Schizophrenic Deficits: Neuroleptics and the Prefrontal Cortex—A Reply

by Jonathan D. Cohen and David Servan-Schreiber

Abstract

In their commentary, Jobe et al. point out that the primary action of neuroleptics is to decrease dopamine activity. They note that this fact, along with the therapeutic effect of these medications in schizophrenia, would seem to be inconsistent with the hypothesis that schizophrenia is associated with a decrease of dopamine activity in the prefrontal cortex. In this reply, we clarify our position on the relationship between disturbances of dopamine activity in schizophrenia and the action of neuroleptic medications. In particular, we review a more detailed discussion of this issue that we provided in an earlier report, in which we proposed many of the same ideas described by Jobe et al., that may reconcile the pharmacological and behavioral effects of neuroleptics with our theory concerning disturbances of dopamine in schizophrenia. Chief among these is the possibility that neuroleptics may help correct an imbalance in dopaminergic activity between cortical and subcortical systems.


It is a sincere pleasure to see that our article on connectionist models of dopamine effects and schizophrenic deficits has attracted the attention of an established and respected group of researchers interested in schizophrenia, and opened a discussion of such models and their implications for this illness. Jobe et al. (1994, this issue) correctly summarize one of the central ideas of our article (Cohen and Servan-Schreiber 1993)—the relation between “gain,” dopamine, and cognitive deficits—and appropriately point out some of its limitations. They also suggest alternative hypotheses within the framework laid out by our models. This type of analysis is precisely the kind of discussion we hoped that our models would generate, and we are gratified to see such exchanges begin to take place.

Furthermore, we agree to a large extent with the analysis of Jobe et al. Our intention in this rejoinder is simply to clarify our position with regard to the issues raised in their commentary.

The focus of their commentary is on how the effects of neuroleptic medication on dopamine activity relate to our hypothesis concerning reductions of dopamine activity in the prefrontal cortex (PFC). Jobe et al. (1994, this issue) correctly point out that it is difficult to reconcile the fact that neuroleptics block dopamine activity while at the same time improving (or at least not further impairing) schizophrenic cognitive performance if, as we have hypothesized, performance deficits are due to a reduction of dopamine activity in the first place. In this context, Jobe et al. (1994, this issue, p. 414) state that we predicted “medicated schizophrenia patients should perform better than unmedicated schizophrenia patients on the [Continuous Performance Test] CPT [Rosvold et al. 1956],” and justifiably question this prediction.

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First, we would like to make it clear that we did not make this prediction. Though we presented data concerning the performance of medicated patients in our article, regrettably (and due primarily to space constraints) we did not specifically discuss the influence of neuroleptic medication. Predictions were made only about the performance of unmedicated and not medicated patients.

Nevertheless, as Jobe et al. (1994, this issue) point out, a straightforward application of our models predicts that decreased dopaminergic activity (as would be expected from neuroleptic effects) should reduce gain and therefore impair information processing and performance. What needs to be explained, therefore, is why neuroleptics, which do impair performance in normal subjects (Yano et al. 1991), may be of benefit to patients with schizophrenia. Though we failed to discuss this issue in the target article, we did provide a direct and detailed discussion of it in an earlier presentation of our work (Cohen and Servan-Schreiber 1992, p. 67). In that discussion, we cited evidence from preclinical studies suggesting—much as Jobe et al. propose—a possible reconciliation or the neurophysiological effects of neuroleptics with their behavioral effects in patients with schizophrenia. In fact, we reached many of the same conclusions offered by Jobe et al. in their commentary. However, many of the details of our arguments are complementary to theirs, and so we will briefly review them here.

First, some animal studies suggest complex feedback relations between cortical and subcortical dopamine activity. For example, Pycock et al. (1980) have shown that a selective destruction of dopamine afferents in rat frontal cortex results in a state of chronic dopamine hyperactivity in subcortical areas. This indicates that states of dopamine hypo- and hyperactivity can coexist in different brain regions and may even be causally related (Tassin et al. 1982; Deutch et al. 1990; Grace 1991; Jaswick and Weinberger 1992). It is tempting to use this and other similar findings to explain the coexistence of "positive" (e.g., hallucinations, delusions) and "negative" symptoms of schizophrenia, and to reconcile theories postulating increased or decreased dopamine activity in schizophrenia (Weinberger 1987; Grace 1991).

Second, studies of the effect of neuroleptics on dopamine synthesis have suggested that the mesolimbic and mesocortical dopamine systems respond differently to chronic administration of these medications (Bannon et al. 1987; Grace 1991). These studies have shown—in rodents, primates, and humans—that tolerance to activation of synthesis develops rapidly in the striatal and limbic areas, whereas it develops slowly and remains limited in the PFC (Scatton 1977; Scatton et al. 1977; Baco-poulos et al. 1979; Roth et al. 1980). Moreover, during chronic administration of neuroleptics, most dopamine cells enter a state of depolarization inactivation. However, a small number of cells remain active, and the majority of these have been identified as mesocortical cells projecting to the PFC (Chiodo and Bunney 1983).

Overall, these data suggest that dopamine tone in prefrontal areas is less affected by neuroleptics than limbic and striatal dopamine. Thus, much as Jobe et al. (1994, this issue) have also suggested, the net result of neuroleptic administration might actually be to enhance dopamine activity in the PFC, or at least spare it relative to other brain regions.

As Jobe et al. (1994, this issue) independently conjectured, the above considerations lead us to expect that neuroleptics would either have no influence on the cognitive deficits we have addressed with our models, or might lead to improvements by strengthening context effects (i.e., prefrontally mediated processes) relative to more automatic responses (Cohen and Servan-Schreiber 1992, p. 67). We have now collected and analyzed additional data that bear on this question. We found that neuroleptic-treated patients with schizophrenia, in fact, performed more poorly overall on the CPT-AX than unmedicated patients. However, they did not show the predicted effect of delay, as was observed in the unmedicated patients. That is, patients receiving medication performed equally well in the long- and short-delay conditions, whereas the unmedicated patients, as predicted, performed worse in the long-delay condition (Cohen et al., submitted for publication). It is as if neuroleptics produced a generalized impairment of processing, independently of memory for context, while at the same time protecting patients from the degrading effects of noise during the long-delay condition. This is consistent with the idea that neuroleptics produce a reduction of gain outside of the PFC, while at the same time either increasing or sparing it within PFC. Along these lines, it is possible that deficits in standard versions of the CPT are related more to mechanisms concerned with rapid processing of visual information (Nuechterlein 1984; Green and
Walker 1986; Walker and Lewine 1988; Nuechterlein et al. 1992; Strauss 1993) than the representation of context. Such mechanisms may be affected adversely by neuroleptics, whereas mechanisms underlying the PFC function may be augmented or at least spared by the same medications. Additional evidence for such an explanation can be found in Berman et al. (1992). In their twin study, these authors found that subjects exposed to more neuroleptics than their siblings showed less hypofrontality when performing the Wisconsin Card Sorting Test (Heaton 1981).

Jobe et al. (1994, this issue) are also correct in emphasizing that our models do not address clinical aspects of schizophrenia that seem to uniquely characterize this disorder, such as hallucinations and delusions. We agree that these represent an important challenge for future work. This too was discussed in our earlier report, where we considered the specificity of our models to schizophrenia and their applicability to the symptoms of this illness (Cohen and Servan-Schreiber 1993; pp. 67–68). We pointed out that disturbances other than a reduction of dopamine in the PFC are no doubt involved in schizophrenia, and that these may play an important role in producing some of the clinical symptoms observed in this illness. A number of specific brain regions have been implicated such as the hippocampus (Kovelman and Scheibel 1984; Conrad et al. 1991) and various subcortical structures, including the thalamus (Crosson and Hughes 1987), the globus pallidus (Early et al. 1987), and the basal ganglia (Stevens 1973), as have neurotransmitters other than dopamine such as norepinephrine (Lake et al. 1980; van Kammen et al. 1989) and serotonin (Geyer and Bragg 1987). The involvement of such other systems may well be needed to account both for symptoms specific to schizophrenia, as well as for the significant differences between schizophrenia and other illnesses that affect dopamine, such as Parkinson’s disease.

In this context, we have acknowledged that our models, in their present form, are limited in the scope of biological systems that they address. Nevertheless, by delineating aspects of the physiology and behavioral consequences of reduced dopaminergic tone in the PFC, we believe that they may help refine our understanding of this component of schizophrenia. For example, applications of the models to other tasks may be useful in identifying aspects of behavior that will and will not be affected by variations in dopaminergic activity in the PFC. Furthermore, our model of the neuromodulatory effects of dopamine provides a starting point for exploring the involvement of dopaminergic disturbances in other areas, for example, the effects of an increase in dopamine activity that has been hypothesized for limbic and subcortical areas. By developing models that correspond to the functions of these brain areas (e.g., declarative memory, planning, perception, and motor control; see Cohen and O’Reilly, in press), it may be possible to account for symptoms of schizophrenia not addressed in this article (Hoffman 1987; Hoffman et al., submitted for publication). Finally, by providing an example of how important features of biological processes can be captured within the connectionist framework and how these can be related to specific behavioral phenomena, the models may begin to provide a framework for exploring other neuromodulatory systems and their relation to information processing behavior.

In conclusion, we hope that our article in the Schizophrenia Bulletin (Cohen and Servan-Schreiber 1993), in spite of its limitations, has achieved its goal of describing a new set of intellectual tools that may be useful in trying to understand the multiple and disconcerting symptoms of schizophrenic disorders, and their relation to underlying biological abnormalities. We are grateful to Jobe et al. (1994, this issue) for helping clarify some of the issues that we did not address in our article in the Schizophrenia Bulletin, and we refer interested readers to our previous report (Cohen and Servan-Schreiber 1992) for a more detailed discussion of such questions.

References


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