation of the cue. On some trials this occurred as a complete failure to update. On other trials the dynamics were more complex. In particular, on these trials it seemed that updating did initially occur, but that the change in activation dynamics was not complete, so that the new context representation that was supposed to be fully activated to a level where it could be stably sustained, instead only received partial activation. As a consequence of this partial update, the new context representation was overly susceptible to the intrinsic noise present in the system, and decayed away over the delay period. The second mechanism causing a delay-related decrease in performance was that even on trials in which the correct representation was fully updated, the maintenance of this representation was less robust. Specifically, the increased levels of tonic gating unit activity during the delay period resulted in increased susceptibility to noise, and thus an increased tendency for the representation to decay. Because the effects of noise accumulate over time,

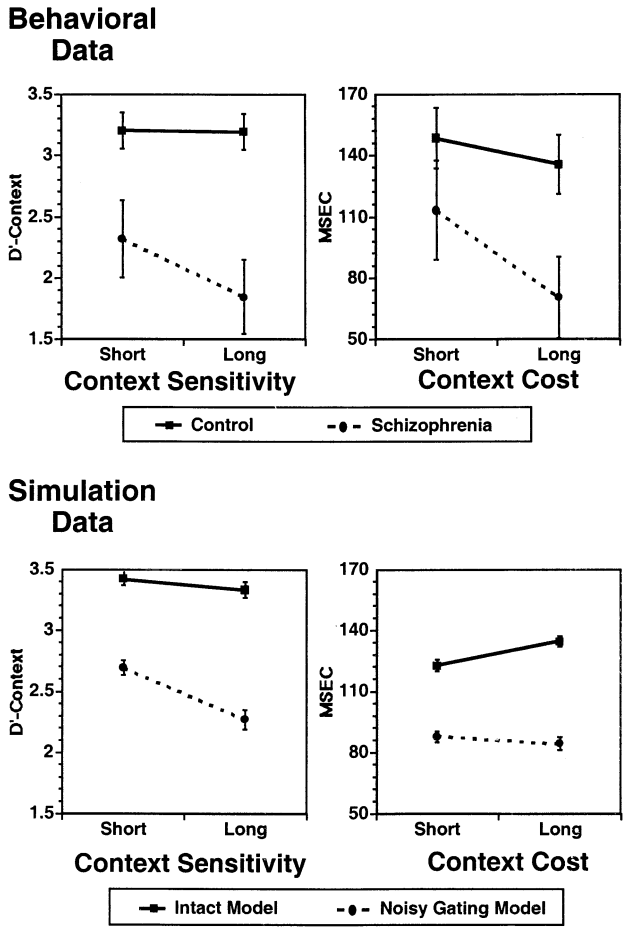


Figure 3. AX-CPT Data: Behavioral and Simulation. These figures show data for both context sensitivity and context cost performance measures for controls and patients with schizophrenia. The upper plots show the behavioral data and the lower plots show simulation data. The simulation captures both the overall reduction of context sensitivity and context cost in schizophrenia, as well as the interaction with delay.

the probability that a context representation would decay also increased with delay.

Discussion

The results of this simulation study suggest that the gating model of the AX-CPT task was able to successfully capture the specific pattern of behavioral performance observed both in healthy controls and in patients in schizophrenia. Thus, the model compares favorably to the AX-CPT model developed previously, that also accounted for this dataset (Braver et al 1999). The current model significantly refines and extends the account of the mechanisms hypothesized to underlie schizophrenic deficits in task performance. The earlier model accounted for these performance deficits by suggesting that, in schizophrenia, DA activity is tonically reduced in PFC. In the current model, the mechanism responsible for producing AX-CPT performance deficits is increased noise levels in mesocortical DA. This particular disturbance resulted in both increased tonic activity and decreased phasic activity in the gating system. As suggested by the results of prior work (Braver and Cohen in press b), the increased tonic activity produced deficits in the maintenance of context, whereas the decreased phasic activity produced deficits in updating the representation of context.

The functional distinction in the model between disturbances in phasic and tonic DA activity is an important advance in the theoretical account of the pathophysiology of schizophrenia. It is worth noting that the gating account also seems to be more consistent with neurobiological data. In particular, Grace (1991), has postulated that schizophrenia is associated with disturbances in both tonic and phasic DA activity, based on an analysis of neuroleptic-effects on DA physiology. Importantly, however, Grace's model predicts that patients with schizophrenia suffer from increased phasic and decreased tonic DA, that is opposite to the account provided by the current model. Thus, further work will be needed to examine these two models in greater detail to determine that provides a better account of the data.

In the current simulation, a single disturbance—increased noise levels in gating unit activity—was found to capture the pattern of performance deficits exhibited by patients in the AX-CPT. This occurred because increasing gating unit noise affected both tonic and phasic activity levels. The model also holds open the possibility that tonic and phasic DA activity can be independently affected by different mechanisms. Moreover, because tonic DA activity is associated with the active maintenance of context, and phasic DA activity is associated with the updating of context, the model also suggests that deficits in these two processes are dissociable in principle. This raises the intriguing possibility that different patient subgroups might suffer from independent disturbances in these two components of DA function. If patients from both subgroups were present in the data set, the averaged results would seem as if both deficits were present. This hypothesis could be tested by examining the clinical symptomatology of patients more closely, to examine whether there are relationships between different symptom subtypes and the prevalence of disturbances in updating vs. maintenance of context information. In particular, a specific disturbance in context updating would be revealed as reduced context sensitivity and context cost, but no effect of delay on performance. A specific disturbance in context maintenance would be revealed as normal performance levels at the short delay, but a significant effect of delay, such that both context sensitivity and context cost are reduced at the

long delay. Thus, the model provides a possible means of relating clinical heterogeneity to particular neurobiological mechanisms.

Another advance of the current model over our previous model is that it can potentially account for both normal and schizophrenic behavioral data in a much wider range of cognitive control tasks. The previous model could simulate tasks that required the maintenance of context information over unfilled delay periods. The current model suggests how context information in PFC can be actively maintained in the face of interference, and how this function might be disturbed in schizophrenia. In the model, the degree of interference produced by irrelevant items is directly related to the degree of phasic DA activity that occurs with the presentation of each item. We have recently shown how this mechanism could account provide an account of distractor-based interference effects on behavioral performance in healthy individuals (Braver et al 1997a). If patients with schizophrenia show increased phasic DA responses to irrelevant items, this could potentially account for the commonly observed finding that patients are more susceptible to interference effects from distractors (e.g., Neuchterlein and Dawson 1984). This question provides an important direction for our future research.

It is interesting to note that our hypothesis regarding impaired gating in schizophrenia is conceptually analogous to ideas about faulty sensory gating as indexed by the P50 component in ERP waveforms (Adler et al 1998; Swerdlow and Geyer 1998). It is possible that these two phenomena both rely on mechanisms involving the prefrontal cortex and/or the dopamine system. One source of support for this idea comes from the literature on prefrontal lesion patients, who also show deficits in gating irrelevant sensory information. Also consistent is the hypothesized involvement of the dopamine system in sensory gating phenomena (Swerdlow and Geyer 1998). However, the hypothesis discussed in the paper deals with the gating of a specific type of information (i.e., context) into working memory. Thus, it is not at all clear whether the same mechanisms also are responsible for gating a broader class of information into primary perceptual systems.

We believe that our theory and the computational modeling approach we have used to examine it have both promise and potential. Nevertheless, significant challenges remain for a comprehensive theory of cognitive control and its disturbance in schizophrenia. First, our theory in its current form has some limitations. At the basic conceptual level, we have made a link between dopamine-mediated updating of context information and its relationship to reward prediction. However, we have not demonstrated that such a mechanism can learn to gate task-relevant information into memory that itself is not directly predictive of reward. At the empirical level, we have not provided an account of performance in more complex tasks requiring cognitive control, such as those that involve reasoning, problem solving, or ecologically important domains such as language production. As such, we have not demonstrated how our theory can account for deficits in these more complex domains among patients with schizophrenia. At the neurobiological level, important work remains to be done to validate the neurobiological implication of our theory. One advance of this model over previous work is that a qualitative distinction is made between phasic and tonic dopamine activity, that is consistent with current data on dopamine function. Our hypothesis that phasic dopamine is decreased, whereas tonic dopamine is increased, in schizophrenia currently has no empirical support. In fact, this predictions in conflict with Grace's (1991) influential theory of the neurobiology of schizophrenia. These issues all remain challenges for further theoretical and empirical work.

Conclusions

The simulation presented in this article establishes the computational and empirical plausibility of a new theory regarding the role that DA may play in cognitive impairments in schizophrenia. Specifically, the simulation demonstrated that disturbances to a gating mechanism can account for the behavioral impairments observed in schizophrenia patients during performance of a simple cognitive control task. This result has important implications for understanding cognitive deficits in schizophrenia. The theory we have presented in this article provides an account of these deficits in terms of both psychological and physiological mechanisms. At the psychological level, the theory suggests that a wide range of cognitive deficits in schizophrenia can be understood in terms of a common underlying impairment—a disturbance in the ability to represent, maintain, and update context information. This function is argued to be central to successful cognitive control and can explain why cognitive control failures are frequently observed in patients with schizophrenia. At the physiological level, the theory suggests that patients suffer from disturbances in both tonic and phasic DA activity levels. Consequently, the DA projection to PFC produces an abnormal modulation of PFC dynamics. This results in an inability to both switch into new activity states and sustain current states. Our use of computational models provide a means to link these two levels of explanation, with simulations demonstrating how these hypothesized physiological deficits in PFC and DA might lead to specific impairments in cognitive function. In particular, the modeling work suggests that dysfunctional DA-mediated modulation of PFC might contribute to deficits in

both the maintenance and updating of internally represented context information.

Importantly, the theory and model presented here also may help to provide new insights on seemingly puzzling findings in the cognitive literature in schizophrenia. For example, our work may help to provide a unified account that can explain why patients seem to suffer from otherwise seemingly unrelated cognitive impairments: perseveration and switching problems (Frith and Done 1983; Malmo 1974), distractibility and susceptibility to interference (Nuechterlein and Dawson 1984), and working memory failures (Gold et al 1997; Servan-Schreiber et al 1996; Wexler et al 1998). Additionally, the theory may help to bring researchers examining the neurobiology of schizophrenia into closer contact with those examining psychological function. Specifically, the theory takes into account known physiological properties of both the DA system and PFC, and demonstrates how a particular physiological disturbance (i.e., tonic and phasic DA dysfunction in projections to PFC) might lead to precise and quantifiable consequences for behavior. Thus, even in light of the limitations of our current theory, we hope that our contribution can provide a crucial point of contact between behavioral and basic neuroscience research. This may lead to the development of more refined animal models, and to new ways of examining hypotheses drawn from neurobiologically-based research (e.g., Grace 1991).

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