Servan-Schreiber et al. Our patients with multiepisode schizophrenia showed, in fact, specific types of errors (B-X errors) that can be interpreted as the inability to use contextual information to inhibit habitual response to an ambiguous stimulus and to maintain information across delay; without, however, a general attention deficit (no difference in A-Y errors).

Servan-Schreiber et al found the main source of difference in the unmedicated group with schizophrenia but not in the multiepisode medicated one, while we found significant differences in cognitive task functioning in our medicated patients with multiepisode schizophrenia. One possible explanation is that our these patients may be more acutely ill or receiving less medication, so that they might resemble the unmedicated group of Servan-Schreiber el al. The relationships among symptoms, antipsychotic therapy, and context-dependent performance will be an important research issue to be investigated as our samples become larger.

Although our sample with multiepisode schizophrenia is slightly smaller than that of Servan-Schreiber et al, the controls were a larger sample of healthy subjects instead of psychiatrically hospitalized patients. Thus, a sampling factor could explain part of our results.

The theory of the processing of context information may help to explain the different neuropsychological impairments that are hypothesized at the basis of the characteristic behaviors and symptoms of patients with schizophrenia.[6] This theory may stimulate research strategies to identify basic cognitive processes that should account for the heterogeneity of symptoms and cognitive deficits in schizophrenia.

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1. Servan-Schreiber D, Cohen JD, Steingard S. Schizophrenic deficits in the processing of context. *Arch Gen Psychiatry*. 1996;53:1105-1112.
2. Cohen JD, Servan-Shreiber D. A theory of dopamine function and its role in cognitive deficits in schizophrenia. *Schizophr Bull*. 1993;19:85-104.
3. Schneider W. *MEL User's Guide: Computer Techniques for Real-Time Psychological Experimentation*. Pittsburgh, Pa; Psychological Software Tools Inc: 1990.
4. Grier JB. Nonparametric indexes for sensitivity and bias. *Psychol Bull*. 1971; 75:424-429.
5. McNicol D. *A Primer of Signal Detection Theory*. George Allen & Unwin Publishers Ltd; London, England: 1972.
6. Cohen JD, Servan-Shreiber D. Context, cortex, and dopamine: a connectionist approach to behavior and biology in schizophrenia. *Psychol Rev*. 1992;99: 45-77.

In reply

We were pleased to learn of the recent replication by Stratta et al of our findings with the A-X Continuous Performance Test (CPT), and are grateful that a group of respected colleagues felt this paradigm worthy of further study. Given the number of conflicting findings and methodological complexities present in studies of cognition in schizophrenia, it is critical to demonstrate replications across laboratories as well as within laboratories. As presented in the article by Servan-Schreiber et al,[1] we found selective deficits in context processing only among unmedicated patients with schizophrenia. In contrast, Stratta et al found such deficits in medicated patients with multiepisode schizophrenia. Interestingly, we have also recently replicated this finding with medicated patients with multiepisode schizophrenia.[2] As pointed out by Stratta et al, such findings raise new questions about the relationship between context processing deficits and medication status, stage of illness, and clinical symptoms. Given the cross-sectional nature of both our own research and that of Stratta et al, future studies using longitudinal designs may be particularly helpful in resolving these questions. By examining the same patients at multiple points (ie, medicated and unmedicated, acute and remitted illness, early and later in illness course), it may be possible to determine the role context processing deficits play in the pathophysiology of schizophrenia.

We have also begun to use the A-X CPT to address computational, behavioral, and neurobiological issues regarding the context processing hypothesis. First, we have implemented a neural network model of the A-X CPT that simulates context processing deficits in schizophrenia as arising from dopamine abnormalities in prefrontal cortex, in exactly the manner as employed by Cohen and Servan-Schreiber.[3] This model accounted for the findings of the previous study by Servan-Schreiber et al[1] but also made new predictions regarding patient performance, including: 1) a double dissociation in accuracy at the long interstimulus interval (ISI) condition (more B-X errors than controls, but fewer A-Y errors); and 2) relatively fast reaction times in the A-Y condition.[4,5] To better test these predictions, we have refined the task paradigm to require responses to all stimuli, which allows for collection of reaction times on every trial (while also reducing ceiling effects by increasing task difficulty). Preliminary results with these refinements suggest that the model predictions will be confirmed.[6] Second, in our previous article[1] we hypothesized that the ISI manipulation in the A-X CPT would engage prefrontal mechanisms necessary for maintaining context information. We have recently found support for this hypothesis using functional magnetic resonance imaging, by demonstrating greater activity in dorsolateral prefrontal cortex in the long ISI condition relative to the short ISI condition.[7] Lastly, we have made progress in providing convergent validation for the context hypothesis. We have found that patients with schizophrenia demonstrate specific deficits in additional tasks (the Stroop test and a lexical disambiguation task) that were modified to increase their sensitivity to context processing, and that such deficits correlate with A-X CPT deficits.[2] Furthermore, among healthy controls, we have found that task deficits strikingly similar to those found in patients with schizophrenia can be produced in the A-X CPT by task manipulations that increase the difficulty of maintaining context. In contrast, manipulations that also increase task difficulty, but in a nonspecific manner, do not produce such a pattern of deficits.[6]

In combination with the replication of Stratta et al, we believe that these findings provide additional support for the hypothesis that at least a subset of patients with schizophrenia suffer from a disturbance in context processing. As Stratta et al suggest, we must now clearly relate these cognitive deficits to the clinical symptoms and course of schizophrenia.

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1. Servan-Schreiber D, Cohen JD, Steingard S. Schizophrenic deficits in the processing of context: a test of a theoretical model. *Arch Gen Psychiatry*. 1996; 53:1105-1112.
2. Cohen JD, Barch DM, Servan-Schreiber D, Carter CS. Context processing disturbances in schizophrenia: empirical test of a theoretical model. *Schizophr Res*. 1997;24:130.
3. Cohen JD, Servan-Schreiber D. Context, cortex and dopamine: a connectionist approach to behavior and biology in schizophrenia. *Psychol Rev*. 1992;99: 45-77.
4. Braver TS, Cohen JD, Servan-Schreiber D. A computational model of prefrontal cortex function. In: Touretzky DS, Tesauro G, Leen TK, eds. *Advances in Neural Information Processing Systems*. Cambridge, Mass; MIT Press: 1995;7: 141-148.
5. Cohen JD, Braver TS, O'Reilly R. A computational approach to prefrontal cortex, cognitive control, and schizophrenia: recent developments and current challenges. *Philos Trans R Soc Lond B Biol Sci*. 1996;346:1515-1527.
6. Braver TS, Barch DM, Cohen ID. Inducing schizophrenic-like performance in normal subjects: empirical and computational support for a theory of working memory. Presented at the 11th Annual Meeting of the Society for Research in Psychopathology; September 29, 1996; Atlanta, Ga.
7. Barch DM, Braver TS, Nystrom L, Forman SD, Noll DC, Cohen JD. Dissociating working memory from task difficulty in human prefrontal cortex. *Neuropsychologia*. In press.

Sustained Remission of Positive and Negative Symptoms of Schizophrenia Following Treatment With Eicosapentaenoic Acid

Recently, a membrane phospholipid hypothesis of schizophrenia has been proposed[1] that not only provides an underlying explanation for those aspects of schizophrenia traditionally explained by the dopamine hypothesis, but also can account for many other clinical features. These include the inverse relationship between schizophrenia and some inflammatory disorders; the high resistance to pain shown by some patients; the dramatic remission of symptoms that may occur with pyrexia; the increased risk associated with exposure to viral infections or maternal malnutrition during fetal development; and the difference in severity and prognosis in different countries.[2] Recent biochemical, cerebral magnetic resonance spectroscopy, and molecular genetics findings suggest that schizophrenia is associated with a cell membrane deficiency of arachidonic acid and docosahexaenoic acid (DHA), arising from excess activity of 1 of the phospholipase A_2 (PLA_2) group of enzymes.[3-7] Thus, there is mounting evidence for the membrane phospholipid hypothesis; however, an important issue for clinicians is whether it has any useful implications for treatment.

Atypical antipsychotics such as clozapine represent a considerable improvement over standard neuroleptics. However, the mechanism of action of clozapine has not adequately been explained on the basis of neurotransmitter actions, and it is therefore interesting that almost 2 decades ago it was suggested that the structure and pharmacological actions of clozapine are consistent with its being a prostaglandin E analog. The E prostaglandins are potent stimulators of cyclic adenosine monophosphate formation, and cyclic adenosine monophosphate inhibits PLA_2.[8] Furthermore, pharmacotherapy with clozapine has recently been shown to be associated with a dramatic rise in erythrocyte membrane concentrations of certain polyunsaturated fatty acids.[9] These observations raise the possibility that clozapine may be a successful drug because its primary action is on membrane phospholipid composition.[7]

The phospholipid hypothesis leads to the prediction that treatment with PLA_2 inhibitors should result in clinical improvement in schizophrenia.[7] Eicosapentaenoic acid (EPA) is a PLA_2 inhibitor[10] which is also a constituent of brain phospholipids and a precursor of DHA. We report the case of an unmedicated patient with schizophrenia in whom treatment with EPA was associated with a dramatic and sustained reduction in both positive and negative symptoms.

Report of a Case. A 31-year-old man first came to the attention of our local psychiatric service at the age of 28 years when he was diagnosed as suffering from schizophrenia as defined by the *DSM-IV*. At that time he was suffering from daily auditory hallucinations and a complex delusional system, both of which started in his early teenage years. Although his profile had always been predominantly one of unremitting positive symptoms, more recently he had also begun to suffer from negative symptoms, including anhedonia and social anxiety and withdrawal. Furthermore, his basic skills in coping with the practicalities of life were not well developed. At the time of diagnosis he was prescribed sulpiride. He only ever took 1 tablet (200 mg) of sulpiride, and immediately discontinued the medication because of a severe extrapyramidal reaction. He refused neuroleptics thereafter, and so has otherwise remained free of antipsychotic medication.

In an attempt to understand his symptoms, he has been a keen participant in several research studies since his first presentation. His case has thus been extremely well documented since 1994. In 1996, he gave full informed consent to enter into an open single-case study of treatment with EPA provided as an emulsion, which delivered as 2 g of EPA per day in a 30-mL dose (Scotia Pharmaceuticals, Stirling, Scotland).

He underwent psychiatric symptom rating just before treatment commenced and then at monthly intervals for 6 months, using the Schedules for the Assess-