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

Servan-Schreiber et al found the main source of dif-
ference in the unmedicated group with schizophrenia but
not in the multipiepisode medicated one, while we found
significant differences in cognitive task functioning in our
medicated patients with multipiepisode 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 et
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 multipiepisode schizophrenia
is slightly smaller than that of Servan-Schreiber et al.,
the controls were a larger sample of healthy subjects in-
stead of psychiatrically hospitalized patients. Thus, a sam-
plesize difference could also be part of the problem.

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. This theory may stimulate research stra-
gegies to identify basic cognitive processes that should ac-
count for the heterogeneity of symptoms and cognitive
deficits in schizophrenia.

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In reply

We were pleased to learn of the recent replication by
Stratta et al. of our findings with the A-X Continuous Per-
formance 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 meth-
odological complexities present in studies of cognition in
schizophrenia, it is critical to demonstrate replications
across laboratories as well as within laboratories. As pre-
sented in the article by Servan-Schreiber et al., we found
selective deficits in context processing only among unmed-
cated patients with schizophrenia. In contrast, Stratta et al
found such deficits in medicated patients with multipiep-
isode schizophrenia. Interestingly, we have also recently repli-
cated this finding with medicated patients with multipie-
pisode schizophrenia. 1 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 particu-
larly helpful in resolving these questions. By examining
the same patients at multiple points (i.e., 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 schizo-
phrenia as arising from dopamine abnormalities in pre-
frontal cortex, in exactly the manner employed by
Cohen and Servan-Schreiber. 2 This model accounted for
the findings of the previous study by Servan-Schreiber et al
but also made new predictions regarding patient per-
formance, 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. 3 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 dif-
ciculty). Preliminary results with these refinements sug-
gest that the model predictions will be confirmed. 4 Sec-
ond, in our previous article 4 we hypothesized that the ISI
manipulation in the A-X CPT would engage prefrontal
mechanisms necessary for maintaining context informa-
tion. We have recently found support for this hypothesis
using functional magnetic resonance imaging, by demon-
strating greater activity in dorsolateral prefrontal cortex
in the long ISI condition relative to the short ISI condi-
tion. 5 Lastly, we have made progress in providing conver-
gent validation for the context hypothesis. We have found
that patients with schizophrenia demonstrate specific
deficits in additional tasks (the Stroop task 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. 6 Furthermore, among
healthy controls, we have found that task deficits strik-
ingly similar to those found in patients with schizophre-
nia can be produced in the A-X CPT by task manipula-
tions that increase the difficulty of maintaining context.
In contrast, manipulations that also increase task dif-
culty, 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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Sustained Remission of Positive and Negative Symptoms of Schizophrenia Following Treatment With Eicosapentaenoic Acid

Recently, a membrane phospholipid hypothesis of schizophrenia has been proposed1 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 A1 (PLA1) group of enzymes.3 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 prostanoid E analog. The E prostanoids are potent stimulators of cyclic adenosine monophosphate formation, and cyclic adenosine monophosphate inhibits PLA1.4 Furthermore, pharmacotherapy with clozapine has recently been shown to be associated with a dramatic rise in erythrocyte membrane concentrations of certain polysaturated fatty acids.5 These observations raise the possibility that clozapine may be a successful drug because its primary action is on membrane phospholipid composition.

The phospholipid hypothesis leads to the prediction that treatment with PLA1 inhibitors should result in clinical improvement in schizophrenia.6 Eicosapentaenoic acid (EPA) is a PLA1 inhibitor6 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.7 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 unrelenting 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-