A Theory of Dopamine Function and Its Role in Cognitive Deficits in Schizophrenia

by Jonathan D. Cohen and David Servan-Schreiber

Abstract

In spite of extensive research on the biological and behavioral correlates of dopamine (DA) function, little is known about the mechanisms by which DA may produce the cognitive deficits observed in schizophrenia. Neural network simulation models offer a framework for exploring how DA effects at the physiological level may influence behavior. We focus on findings suggesting that DA modulates neuronal activity by enhancing the ability of neurons to transmit signals and reduce distortion by noise. These phenomena can be captured in simulations by increasing the gain of individual units of a network. When gain is increased diffusely, improvement in signal detection performance of such a network parallels the improvement in performance of human subjects receiving DA agonists. Furthermore, decreasing gain in a network module supporting a memory function analogous to that of prefrontal cortex results in deterioration of performance equivalent to that of schizophrenic subjects. A test of predictions made by such networks about the performance of schizophrenic patients in a new variant of the Continuous Performance Test is discussed. Preliminary data are consistent with predictions and support the account of schizophrenic cognitive deficits in terms of the theory of DA function suggested by the models.

There is no need to review the evidence linking schizophrenia with disturbances of dopamine (DA) function or the list of cognitive deficits that have been associated with this illness. However, it is unsettling, if not surprising, that despite the large bodies of data supporting these observations, we still have such a poor understanding of the relationship between dopaminergic dysfunction and cognitive deficits in schizophrenia.

This lack of understanding has not been for want of empirical research on the relationship between DA and behavior. For example, many animal and clinical studies have demonstrated that DA plays an important role in regulating motor function (e.g., Ungerstedt 1971a, 1971b, 1971c; Carli et al. 1985). Similarly, there are human pharmacological studies showing that DA influences sensory processes, for example, excess DA activity can produce auditory hallucinations (Angrist and Gershon 1970; Bell 1973; Janowsky and Rich 1979). And there is a substantial literature concerning the effects of DA on learning and signal-detection performance (e.g., Rapoport et al. 1980; Klorman et al. 1984). In addition, there exists almost 30 years of research on the neurophysiological effects of DA at the cellular level. In spite of this impressive accumulation of biological and behavioral findings, there are few theories on how DA influences behavior. More importantly for the current context, this research has shed little light on the mechanisms by which DA may produce the cognitive deficits observed in schizophrenia.

This article addresses this issue by joining a convergent set of
methodologies that we believe are helpful in relating neurophysiological findings to behavioral data: computer simulation models and cognitive psychological experiments. We start by showing how anatomical and physiological observations about DA function at the neurophysiological level can be captured in computer simulation models of simple neural networks. In particular, we focus on findings suggesting that DA plays a modulatory role in the brain, by enhancing the ability of neurons to transmit signals and reduce their distortion by noise. This can be captured in simulation models by changes in a parameter, called gain, that influences the responsiveness of individual units to their afferent input.

We then show how such models can be used to simulate performance in behavioral tasks, and to examine the influence that DA may have on performance in such tasks. As an example, we describe a model of one such task: the Continuous Performance Test (CPT; Rosvold et al. 1956). We demonstrate that the influence of DA agonists on performance in this task can be simulated by increasing the value of the gain parameter in the network. Furthermore, we show that the performance of schizophrenic subjects in the same task can be simulated by reducing the value of this parameter in a part of the network that supports a specific memory function.

Finally, we report data concerning schizophrenic performance in a new variant of the CPT that was designed to test specific predictions made by our theory of DA function. The data provide support for both our theory of DA function and our account of the behavioral deficits observed in schizophrenia.

We conclude with some general comments about the role of simulation modeling and cognitive methodology in schizophrenia research.

**Catecholamines and Information Processing**

Our theory about the influence of DA on information processing is based on empirical observations about catecholamine systems in the brain and computer models that we have derived from these observations. There is extensive literature on the anatomy, physiology, and behavioral correlates of catecholamines—one that encompasses a wide variety of phenomena. However, in this article we focus on one function of DA at the cellular level that we have found to be particularly relevant to both normal cognitive function and its disturbance in schizophrenia. We start by highlighting some selected aspects of the anatomy and physiology of catecholamine systems and show how these can be modeled in neural network simulations that address their implications at the information-processing level.

**Implications of the Anatomy and Physiology of Catecholaminergic Systems.** Anatomical observations show that catecholamine systems are well suited to the simultaneous modulation of neuronal activity throughout wide areas of the neocortex. DA and norepinephrine (NE) neurons originate in the brain stem, and their nuclei of origin constitute part of a structure once referred to as the reticular activating system (Moruzzi and Magoun 1949). Their ascending fibers project to many subcortical and cortical structures in a number of ways. In primate brains, dopaminergic projections to cortex is distinct from that of other subcortical systems (e.g., the thalamus), which involve projections to sharply delineated cortical areas and maintain a topographic order. Catecholaminergic projections are distributed in a tangential fashion. They intersect topographically organized thalamic projections in the cortical columns and branch profusely along the surface of the cortex. A single axon from a DA or NE neuron may therefore traverse several functionally distinct cortical regions. This anatomical organization is well suited to a diffuse, modulatory action rather than to spatially precise transmission of discrete sensory or motor signals.

The catecholaminergic systems also have physiological properties that set them apart from other...
Figure 1. Schematic representation of projections from dopaminergic cell bodies to cortical and subcortical areas

Frontal Cortex
Gyrus Cinguli
Corpus Callosum
Basal Ganglia
N. Accumbens
Olfactory Tubercle
Medial Forebrain Bundle
Hypothalamus
Pituitary
S. Nigro
Tegmentum
Midbrain
Entorhinal Cortex

types of neural systems (for a review, see Aghajanian and VanderMaelen 1986). Their conduction velocity is slow compared to other neural systems, and their baseline rate of firing is low and stable, resulting in a steady state of transmitter release. These neurons also exhibit a constricted range of firing, and they are not able to sustain high levels of activity. They behave as if it were more important for NE and DA release to be maintained at a constant level than to fluctuate in response to transient signals. Once these transmitters are released, their influence on the target cell may last several seconds or even minutes, in contrast to the millisecond duration following release of amino acids such as gamma-aminobutyric acid (GABA) or glutamic acid (GLU). Finally, at least in the locus ceruleus, neurons fire in a uniform fashion, independently of the source of stimulation. The locus ceruleus appears to be weighing inputs from its two or possibly three afferents and then distributing a uniform message (Aston-Jones et al. 1986).

These anatomical and physiological observations suggest that catecholamines may be acting more like hormone systems than traditional neurotransmitters (Stricker and Zigmond 1986). They would be tempering brain function much as the sympathoadrenal system modulates the behavior of peripheral organs. The nature of the lesions and the treatment of symptoms in Parkinson’s disease illustrates this analogy. More than 70 percent of the brain’s DA supply must be exhausted before behavioral deficits are noticeable in Parkinson’s disease. This implies that the function of degenerated fibers can be replaced by DA released from adjacent fibers that do not have the same spatial specificity. In fact, many symptoms of Parkinson’s disease can be alleviated with an exogenous DA precursor (L-dopa) administered orally. This restoration of function with replacement therapy is comparable to the treatment of hormone-deficit states such as adrenal insufficiency or hypothyroidism. Such replacement therapy contrasts with the unpredictable effects of attempting to restore function with GLU following a cortical cerebrovascular accident.

In summary, the release of DA or NE occurs throughout large brain areas in a steady and often synchronous manner, suggesting that these systems are optimized to determine the state of processing for neural modules. The state-setting function of catecholaminergic systems may have important implications at the information-processing level.

Effects of Catecholamines on Postsynaptic Cell Function. How can DA and NE act to influence the state of processing of target areas? Although this is still an active area of research, evidence suggests that these neurotransmitters, unlike most transmitters may not act by directly increasing or decreasing the firing rate of target cells. Rather, DA and NE seem to be modulating the responsiveness of these cells to other afferent inputs.

Both the stimulation of the locus ceruleus and direct local (iontophoretic) application of NE to target cells produce a potentiation of their usual response to afferent inputs (Foote et al. 1975; Waterhouse and Woodward 1980). Potentiation of responses occurs independently of whether the afferent input is inhibitory or excitatory (Segall and Bloom 1976; Woodward et al. 1979). For example, in the presence of NE, visual cortical cells respond more strongly to their prototypical in-
puts, such as a light bar moving in a certain direction and with a specific orientation (Livingstone and Hubel 1981; Kasamatu and Heggelund 1982). Conversely, the activity of these cells tends to be more inhibited in the presence of NE when an input is presented to which the cells do not usually respond. The same kind of response potentiation has been demonstrated with DA in the striatum and, under certain circumstances, in the prefrontal cortex (Aou et al. 1983; Schneider et al. 1984; Sawaguchi and Matsumura 1985; Chiodo and Berger 1986).

These observations have led many investigators to postulate that catecholamines increase the signal-to-noise ratio of target cells, since they enhance responses to prototypical signals but not to noise (Foote et al. 1975; Chiodo and Berger 1986). It is interesting that this increase in signal-to-noise ratio often occurs in the absence of any change in the spontaneous firing rate of the target cells. In other words, contrary to what is commonly assumed, DA does not either raise or decrease the threshold above which the cell fires. The enhancement of excitatory inputs relates to the background firing rate—noise—and to an absolute increase in signal strength. Thus, catecholamine systems appear to be configured to diffusely modulate neuronal activity in target brain areas and, at the cellular level, appear to do so by changing the response characteristics of individual neurons.

**Modeling Catecholamine Effects Within the Connectionist Framework**

We have constructed a set of simulation models that show how the connectionist framework can be used to link biological and behavioral effects of catecholamines, DA in particular (Servan-Schreiber et al. 1990; Cohen and Servan-Schreiber 1992). Below, we present a set of models of signal-detection performance that addresses the role that DA may be playing in enhancing the signal-to-noise ratio of information transmission in the brain. The first model focuses on the change in performance observed in human subjects who are administered central nervous system (CNS) stimulants such as amphetamines or methylphenidate. The second model shows how the principles may account for decreases in signal-detection performance observed in schizophrenic subjects. In both cases, we show that a simulation of enhanced or decreased dopaminergic transmission results in changes in model performance similar to those observed in human subjects under similar conditions. The following section provides a brief overview of the connectionist framework within which these models were developed.

**The Connectionist Framework.**

The simulation models discussed here draw upon the principles of parallel distributed processing (PDP) (McClelland and Rumelhart 1986; Rumelhart and McClelland 1986a; McGlashan and Fenton 1993, this issue). These principles provide a framework for building computer models that can simulate cognitive phenomena. At the same time PDP principles are meant to capture salient details of the mechanisms underlying information processing in the brain. It is hoped that this will lead to more realistic models of cognitive phenomena and make it possible to relate behavior directly to biological processes (see Rumelhart and McClelland 1986b). Connectionist models have been used to explain a variety of biological and behavioral phenomena. These include computation of spatial orientation from retinal and eye-position information (Zipser and Andersen 1988), computation of object shape from shading information (Lehky and Sejnowski 1988), acquisition of regular and irregular verb forms in English (Rumelhart and McClelland 1986c), text-to-speech translation and disturbances of this phenomenon in surface dyslexia (Seidenberg and McClelland 1989), and access to word meaning from word form in deep dyslexia (Hinton and Shallice 1991).

Despite their different goals, these models have certain common features. They are composed of large numbers of simple processing units and have weighted connections between units that form pathways. Information in each model is represented as a pattern of activation over units, and processing occurs through the spread of activation among units. These features reflect a set of principles that lie at the heart of connectionist models as described in the following sections.

**Units and connections.** The functional element of connectionist models is the processing unit (see figure 2). The operation of a unit is analogous to the operation of either a single neuron or an aggregate of neurons performing a similar computation. Each unit receives excitatory and inhibitory influences from other units. On the basis of these influences, the unit computes its level of activation, which is analogous to the firing rate or probability of firing of a neuron or group of neurons. This activation
Figure 2. Schematic representation of a typical unit in a connectionist system

Figure 2 shows a typical unit in a connectionist system. The activation of unit $i$ is transmitted along its output connections to other units, a process known as spreading activation. The activation of each unit is bounded, usually between 0 and 1. Connections between units can be inhibitory or excitatory and are graded in strength. This strength is captured by the weight of each connection, which is typically an unbounded value (i.e., it can be a very large positive or negative value).

An activation rule. How does a unit determine its level of activation based on its inputs? Typically, the activation arriving from other units along each input connection is multiplied by the weight of that connection, and all of these products are summed to arrive at the net input. This can be thought of as the aggregate influence that other units have on the activation of a given unit. The net input can be very large, for example, if there are a large number of input connections along which activation is arriving or a smaller number that have very large weights. While the net input to a unit is unbounded, the actual activation of a unit is bounded. Therefore, a rule is needed to transform the unbounded net input into a bounded activation value (e.g., between 0 and 1). One commonly used rule is the logistic activation function (see figure 3, gain = 1.0). Notice that this is a nonlinear function, that is, the effect on the activation value of changing the net input varies at different points along the curve. For example, changes in the net input close to zero have a much greater effect on activation than changes in the net input when it is very large (in either the positive or negative direction). Such functions have been shown to be characteristic of actual neural systems (Freeman 1979).

Modules and pathways. Typically, units are grouped into modules, and modules are connected into pathways. Modules can be thought of as groups of units that are highly interconnected and serve a particular information-processing function. For example, a network may be divided into an input module (used to represent sensory information), an output module (used to represent the system's response), and one or more intermediate modules (used to mediate associations or modulate the flow of processing between input and output).

Processing. Processing occurs by the propagation of signals (spread of activation) among units within and between modules. For example, the experimenter might set the activation values of the input units and then observe the flow of activation to other units in the network. The direction and degree of this flow are, of course, determined by the pattern of connectivity and weights of connections in the network.

Representations. Information in the models is represented as patterns of activation. For example, external stimuli can be represented as particular patterns of activation over the input units in a network. The pattern of activation over intermediate units can be thought of as the system's interpretation or internal representation of that stimulus, and the pattern of activation that appears over the output units represents its response to the stimulus.

Knowledge. Knowledge in any system is the ability to generate the appropriate response for a particular input. In connectionist models, all of the knowledge in a network resides in its set of connection weights.

The arithmetic formula used to compute the net input is:

$$\text{net input} = \sum_i w_i a_i$$

where $w_i$ represents the weight of the connection between sending unit $i$ and the receiving unit, and $a_i$ is the activation of the sending unit.
Learning. Because knowledge is in the set of connection weights, learning consists of adjusting these weights. An important constraint on the method of learning, however, is that when new associations are learned and connections are adjusted accordingly, old associations should not be lost. In some cases—for example, when the number of units is small—these weights can be set directly by the modeler. In other cases, connections in a pathway are set by learning. Although a number of different connectionist learning techniques have been described, the generalized delta rule, or backpropagation algorithm (Rumelhart et al. 1986), is in widest use. In brief, this involves the following series of operations: (1) present an input pattern to the network; (2) allow activation to spread to the output level; (3) compute the difference (error) for each output unit between its current activation and the one desired (i.e., the one specified by the target or teaching pattern); and (4) backpropagate these error signals toward the input units. Connection weights between units are then adjusted as a function of these error signals. After repetitive presentations of the material (i.e., the set of input patterns and their corresponding output patterns), the progressive weight adjustments result in a reduction of error at the output level. When training is completed successfully, the network is able to produce the appropriate pattern of activation on the output module for each input pattern presented on the input module.

A common criticism of this algorithm is that it is not biologically plausible. It is difficult to imagine that real neural systems rely on the backpropagation of error signals for learning. However, backpropagation implements the general phenomenon of gradient descent—the gradual reduction of error by incremental adjustments in connection weights. Gradient descent is a powerful concept for describing many of the details of human learning behavior. Thus, backpropagation may offer a reasonable approximation of the type of learning that occurs in neural systems, even if the actual algorithm is different.

With these principles in mind, it is important to recognize that most network models are not intended to be detailed circuit diagrams of biological networks. Rather, like statistical mechanical models in physics and chemistry, the models are designed to capture those features of a lower level system (information-processing mechanisms in the brain) that are most relevant at a higher level of analysis (cognition and behavior). Thus, an important goal of such models is to examine the effects of biological variables on behavior without having to reproduce the entire brain.

Using the connectionist framework, we have developed simulation models of several tasks that relate to catecholaminergic effects on normal and schizophrenic cognition. The models differ in some of their details so that the differences between the different tasks can be accommodated. But they all rely on the common set of information-processing principles described above. Each model was designed to first simulate normal
performance in the relevant task. Once we had established the ability of each model to capture normal performance in the corresponding task, we examined the effects of a parameter change that simulates catecholamine effects at the cellular level. We begin our description of the models by showing how the physiological influence of DA and NE can be simulated by changes in the gain parameter of individual units. We then describe a simulation of CNS stimulant effects on performance in the CPT, as well as a simulation of schizophrenic performance in that task.

Simulation of Physiological Effects of DA. Recall that DA and NE potentiate the responses of target cells to other afferent inputs, either excitatory or inhibitory. In the models, we simulate this potentiation of neural responses as a change in a parameter of the function relating a unit's input to its activation value. We first assume that the relationship between the input to a neuron and the neuron's frequency of firing can be simulated as a nonlinear function relating the net input of a model unit to its activation value. Physiological experiments suggest that in biological systems the shape of this function is sigmoid, with its steepest slope around the baseline firing rate (Freeman 1979; Burnod and Korn 1989). The same experiments also indicate that small increments in excitatory drive result in greater changes in firing frequency than equivalent increments in inhibitory input. These properties can be captured by a logistic function with a constant negative bias.

 activation = \frac{1}{1 + e^{-(gain \times net \ input + bias)}}

(See figure 3, gain = 1.0.)

The potentiating effects of DA or NE can be simulated by increasing the gain parameter of the logistic function. As figure 3 (gain = 2.0) illustrates, with a higher gain the unit is more sensitive to afferent signals, while its baseline firing rate (net input = 0) remains the same. Elsewhere, we have shown that such a change in gain can simulate a number of different catecholaminergic effects at both the biological and behavioral levels, for example, the influence of catecholamines on the receptive field of individual units, the influence of amphetamines on stimulus detection in humans, and stimulus response generalization in both humans and rats (Servan-Schreiber 1990; Servan-Schreiber et al. 1990).

A more detailed model of DA effects on target cells, which incorporates the observation of inhibitory effects of DA, is also described by Servan-Schreiber (1990). These models have allowed us to make specific predictions about the effects of DA at the physiological level. For example, the model predicts that although DA release may not affect the firing rate of the target cell, it should affect the variance of the interspike interval. This is because the effect of noisy inputs is to drive the firing rate either up or down with equal frequency, which does not result in a change in the mean baseline firing rate. However, each deviation will be of greater magnitude when gain is increased, resulting in a greater variance.

To simulate the effect of either DA or NE in an entire network of units, we change gain equally for all the units in the model that are assumed to be influenced by that neuromodulator. For example, when simulating the effects of stimulants that are presumed to enhance the transmission of DA and NE (e.g., methylphenidate), we increase the gain equally for all units in the model. Conversely, when simulating a decrease in DA in the prefrontal cortex, we reduce the gain of units only in the module that is assumed to support the role of that particular brain area.

Finally, note that in the simulations described below, we have not concerned ourselves with the details of the mechanisms through which potentiating effects arise at the cellular level. We have focused instead on their functional significance by capturing the effects of potentiation with a single parameter (gain).

Simulation of the Behavioral Effects of CNS Stimulants. We explored the relevance of our model of physiological effects of catecholamines in simulations of the effect of CNS stimulants on signal-detection performance. It has long been established that CNS stimulants such as amphetamines can improve the signal-detection performance of human subjects. Some of the first demonstrations were performed during World War II with radar operators. Since then, this particular effect of stimulants has been demonstrated in the laboratory using different sensory modalities, with animal and human subjects. For example, Hink and colleagues (1978) have shown that methylphenidate increases the ability of human subjects to discriminate between auditory signals arising from contiguous spatial locations. Campbell and Raskin (1981) have found that rat pups discriminate better between members of their species and artificial substitutes following administration.
of amphetamines. Similarly, Doty and Ferguson-Segall (1987) demonstrated that rats can detect particular odors more accurately when given amphetamines.

Here, we focus on a task that has been extensively used in psychophysiology and psychiatry to study the effect of drugs on attention and signal detection: the CPT. This task was chosen because of its face validity with respect to several real-world situations and its high sensitivity to variations in attentional states. Subjects are asked to detect a target event among a continuous stream of inputs and to respond only to this event. In a typical version of the task, the “CPT-double,” subjects monitor a computer display on which single letters are presented consecutively, each for a brief time (e.g., 50 ms). The subjects are asked to press a button every time two identical letters are presented consecutively and to refrain from pressing the button in all other instances. Subjects typically fail to report some target events—their “miss rate” hovers around 15 to 20 percent—and inappropriately press the button when no target event has occurred—about 1 percent “false alarms.” Several independent studies of changes in human performance on the CPT have demonstrated that CNS stimulants improve the discrimination ability of subjects, that is, increase d-prime, without affecting their response criterion; that is, the number of misses is reliably reduced with no change in the number of false alarms (Rapoport et al. 1980; Klorman et al. 1984; Peloquin and Klorman 1986). (The terms “d-prime” and “response criterion” refer to the traditional signal-detection theory measures [Green and Swets 1966]. D-prime is a measure of subjects’ ability to discriminate between a signal and noise. The response criterion measures subjects’ tendency to respond independent of their ability to discriminate.)

The following simulation shows that, as predicted from anatomical and physiological observations, a uniform and widespread increase in gain in a network of neural-like elements performing the CPT can account for catecholamine-induced performance improvements in this task.

Network architecture, processing, and training. The network consisted of four modules: an input module, an intermediate (associative) module, a module for representing the prior stimulus, and a response module (see figure 4; for details see Cohen and Servan-Schreiber 1992). The input module represented the visual features of individual letters. Stimulus presentation was simulated by activating the input units corresponding to the features of the stimulus letter. This produced a unique pattern of activation for each stimulus. The network was trained with the backpropagation algorithm to record the presentation of a given input pattern by activating the appropriate unit in

![Figure 4. Network used to simulate the CPT double task](https://academic.oup.com/schizophreniabulletin/article-abstract/19/1/85/1895784)

**Figure 4. Network used to simulate the CPT double task**

**Response Module**

**Prior Stimulus Module**

**Feature Input Module**

**Note.**—CPT = Continuous Performance Test (Rosvold 1956). Note the bidirectional connections between units in the intermediate and prior stimulus modules.
the prior stimulus module. In addition, the network was trained to activate the unit in the response module whenever a stimulus letter appeared twice or more in a row. This meant that the network had to use the information stored in the prior stimulus module. This occurred along a set of connections from the prior stimulus module back to the intermediate module. Intermediate units could thus receive bottom-up information from the feature units (representing the current input) and top-down information from the prior stimulus units. This allowed the network to compare the current and previous inputs and learn to activate the response unit whenever two consecutive letters were identical.

Following training, the network was able to perform the CPT-double task perfectly for a set of 10 different stimuli. Normal subjects in Peloquin and Klorman's study (1986) missed on 11.7 percent of trials and produced false alarms on 0.6 percent (see figure 5). We added noise to processing to simulate these results. Noise in neural systems is usually attributed to afferent signals that are independent of the relevant stimulus (Hebb 1955). To simulate this distortion of input, we added a small amount of random, normally distributed noise to the net input of each unit on every processing cycle. The overall amount of noise was adjusted to match the performance of the network with that of human subjects in the placebo condition. False alarms and misses in the simulation were recorded over 5,000 trials. The 99 percent confidence interval for the miss rate was ±1.0 percent and ±0.5 percent for the false alarm rate. The results of this simulation appear in figure 5 (gain = 1.0).

The administration of methylphenidate is assumed to diffusely and tonically enhance the transmission of DA and NE in the CNS. To simulate this in the model, we increased the gain of all units in the network from 1.0 to 1.1 and measured the model's performance over another 5,000 trials. No other features of the model were changed. With this "modulation" of units in the model, the number of misses decreased to 6.6 percent, but the number of false alarms did not change significantly (0.78%). As in the subjects, this corresponds to a true increase in signal detection (as measured by the d-prime statistic of signal-detection theory), with no change in response criterion. The enhancement of signal-detection performance in the simulation is a robust effect. It appears when gain is increased in the intermediate module only, in the output module only, or in both modules. The improvement in performance results from a reduction of the distortion (from internal noise) of the distributed representation of the relevant information over the module where gain is increased. (See Servan-Schreiber et al. [1990] for a mathematical analysis of changes in signal-detection performance in relation to gain.)

In summary, the model shows that an important consequence of DA and NE cellular effects may be to affect the quality of a signal represented over a network of cells. The model is also useful in

Figure 5. Comparison of empirical and simulation data regarding the effects of central nervous stimulants on performance in the CPT task

Empirical Data
- Misses
- False Alarms

Simulation
- Misses
- False Alarms

showing that at least some behavioral effects of DA and NE can be understood in terms of specific physiological observations. However, this model has some important limitations and raises some new questions.

In this simulation, increasing gain appears to make it easier for the system to distinguish between the presence and absence of a signal. If this were so, why wouldn't the brain be operating at maximum gain all the time? There are in fact several possible drawbacks of higher gain values in a biological system. First, at lower gain, the presence of noise guarantees some variability in response selection. Higher gain may induce stereotyped responses. Variability of responses may be a necessary and adaptive feature of biological systems, particularly in the context of new environments and during learning.

Second, under some circumstances, what we have regarded as noise in the input to a unit may be the expression of a weak signal that may be useful to subsequent stages of processing and ultimately an important determinant of the system's response. With high values of the gain, the representation of this weak signal would be eliminated early in processing in favor of stronger signals. This phenomenon is analogous to the effect of contrast enhancement on photocopy machines: when the machine transforms gray areas into either black or white, some valuable information may be lost.

And last, although high gain improves signal-detection performance, it may drain energy. Cortical neurons appear to operate at high gain in states of wakefulness and arousal and at low gain during sleep (Aston-Jones and Bloom 1981; Livingstone and Hubel 1981), and autoradiography studies suggest a correlation between catecholamine release and increased deoxyglucose metabolism (McCulloch et al. 1982). These observations are not surprising. The communication channels in the brain, like all communication pathways, have finite bandwidths that are determined by their physical characteristics. A well-known information theory (Shannon and Weaver 1963), posits that the information capacity of such channels, operating in the presence of noise, is a function of the power emitted into them to transmit a signal. Hence sending information over these channels at the rates associated with wakeful or alert behavior—that is, at higher gain—requires higher power consumption, or an increased rate of energy expenditure.

The simulation also has significant limitations as a model of DA effects. First, the effects of enhanced dopaminergic and noradrenergic transmission are lumped together, ignoring the fact that separate manipulations of these two modulatory systems have very different effects on behavior. Second, processing in the model occurs in a single time step, at the end of which either a response occurs or it does not. The model therefore cannot be used to address effects on other aspects of behavior, such as the initiation and vigor of responses or the relation between speed and accuracy of responses. Yet DA seems to be intimately connected to precisely these aspects of behavior, as evidenced by the motor deficits following lesions to the DA system and the increase in motor activity resulting from stimulation of the DA system. We have begun to address some of these limitations by developing models of the time course of information processing, as well as the relation between speed and accuracy in a well-studied cognitive paradigm: the Eriksen choice-reaction time task (Eriksen and Eriksen 1974). These simulations and preliminary empirical results using DA agonists and antagonists in a variant of the Eriksen task are described elsewhere (Naylor et al. 1985; Halliday et al. 1987, 1991; Servan-Schreiber 1990; Servan-Schreiber and Cohen 1991).

**Disturbances of DA and Cognitive Deficits in Schizophrenia**

Up to this point, we have considered the effects that increases in catecholamines have on information processing. The same principles can be used to investigate the effects of decreases in catecholamine activity. This is of particular relevance to the study of schizophrenia, which many have suggested may be associated with a reduction of DA activity, particularly in the prefrontal cortex (PFC) (Crow 1980; Mackay 1980; Weinberger 1987; Cohen and Servan-Schreiber 1992). Below, we consider the role that such a disturbance may have in producing some of the cognitive deficits observed in schizophrenia.

**DA and the Function of PFC.** Attention has focused recently on the importance of DA activity in PFC and its disturbance in schizophrenia. For example, Brozoski and colleagues (1979) have shown that selective deficits in behavioral tasks that result from lesions of PFC can also be induced by re-
ducing dopaminergic tone to this area (e.g., by lesions of the ventral tegmental area). Furthermore, these deficits can be reversed by the direct application of dopaminergic agents to PFC. Similar findings have been reported by Simon and coworkers (1980), and Diamond (personal communication, 1992) has recently found that children being treated for phenylketonuria—who have demonstrably higher plasma levels of phenylalanine, suggestive of lower levels of homovanillic acid (HVA)—show selective deficits on tasks sensitive to PFC function. These findings all suggest that behaviorally relevant functions of PFC rely on adequate dopaminergic tone. Schizophrenic patients also show deficits on tasks that are sensitive to PFC function (Kolb and Whishaw 1983; Weinberger et al. 1986; Park and Holzman, in press), as well as hypofrontality in measures of PFC blood flow and metabolism. Furthermore, at least one study has found a correlation between task performance, cerebrospinal fluid concentrations of HVA (a DA metabolite), and PFC activation by regional blood flow (Weinberger et al. 1988). However, while these findings suggest that there is an important relationship between DA tone in PFC and cognitive deficits in schizophrenia, the role of DA in the PFC and its relation to changes in behavior observed in schizophrenic subjects remain to be explained.

We have begun to address this issue using the computer simulation techniques described above. Using simulation models of cognitive tasks and gain as a model of DA function, we have been able to provide an account of the changes in behavior that result from a reduction of DA in PFC. The models are based on the assumption that PFC is responsible for representing and maintaining information necessary for the subsequent selection of action—what we have referred to as the internal representation of contextual information. This concept is closely related to the ideas of Goldman-Rakic concerning the role of PFC in working memory (Goldman-Rakic 1987). In a series of simulation models, we have demonstrated that a reduction of gain in a component of the models responsible for representing and maintaining context results in behavioral changes that quantitatively match the performance of schizophrenic subjects in attention and language tasks. These models are described in detail elsewhere (Cohen and Servan-Schreiber 1992).

Here, we focus on one of these: the CPT model.

Simulation of Performance in the CPT. Schizophrenic subjects show consistent deficits in the CPT. This is particularly true for variants that place a large demand on the active maintenance of internal representations of context. For example, in the CPT-double, a target consists of any consecutive occurrence of a stimulus (e.g., a B immediately following a B). Thus, subjects must be able to use a representation of the previous stimulus as context for responding to the subsequent one. In the model, this representation is maintained in the prior stimulus module (see figure 4). Schizophrenic subjects perform poorly in the CPT-double and similar variants in which the correct response depends on a prior stimulus (Nuechterlein and Dawson 1984; Cornblatt et al. 1989). If this impairment can be explained by a reduction of dopaminergic tone in PFC that results in the degradation of internal representations of context, then we should be able to simulate schizophrenic subjects’ deficits in the CPT-double by reducing gain in the prior stimulus module. This module is responsible for representing and maintaining context in the model.

We tested this idea by using the model described earlier to simulate the performance of schizophrenic and control subjects in the CPT-double. Parameters of the model were adjusted to match the performance of control subjects in a recent empirical study (Cornblatt et al. 1989). Figure 6 compares the model’s performance (panel B, Normal Gain) with that of human control subjects (panel A, Normal). At baseline, the model, like the controls, shows misses on 17 percent of trials and false alarms on 5 percent. To simulate performance of the schizophrenic subjects in this task, we simply decreased the gain of units in the prior stimulus module to 0.6. This was exactly the same value used to simulate schizophrenic deficits in other tasks; see Cohen and Servan-Schreiber (1992). No other changes were made to the model. The percentage of misses increased to 44.9 percent, while false alarms increased slightly to 8.9 percent. These results closely match the empirical data for schizophrenic subjects (figure 6).

Although some authors have interpreted schizophrenic subjects’ performance in the CPT as a deficit in sensory processing, our model suggests an alternative hypothesis: performance deficits are due to a degradation in the internal representation required as context for processing the current stimulus. In the model, this was induced by decreasing gain in the
prior stimulus module. These results further support the idea that gain is a useful model of DA function and provide an explanation for how a reduction of DA in PFC can account for some of the cognitive deficits observed in schizophrenia.

While these findings are encouraging, our theory would be more compelling if it could make new, empirically testable predictions. The theory predicts specific ways in which standard cognitive tasks can be manipulated to make them more sensitive to disturbances of DA in PFC and how subjects will perform in such tasks. First, it suggests that tasks will be most sensitive when a correct response must compete with an otherwise stronger or more dominant incorrect response. This is because, under such conditions, the weaker response relies heavily on the ability to use context to override the stronger competing response. Thus, strengthening the bias toward competing responses provides a means for assessing the ability to represent and use context. Our theory predicts that disturbances in PFC should lead to failures in this ability and therefore greater numbers of inappropriate competing responses.

The theory also predicts that the ability to maintain context representations relies on dopaminergic tone in PFC. Reduced DA activity results in a decrease in gain, which weakens context representations. This makes them more susceptible to the cumulative, degrading effects of noise. If a contextual representation is used quickly, this effect is less significant, and the representation may be sufficient to overcome a strong competing response. However, as time passes, the effects of noise accumulate, and the representation may no longer be strong enough to reliably mediate the weaker of two competing responses. This effect can be tested by varying the delay between the presentation of

Figure 6. Comparison of empirical (panel A) and simulation (panel B) data on normal and schizophrenic performance in the CPT task

![Graphical representation of data comparison between normal and schizophrenic performance in the CPT task.](https://academic.oup.com/schizophreniabulletin/article-abstract/19/1/85/1895784)
context information and a target stimulus. Failure to maintain context should result in poorer performance at longer intervals.

There is evidence that schizophrenic subjects do perform poorly in tasks that involve response competition and delays, for example, the Stroop task (Stroop 1935) and lexical disambiguation tasks (for a review see Cohen and Servan-Schreiber 1992). However, we are not aware of any studies that test both of these factors in a single, prospective design. To test the predictions made by our theory, we developed a variant of the CPT-AX that involved a strong response tendency and varied the context-stimulus delay. In the section that follows, we provide a general description of this task and our primary results; a detailed description of the task and a complete analysis of the results are reported elsewhere (Cohen et al., submitted for publication).

A Test of Predictions in the CPT-AX. In the standard version of the CPT-AX, subjects respond to a target letter only when it occurs following a designated cue. For example, subjects might be instructed to respond to the letter X only when it follows an A. As in the CPT-double, the prior stimulus provides the context necessary for evaluating the current stimulus. That is, the response to the target letter X depends on the identity of the prior stimulus (respond if it was A, but not if it was any other letter). Schizophrenic subjects show reliable deficits in this version of the task (Nuechterlein and Dawson 1984). However, target events usually comprise only 10 to 30 percent of trials, and the primary observation is that schizophrenic subjects fail to respond to the target (i.e., have an increased number of misses) more often than controls, but there is no increase in false alarms (responses to distractors). An increase in misses is consistent with an impaired ability to maintain context. Insensitivity to the cue at the time of response would produce uncertainty as to whether or not to respond to the target and therefore a decision not to respond on some trials. However, misses could also represent a failure to encode the target itself caused by a deficit in stimulus encoding or general inattention (given the low frequency of targets). The low target frequency is also insufficient to produce a strong tendency to respond to it in the absence of the cue. A higher target frequency would induce such a tendency, which, as discussed above, could provide a measure of the failure to use context.

Another limitation in the standard implementation of this task is that stimuli are usually presented at a rate of about 1 per second or less. This is, at best, just at the threshold of the temporal delay needed to elicit performance deficits in PFC-impaired subjects (Diamond and Goldman-Rakic 1989). Longer delays are typically more reliable in producing such deficits.

To test the predictions discussed above, we modified the CPT-AX to introduce a dominant response tendency and a variable delay between the context and stimulus. First, we modified the frequency of events so that the target occurred in context (A–X) in 80 percent of trials, a distractor preceded the target (e.g., B–X) in 10 percent of trials, and the cue was followed by a distractor (e.g., A–Y) in the remaining 10 percent of trials. Increasing the target frequency in this way served not only to engage subjects more actively in the task, but also to introduce a strong tendency to respond to the target whenever it appeared, independent of context. It was correct to respond to X about 90 percent of the time. The ability to suppress responses to X when it occurred out of context can be used to assess how well subjects use context of the previous letter to control this strong response tendency. We predicted that the failure of schizophrenic subjects to suppress a response to X would manifest as a greater number of BX false alarms.

In addition to manipulating target frequency, we also manipulated the delay between stimuli (interstimulus interval [ISI]) to test subjects’ ability to retain the relevant contextual information over time. We used two ISIs: 1 second and 5 seconds. We predicted that for control subjects performance would improve in the 5-second ISI condition, which is consistent with the observation by others that subjects typically perform better in slower paced tasks (Parasuraman 1979). However, we predicted the reverse for schizophrenic subjects. A reduction of DA in PFC should, as we have argued above, result in a worsening of performance with time, as weakened context representations succumb to degradation by noise. Specifically, we predicted that there would be an increase in the number of BX false alarms at the longer ISI, that is, responses to the target independent of context.

We studied three groups of subjects in this task: (1) newly admitted schizophrenic subjects who had a documented history of noncompliance with medication for
1 month or more before admission and who were tested before receiving neuroleptic medication; (2) newly admitted schizophrenic subjects who were receiving neuroleptic medication at the time of admission and who were tested while continuing to receive the same medication; and (3) non-schizophrenic patients hospitalized with psychiatric diagnoses, the majority of whom had a diagnosis of major depressive disorder. Each subject was tested in two blocks of our modified CPT-AX task, one with the short ISI (1 second) and one with the long ISI (5 seconds). The results of this experiment are presented in figure 7.

Overall, our findings were consistent with other studies of performance of schizophrenic subjects in the CPT. Medicated and unmedicated schizophrenic patients showed generally poorer performance compared with patient controls (panel A; $p < 0.002$ for overall d-prime in controls vs. each group of schizophrenic subjects). The purpose of this task, however, was to test predictions about the specific patterns of performance across the different conditions of the task. As predicted, control subjects showed an improvement in their overall performance (as measured by d-prime) in the long ISI condition. While schizophrenic subjects did

Figure 7. Performance of schizophrenic subjects with and without medication and patient controls in a variant of the CPT AX

Overall Performance

<table>
<thead>
<tr>
<th>D-prime</th>
<th>Patient Ctls</th>
<th>Schiz (meds)</th>
<th>Schiz (no meds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short ISI</td>
<td>5</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Long ISI</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Note.—CPT = Continuous Performance Test (Rosvold 1956). Panel A shows d-prime scores (calculated from hit rates and all false alarms) for the three groups in the two interstimulus interval (ISI) conditions. Panel B shows the proportion of the total number of catch trials of BX (context inappropriate) responses.
not show the decrement in overall performance that we had expected, there were significant differences across ISI in specific types of errors. Before turning to these, however, note that the improvement in the performance of controls at the long ISI and the absence of any significant differences for schizophrenic subjects means that any increases in particular types of errors at the long ISI cannot be attributed to the greater overall difficulty of the task in this condition.

Panel B of figure 7 shows the number of BX (context-independent) false alarms as a proportion of the total number possible. As predicted, schizophrenic subjects showed a significantly greater number of BX false alarms than controls (p < 0.05 for controls vs. each group of schizophrenic subjects). While the number of such errors generated by medicated subjects did not show a sensitivity to ISI, those of unmedicated subjects did. Unmedicated subjects made a significantly greater number of BX errors at the long ISI (figure 7, panel B), as predicted by our hypothesis. A failure to use context to override the strong tendency to respond to X, established by the high frequency with which it was correct to do so in the task, led to responses to X when it was not preceded by the cue.

Although the findings of this study indicate that further research is necessary (e.g., a validation of the effects of medication), the results seem to support our overall approach. The theory provided both the motivation and guidelines for refining a standard task to make it more selective for the deficits of schizophrenic subjects. It also provided detailed predictions about the specific pattern of performance that should result. The data from this task offer good initial support for this theory. However, they are restricted to accuracy data and do not directly address the time course of processing. Experimental paradigms that provide more direct information about the time course of processing will offer opportunities for more direct confirmation of our theory concerning the interactions between disturbances of gain and the processing of context. The modeling framework we have described in this article can also be used to simulate performance in these types of paradigms, such as the Eriksen response-competition task. We have recently begun both modeling and empirical work along these lines (see Cohen et al. 1992).

**Summary**

This article has described how computer simulation models of neural networks can be used to integrate anatomical and physiological observations about the DA system with behavioral measures of information processing. The models suggest that the modulatory action of DA enhances the quality of information transmission by making it less susceptible to distortion by internal or external noise. In normal subjects, enhanced dopaminergic transmission is associated with increased signal-detection performance. The models account for this in terms of an increase in the gain of individual processing units. Schizophrenic subjects show deficits in signal-detection performance. The models suggest that this can be accounted for by a reduction in gain of units in a module that supports the representation of context, which we have associated with the function of PFC.

To test this idea, we designed a new variant of the CPT. We increased target frequency to induce a strong response bias to the target, which had to be overcome by representations of context. We also added a variable delay between context and target to test for the durability of context representations. According to the theory, a decrease in dopaminergic activity in the PFC should result in a decrease in the signal-to-noise ratio of information transmission by neuronal populations in this brain area. This, in turn, should produce a degradation in the quality of internal representations of context required to mediate the weaker, but contextually appropriate response of two competing alternatives. Furthermore, deterioration of the representation should occur with time as the effects of noise accumulate. As predicted, unmedicated schizophrenic subjects showed an inability to inhibit a strong response tendency when context dictated the weaker, but contextually appropriate response of two competing alternatives. Furthermore, this deficit worsened significantly at an increased delay between the context and the target, a result that contrasted with the unchanged or improved performance of comparison groups.

**Closing Remarks**

The theory of DA effects that we have presented may not be limited to an account of cognitive deficits. We noted that the role of DA in the facilitation of motor responses and distortions of sensory integration—as in auditory hallucinations—is more commonly emphasized than its effect on signal-to-noise ratio. However,
these three facets of DA effects may be intimately related. For example, using the gain model, we have begun to account for the effect of DA agonists and antagonists on response-related processes (e.g., reaction time distributions, number of premature responses, and number of omissions) in human and animal experiments. In one series of simulations, gain was increased over modules of the network responsible for response selection and expression to simulate the effects of hyperdopaminergic activity induced by DA agonists. This resulted in a faster buildup of activation, which, in turn, resulted in faster reaction times, more premature responses, and fewer omissions, as is typically observed in empirical studies (Naylor et al. 1985; Cole and Robbins 1987). Similarly, excessive gain in modules of a network that integrates sensory information results in a tendency to settle prematurely on erroneous configurations of activation that are only distantly related to the input. This phenomenon is reminiscent of sensory illusions and hallucinations. (See also Hoffman 1987 for studies of the effect of gain in constraint satisfaction networks.) Hence, the same physiological effect of DA—a modulation of signal-to-noise ratio of information transmission, but in different brain regions—may be related to its role in motor function, sensory integration, and cognitive deficits.

The models also provide a new and not-so-intuitive perspective on the relationship between memory and processing, which may have a direct bearing on predictions about the developmental course of cognitive deficits in schizophrenia. We have argued that a disturbance of DA activity in PFC results in a degradation of context representations caused by a reduction of gain in this brain area. We have also pointed out that there is an important relationship between degraded representations and the cumulative effects of noise. When gain is moderately disturbed—as in the simulations of schizophrenic subjects’ performance presented in this article—performance deficits are significantly more apparent after a delay, during which the effects of noise accumulate and degrade susceptible representations. With more severe disturbances of gain, however, the initial representation of context may be degraded far enough to impair performance even on immediate presentation of a target stimulus. In other words, the models predict that with mild to moderate disturbances in gain, processing deficits will be time sensitive; that is, they will appear more as memory deficits. With more severe disturbances, however, deficits will be apparent immediately, that is, they will appear more as processing deficits. If disturbances in the DA system progress with the course of illness, we should see a progression from deficits that appear to be more memory based to ones that appear to be more processing based. We are currently investigating these predictions by looking at the performance of unmedicated, first-break schizophrenic subjects and comparing them to the performance of patients at later stages in their illness.

We have observed that, with normal gain, representations are relatively impervious to the effects of noise but that even moderate reductions in gain can lead to deteriorative effects that are observable only after delays. This is an example of the kind of nonlinear behavior that neural networks demonstrate—behavior that is not immediately or intuitively obvious and that we would not necessarily have predicted without actually running the simulations. Herein lies one of the most important values of computer simulation models: They can provide insights into the dynamic performance of complex systems, insights that are not always obvious from simple inspection of their structure. We cannot over-emphasize the importance of this point. All too often, theories concerning the function of neurophysiological systems are stated in verbal terms and then depicted with box-and-arrow diagrams showing excitatory or inhibitory connections between sub-systems. The assumption is that, by tracing these connections and enumerating their effects as a sequence of steps or actions, we can infer from the drawing how the system will actually perform. However, we have been humbled repeatedly by our failure to predict the behavior of even the simplest of simulations that include recurrent (or feedback) connections and nonlinear response properties—two features that are central characteristics of real neural systems. Hoffman and McGlashan (1993, this issue) also discuss a number of interesting behaviors exhibited by nonlinear dynamic systems that are in no way obvious from descriptions of their structures.

Stated in slightly broader terms, we wish to emphasize the importance of modeling in the discovery process itself. At times, the insights provided by a model may seem in hindsight to be obvious or not to have required the effort involved in constructing a computer simulation. However, we often fail to recognize that the in-
sight and the emerging theory came from the process of developing the model itself. Thus, the models provided an important vehicle for the discovery and not just the testing of new ideas. We feel that it is in this discovery role that the kind of modeling we have described can make its biggest contribution to research on schizophrenia and to brain–behavior relationships in general.

References


Goldman-Rakic, P.S. Prefrontal cortical dysfunction in schizophrenia: The relevance of working memory.


Kolb, B., and Whishaw, I.Q. Performance of schizophrenic patients on tests sensitive to left or right frontal, temporal, or parietal function in neurologic patients. Journal of Nervous and Mental Disease, 171:435–443, 1983.


Weinberger, D.R.; Berman, K.F.; and Zec, R.F. Physiological dys-


Acknowledgments

This research was supported by a National Institute of Mental Health (NIMH) Physician Scientist Award (MH-00673) to J. Cohen, an NIMH Individual Fellow Award (MH-09696) to D. Servan-Schreiber, and an NIMH FIRST Award (MH-47073) and a component of an NIMH Program Project (MH-47566) shared by the two authors. The authors wish to thank Renee Alund, John Gurkliss, Gretchen Haas, Matcheri Keshavan, Nina Schooler, Sandra Steingard, and John Sweeney for their contributions to the experimental study described. They would also like to express gratitude to Jay McClelland and Joe Zubin for providing the intellectual environment in which the ideas expressed in this article could evolve.

The Authors

Jonathan D. Cohen, M.D., Ph.D., is Assistant Professor of Cognitive Neuroscience, Department of Psychology, Carnegie-Mellon University, and Assistant Professor of Psychiatry, University of Pittsburgh School of Medicine, Western Psychiatric Institute and Clinic; David Servan-Schreiber, M.D., Ph.D., is a Resident in Psychiatry, Department of Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh, and Adjunct Professor, School of Computer Science, Carnegie-Mellon University, Pittsburgh, PA. Drs. Cohen and Servan-Schreiber are co-directors of the Laboratory for Clinical Cognitive Neuroscience at Carnegie Mellon University and the University of Pittsburgh.