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**DOPAMINE, FRONTAL CORTEX, AND SCHIZOPHRENIA: MODEL AND DATA**

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**ABSTRACT**

Schizophrenic patients show a variety of deficits in cognitive functions. These deficits have been difficult to understand in terms of a common unifying hypothesis. We describe a connectionist model of the function of prefrontal cortex and of neuromodulation of processing by dopamine. This model suggests that a single deficit may underlie poor performance in a variety of tasks: an impairment in maintaining contextual information over time and using that information to inhibit inappropriate responses. We tested schizophrenic on a new variant of the continuous performance test (CPT) designed specifically to elicit deficits in the processing of contextual information predicted by the models. The results confirmed the prediction.

**Introduction**

Psychiatric disorders are characterized by diffuse deficits that cannot be easily related to a single specific function. The clinical descriptions of psychiatric patients often appeal to terms such as "attention" or "inappropriate behavior" that are not well defined in information processing psychology.

Furthermore, psychiatric disorders typically have a fluctuating course with waxing and waning of symptoms — occasionally with complete remissions — and the symptoms often respond to drug therapies. These observations suggest that there is no simple structural lesion — such as damage to individual "units" or to "connective weights" — which can explain the nature of the deficits.

This state of affairs has left information processing theoreticians with no clear idea of exactly what should be modeled and even less clear ideas about how to model such disorders.
In this work, we have focused on how the modeling of neuromodulation can shed some light on impairments of attention and working memory that are particularly relevant to the deficits displayed by patients who suffer from schizophrenia.

1. Schizophrenia

Schizophrenia is a striking disorder of higher brain functions in which patients appear to have intact elementary information processing mechanisms but nevertheless display diffuse cognitive deficits — for example, in the ability to sustain attention or to solve problems or the concreteness in their interpretation of concepts — as well as gross impairments of social behavior (a familiar example of which is their tendency to address strangers in the street).

At the same time, biological research in schizophrenia has identified some salient abnormalities that can begin to constrain a model of such behavioral anomalies. Specifically, we will focus on the failure of schizophrenic patients to activate their prefrontal cortex during certain cognitive tasks, as documented by positron emission tomography (PET) \(^1\), and a dysfunction of the dopaminergic system \(^2\).\(^5\).

An important contribution of our modeling efforts has been to show how these behavioral and biological observations may be causally related in terms of specific neural mechanisms.

2. Function of Prefrontal Cortex

On the basis of empirical evidence accumulated over the last 30 years, the prefrontal cortex (PFC) has been assumed to support at least two critical higher functions: (1) active memory and (2) behavioral inhibition. The memory function refers to the ability to maintain information "on-line" in order to bridge the gap between the presentation of stimuli in the environment and the time when responses to such stimuli should take place \(^6\).\(^7\). The inhibition function refers to the ability to prevent the expression of habitual responses when these are not appropriate to the present context \(^8\).

Through our modeling work, we have come to believe that these two sets of observations can be described by a single function: the representation and maintenance of context information \(^5\).

3. Function of Dopamine

The cell bodies of dopamine neurons are grouped in small nuclei from which axons diffusely innervate other brain regions in a distributed fashion. The PFC is one of a several brain regions with an important dopaminergic innervation \(^9\). The effect of dopamine release on target neurons is not to excite or inhibit these neurons, but, rather, to modulate how the target neurons respond to other neurotransmitters. We have proposed that this modulation can be characterized as a change in the gain parameter of the activation function of target units \(^10\), such that they are more sensitive to their excitatory or inhibitory inputs (figure 1.).

Hence, dopamine can be thought of as setting a state of information processing in target areas rather than as conveying a specific informational content.

![Figure 1.](image)

4. A Minimalist Model of PFC Function

We have captured our hypothesis about the function of PFC with a simple model of selective attention and response selection (figure 2.) \(^5\). In this model, the flow of processing from an input to an output layer is influenced by the pattern of activation in an additional module — the context module — which we associate with the function of the PFC. The pattern of activation over units in the context module can contain information about the processing of previous stimuli, or about task instructions, or anything else that captures the "context" in which current stimuli are being presented. This pattern interacts with the flow of activation from the input layer at the level of a "hidden" or associative layer. Through this interaction, it can bias processing of incoming stimuli and give rise to "selective attention."

We have implemented this model with a variety of different learning algorithms such as backpropagation ("Jordan Net" \(^11\)), fully recurrent backpropagation \(^12\) and LEABRA (a combination of associative and supervised learning \(^13\)). The phenomena of selective attention and response selection can be observed in all of these implementations and we believe that they are independent of any particular learning algorithm.

Most importantly, explorations of this model allowed us to realize that the traditional PFC functions of "memory" and "inhibition" can be viewed as two aspects of the single mechanism mentioned above: the representation and maintenance of context information.
When the task involves maintaining information over time but no competition between stimuli, the context module appears to have a memory function. However, when the task assigned to this architecture does not involve maintaining the pattern of activation in the context module over time, but requires selective processing of some stimuli and not others based on context information, the context module appears to have an inhibition function.

5. Memory Function in Schizophrenia: The CPT Identical Pairs

The failure of the memory function in schizophrenic patients is well illustrated by the patients' performance on a variant of the continuous performance test called the CPT-Identical Pairs. In this task, subjects are instructed to respond when two consecutive letters in a sequence are identical. Only one letter is presented at any given time. An example of a sequence may be: A .. B .. C .. D .. C .. D .. D, where only the last pair of letters constitutes a target sequence.

In this task, individual stimuli are ambiguous and subjects need to keep in active memory the identity of the previous stimulus in order to respond appropriately. Previous stimuli therefore act as context for response selection.

Schizophrenic patients do not perform well in this task compared to controls, as illustrated in figure 3. 14

6. Inhibition Function in Schizophrenia: The Stroop Task

The failure of the inhibition function can be illustrated with schizophrenics' performance in the Stroop task. In this task, subjects are asked to either read a word (the name of a color, such as 'green' or 'red') or to name the ink color in which the word appears. When the ink color and the word are in conflict (e.g., the word 'red' written in green ink), subjects need the context of the task instructions to select the appropriate response. However, for college-educated adults with average reading experience, reading the word is a much more natural (habitual) response than naming the ink color. The stimuli therefore have both a weak (the ink color) and a strong dimension (the word). Context information is critical when a conflict exists between the two dimensions and the strong response needs to be inhibited (i.e., in the color naming condition with conflict stimuli).

Schizophrenic patients perform particularly poorly in this color-naming conflict condition, as illustrated in figure 4. 15-17.
7. Reduced Gain in PFC Module

After training a model such as the one described in Figure 2, to perform each of these two tasks, we simulated a deficit of dopamine in the prefrontal cortex by reducing gain selectively in the context module of both models (from 1.0 to 0.6).

This reduction of gain results in a decreased response to the cumulative effects of noise over time in the context module; which produces an impairment of "memory." Reduced gain also decreases the ability of the context module to selectively inhibit the strongest of two competing stimulus-response associations; which produces an impairment of "inhibition."

In both cases, the simulations reproduced the pattern of deficits of schizophrenic patients (figures 5 and 6).

It is important to note that only a reduction of gain in the context module produces these deficits. Reducing gain in other modules does not result in a deficit of memory or inhibition, unless the reduction includes the context module. Furthermore, other manipulations (e.g., an increase in processing rate or a reduction of response threshold) fail to elicit the full pattern of effects, suggesting that such generalized deficits are not responsible for this particular phenomenon.
8. New Predictions Derived from the Models: A New Variant of the A-X CPT

Our model of a dopamine deficit in the PFC of schizophrenics provides a good account of schizophrenic performance in the two tasks considered here. However, in order to test such models, it is important to derive new predictions that can be evaluated empirically. The most important insight derived from our models is that the context module supports both functions previously ascribed to the PFC — inhibition and memory — and that this is a consequence of its role in representing and maintaining context information. A direct prediction derived from this understanding is that an impairment of the context module should lead to a significantly heightened deficit in a task that requires both functions to be used at the same time ("memory-based inhibition").

We therefore designed a task that would have such a requirement: a variant of the A-X CPT. This task introduces a strong response bias (habitual response) as well as a variable inter-stimulus interval (ISI) to test the effect of long delays between stimuli 18.

Specifically, subjects are instructed to respond to the letter 'X' only when it follows the letter 'A'. There are three conditions in the task:

- A-X: cue-target, 80% of trials
- A-Y: cue-distractor, 10% of trials
- B-X: distractor-target, 10% of trials

Because it is correct to respond to X eight out of nine times that it occurs, subjects develop a strong tendency to respond to X (habitual response), even when it does not follow an A.

In addition, the task includes two ISIs, 1 second and 5 seconds. With a 1 second interval, demands on memory for the previous stimulus are minimal; however, with a 5 second interval, memory requirements are greater.

On the basis of the model, we therefore predicted that schizophrenic patients would be particularly likely to make B-X false alarms at the long ISI (i.e., fail to inhibit the strong response tendency when there is a greater requirement for memory). This prediction runs counter to what one would predict from the literature on vigilance for two reasons: First, in normal subjects, a longer ISI results in improved performance in continuous performance tests 19. Second, schizophrenics make fewer responses than controls in vigilance tasks (as illustrated by figure 3), rather than committing more false alarms.

9. Results

We conducted an experiment with this new version of the CPT A-X in which we compared schizophrenic patients (medicated and unmedicated) to non-schizophrenic psychiatric patients. This experiment and related data analyses are reported elsewhere 18. Only the main results are summarized here. For simplicity, we focus in this report on the comparison between patient controls and unmedicated schizophrenics.

9.1 Overall Performance (d')

Using the signal detection measure of performance known as d', we found that unmedicated schizophrenic patients performed overall more poorly than control psychiatric patients. Furthermore, whereas the performance of control subjects improved at the long ISI, the performance of schizophrenic patients did not (figure 7).

9.2 False Alarms

Looking specifically at false alarms, we found that both groups made fewer A-Y errors at the longer ISI, confirming that the longer ISI is not simply a harder condition.

Furthermore, as predicted, unmedicated schizophrenic patients committed more B-X false alarms than controls at both ISIs, and this tendency was worse at the longer ISI (figure 8).
9.3 Sensitivity to Context (d'-Context)

The most direct measure of subjects' ability to maintain and use context information in this task is a d' measure based only on A-X responses (hits) and B-X responses (false alarms). This measure directly reflects the use of context ('A' or 'B') to mediate an appropriate response or inhibit an inappropriate response to the same stimulus in both cases ('X').

As revealed by a significant group x ISI interaction, this measure confirmed that unmedicated schizophrenic patients were impaired in their use of context at the short ISI and that this impairment was worsened by a longer ISI (figure 9).

10. Conclusion

We developed a model of PFC that captures both the memory and inhibition functions previously ascribed by different authors to this brain region. The model suggested that these two functions are supported by a single mechanism, the representation and maintenance of context in a module that interacts with processes between stimulus representation and response selection.

Schizophrenic patients are assumed to suffer from a disturbance of dopamine function in the PFC. In the model, the effect of reduced dopamine in the PFC was captured by reducing the gain parameter of the activation function of units in the context module.

Reducing gain produced a decreased resistance to the effects of noise over time, which induced a memory deficit and a decreased resistance to the presence of a dominant response tendency, which induced a deficit of inhibition.

The model predicted a specific pattern of deficits for schizophrenic patients in a new task — a variant of the A-X CPT — that requires memory-based inhibition of a dominant response.

An empirical study of schizophrenic patients comparing them to non-schizophrenic patient controls confirmed the prediction.

11. References


1. Introduction

Our patient's condition is already established. This study investigates the symptoms and their relevance. What do they signify?

A direct correlation has been previously noted between the proposed factors and the patient's condition, and is supported by evidence of a dear relationship...