Counterpoint: A Sensory Gating—Hippocampal Model of Schizophrenia

by Lawrence E. Adler and Merilyne C. Waldo

Abstract

We propose a model for schizophrenia that incorporates findings of impaired auditory sensory gating with a possible structural abnormality of the hippocampus. The deficit in auditory sensory gating would be a genetic schizotaxic factor, necessary in the development of schizophrenia but not sufficient by itself. Genetic or acquired hippocampal dysgenesis or frank damage in combination with the sensory gating deficit would be necessary to produce the full-blown syndrome. We review the relevant literature and reply to Dr. E. Fuller Torrey's hypothesis.

Torrey (1991, this issue) has proposed that damage to the medial temporal cortex, and particularly to the hippocampus, secondary to viral infection in early infancy may be the major cause of schizophrenic symptoms. Although we too hypothesize that there is a critical relationship between hippocampal damage and schizophrenia, we believe the relationship to be more complex and perhaps not best accounted for by a singular viral hypothesis. In this article, we will review the reasoning that led to our model, briefly review the supporting data, and compare our hypothesis with that of Torrey.

Any anatomical hypothesis of schizophrenia must account for a variety of observations. These observations include increasing evidence that (1) schizophrenia is largely a genetic disorder (Tsuang et al., in press); (2) the onset of the disorder in men tends to occur in adolescence and 5–10 years later in women (Wyatt et al. 1988; Stromgren 1989); (3) schizophrenia is associated with abnormal brain morphology in some patients (Andreasen et al. 1982, Bilder et al. 1988; Wyatt et al. 1988); (4) schizophrenia is associated with a wide range of psychophysiological abnormalities, including impaired auditory sensory gating (Adler et al. 1982; Freedman et al. 1987), impaired visual backward masking (Braff and Saccuzzo 1985), an exaggerated acoustic startle response (Braff and Geyer 1978) when compared with normal controls, and impaired eye tracking (Holzman et al. 1973); and (5) many of these psychophysiological abnormalities are also found in the first-degree relatives of schizophrenic patients.

It is our hypothesis that schizophrenia is due to an interaction of two or more factors. One factor would be permissive of schizophrenia—that is, a schizotaxic factor that is necessary but not sufficient by itself to produce the clinical disorder of schizophrenia (Meehl 1962). We hypothesize that this schizotaxic factor is a genetically determined deficit in auditory sensory gating that manifests as schizophrenia in the presence of a second deficit. If, for example, a person who had inherited this lack of sensory gating also suffered hippocampal damage or more generalized brain damage, we would expect that schizophrenia may well result. Within families at risk, we would thus expect to see the following:

1. Identified schizophrenic patients with both a deficit in auditory sensory gating and evidence of a second pathological factor. This second factor could be either inherited or environmental. One candidate for this second factor would be hippocampal pathology, such as decreased hippocampal density.

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campal volume due to viral infection, prenatal or birth trauma, or developmental dysfunction.

2. A high proportion of first-degree relatives would show either a deficit in auditory sensory gating or evidence of a similar second pathological factor. (This assumes some genetic and some environmental input. Siblings would be expected to be at increased risk in either case.) However, only the identified schizophrenic patient (or a family member who would eventually have schizophrenia) would have both deficits.

The viral hypothesis for the origin of schizophrenia has been reviewed in the preceding article by Torrey. He postulates that specific anatomic anomalies, such as increased innervation by relevant nerve pathways or familial variations in the size of the relevant brain areas, might render the medial temporal area more susceptible to viral damage. As yet, there have been no consistent data supporting a viral etiology for schizophrenia either by epidemiological data, viral titers, or antibodies to specific viruses (DeLisi 1987; Torrey et al. 1988).

A major supportive point for the viral etiology of schizophrenic symptoms has been the observation by a number of authors that there appears to be a relative excess in schizophrenic births during the winter months, the time when viral illnesses tend to peak (Torrey et al. 1988; Dalén 1990; Pulver et al. 1990; Torrey and Bowler 1990; Watson 1990). However, although the issue is vigorously debated, Lewis (1990) has provided convincing evidence for the existence of an age-incidence artifact that biases the studies to report an increase of schizophrenic births in the winter months. When this artifact is controlled for, the evidence supporting an increased incidence of schizophrenic births in the winter months becomes less compelling. In addition, the prevalence of schizophrenia in the general population has remained remarkably consistent at about 1 percent of the population (Wyatt et al. 1988) despite fluctuations in potentially relevant viral infections. This was not true of another brain disease, Parkinson’s disease, which did show an increased incidence after an epidemic of von Economo’s encephalitis (Adams and Victor 1989).

Similarly, family studies, including those in adopted-away offspring, suggest a disproportionate genetic effect in the development of schizophrenia. Since Dr. Torrey’s hypothesis suggests that a developmental defect may make viral migration into the nervous system more likely in those destined to have schizophrenia, one would logically expect to see more central nervous system viral infections of all types in the schizophrenic population. But there is little evidence in the literature to substantiate such a hypothesis (DeLisi 1987). This hypothesis also fails to explain why so many first-degree relatives of schizophrenic patients have the same deficit in P50 gating auditory sensory input (Adler et al. 1982). This deficit in P50 auditory sensory gating is not reversed by neuroleptic medication in these patients (Freedman et al. 1983; Adler et al. 1990). Although this defect has also been associated with other psychotic disorders such as mania, it is present only during acute psychotic episodes in schizophrenic patients. In mania, for example, sensory gating normalizes with treatment (Franks et al. 1983; Baker et al. 1987; Adler et al. 1990). Previous research has also demonstrated that up to half of first-degree relatives of schizophrenic patients have the same deficit in P50 auditory sensory gating as the identified patient, although subtle differences in other parameters such as latency or amplitude of the wave may exist (Siegel et al. 1984; Waldo 1990). While deficits in auditory P50 gating have been associated with other illnesses and with subtle differences in psychological functioning in
nonschizophrenic relatives, in a preliminary study, only the identified patient had both \( P_{50} \) gating deficits and small hippocampal volume (Waldo 1990).

There is not yet sufficient evidence to determine whether the small left hippocampal volume noted in other studies is caused by the illness or is a secondary effect of decreased oxygenation due to birth complications, viral infection, etc. One could alternately postulate a defect in neuronal growth factors affecting hippocampal development (Ayer-LeLievre et al. 1988), abnormalities of cell migration in the developing embryo, or a failure in programmed synaptic elimination in adolescence leading to the failure of inhibitory gating pathways to mature (Feinberg 1983). Similarly, a failure of myelination of the presubiculum and subicular regions of the brain could lead to loss of hippocampal volume (Benes 1989).

Increased myelination of the subicular and presubiculum regions occurs in adolescence. The subicum receives its principal input from \( C_{42} \) of the hippocampus. Thus, Benes suggests, given that the subicum has efferent connections to the fornix, hypothalamus, medial septal nuclei, nucleus accumbens, and medial prefrontal cortex, this late phase of myelination may permit the effect of heretofore unexpressed hippocampal pathology to emerge in widespread symptomatology. Because significant hippocampal abnormalities have been identified only in the clinically ill family member and sensory gating is widespread in the unaffected family members, this would appear to mean that two deficits, one affecting hippocampal development and one related to sensory gating, must be present simultaneously to cause schizophrenia. Finally, it is possible that auditory sensory gating deficits are secondary to a milder form of hippocampal dysgenesis, which cannot be easily measured although frank hippocampal damage is measurable in the severe form. There is no evidence supporting this latter hypothesis, however.

There are other deficits noted in schizophrenic patients that cannot be fully ascribed to a hippocampal origin. In a recent magnetic resonance imaging (MRI) study, male schizophrenic patients had a significantly larger lateral ventricular size and a significantly smaller thalamus than did normal controls (Andreasen et al. 1990). The authors postulate that the decrease in thalamic volume might reflect birth trauma and associated anoxia. Increased ventricular brain ratio has been documented in a variety of other neurological conditions in addition to schizophrenia, including mania (Nasrallah et al. 1982).

The question of whether these deficits are primarily causal of schizophrenia or may be secondary to the same genetic defect that may be expressed as hippocampal volume abnormalities or sensory gating deficits has yet to be resolved. A multimodal hypothesis of schizophrenia such as we propose would suggest that a variety of secondary deficits in combination with a primary sensory gating deficit could result in the full expression of the disease. However, neither Torrey’s hypothesis nor our model adequately accounts for the delayed onset of schizophrenia in women (Wyatt et al. 1988).

It is evident that much of the human and animal literature is beginning to demonstrate that structural abnormalities in the hippocampus and other brain areas, as well as deficits in sensory information processing, are linked to schizophrenia. Additional studies of schizophrenic patients and their first-degree relatives are necessary to determine whether such associations represent a link to defective genes or whether the deficits, particularly those of hippocampal structure, are acquired due to an insult such as anoxia, trauma, or viral infection in a generally susceptible patient.

A number of testable hypotheses result from these questions. For example, if \( P_{50} \) auditory gating defects are secondary to a structural hippocampal lesion, patients and family members with auditory \( P_{50} \) gating deficits should both have diminished hippocampal volume. If the neurophysiological deficits in sensory information processing are genetically determined and are necessary for the development of schizophrenia but not sufficient to cause the clinical disorder, a higher proportion of first-degree relatives should have this deficit than do normal controls. However, only with a second deficit such as diminished hippocampal volume, whether genetic or acquired, would these relatives show the clinical syndrome of schizophrenia. We would expect identified schizophrenic patients to have both the \( P_{50} \) or other neurophysiological gating deficit as well as diminished hippocampal volume. And if a sensory gating deficit were necessary, we would also expect to find evidence of hippocampal damage similar to that which has been found in schizophrenic patients but which has not resulted in the clinical disorder in subjects with normal sensory gating.

The wide variety of presentations of the disorder of schizophrenia has led many to consider that it is not one but several disorders. However, our hypothesis would suggest it is one primary deficit that is triggered by a variety of secondary complications, resulting in differences in...
symptom patterns. Torrey's interesting hypothesis suggests just such an important second factor. Specific anatomic anomalies leading to viral infiltration might well lead to medial temporal damage in some high-risk subjects, resulting in full expression of the disease.

Table 1 compares the viral hypothesis put forth by Torrey with the multifactorial hypothesis that we favor. The true test of the hippocampal hypothesis of schizophrenia, virally induced or otherwise, will be found in carefully designed studies of schizophrenic patients and their relatives. These studies will undoubtedly integrate multiple techniques, such as MRI or positron emission tomography scanning and psychophysiological measures, postmortem studies, viral and antibody studies, and perhaps other techniques that have yet to be developed.

Table 1. Comparison of hypotheses

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<thead>
<tr>
<th>Viral hypothesis</th>
<th>Multifactorial hypothesis</th>
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<tr>
<td>1. Symptoms of schizophrenia secondary to hippocampal damage due to virus.</td>
<td>Symptoms due to hippocampal damage or failure in development and coexisting deficit in auditory sensory gating.</td>
</tr>
<tr>
<td>2. No explanation for neurophysiological findings.</td>
<td>( P_{50} ) gating deficit as inherited schizotaxic factor in patient and in 50% of siblings.</td>
</tr>
<tr>
<td>3. Interaction with genetics unclear. Major genetic defect is putative familial variation in anatomy, making it easier for viral infections to reach hippocampus.</td>
<td>Possible autosomal dominance of ( P_{50} ) gating deficit. Inheritance of developmental deficit of the hippocampus or acquired damage due to virus, birth complications, etc.</td>
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<tr>
<td>4. Adolescent onset in men explained as viral recrudescence or result of previous viral damage.</td>
<td>Hippocampal developmental deficit result of genetic failure or acquired hippocampal damage manifest in adolescence because of a possible failure in subicular or presubicular myelination at that time.</td>
</tr>
<tr>
<td>5. Delayed onset in women is unexplained.</td>
<td>Delayed onset in women is unexplained.</td>
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