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On the Plausibility of "The Neurodevelopmental Hypothesis" of Schizophrenia

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Speculation that schizophrenia is associated with abnormal brain development, the so-called neurodevelopmental hypothesis, has become so popular that it is rarely challenged in the literature. This paper critically examines the evidence for this hypothesis, taking primarily the "devil's advocate" position. The evidence from neuroimaging studies, from studies of prenatal and perinatal intrauterine events and of premorbid development are circumstantial with respect to brain development, many studies are methodologically flawed, and most do not exclude alternative explanations. Evidence from postmortem studies of anomalous cytoarchitecture in limbic and prefrontal cortices is especially noteworthy, as a developmental defect is virtually certain if artifacts can be excluded. Unfortunately, the studies responsible for these findings have serious methodological limitations. The neurobiological plausibility of the hypothesis, which might have been predicted to be its weakest aspect, has proved surprisingly unshakeable in a recent series of animal studies. Ironically, the principal weakness of the neurodevelopmental hypothesis at present is the clinical database on which it rests. ***[Neuropsychopharmacology 14:1S–11S, 1996]***

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A dramatic change in conceptual thinking about the pathogenesis of schizophrenia has taken place over the past few years. Rather than focusing on models of adult onset injury or illness, researchers are now hypothesizing that the disorder has its origin in an abnormality of brain development (Weinberger 1995a). Although the specifics and clinical implications of the putative neurodevelopmental aberration vary somewhat from one version of the story to another, the essentials of the neurodevelopmental hypothesis of schizophrenia can be stated as follows:

> Schizophrenia is related to a defect in brain development. This defect predisposes to a characteristic pattern of brain malfunction in early adult life and to symptoms that respond to antidopaminergic drugs.

The hypothesis has three principal components: a presumption of developmental neuropathology, an expectation that the developmental neuropathology results in some common pattern of brain malfunction in order to produce symptoms that are reliably diagnostic from one individual to another, and the requirement that antidopaminergic drugs ameliorate the manifestations of the condition. There is also an implicit aspect of this hypothesis, which is, in a sense, its most neurobiologically heretical component. The hypothesis predicts that the neurodevelopmental abnormality will be relatively inapparent early in life, or at least not manifest in a diagnostically recognizable form, until after a considerable postnatal delay period. Moreover, after this pro-

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tracted delay period during which brain function may be only minimally affected if at all, the developmental defect is manifest as a profound disruption of normal brain function.

The discussion that follows will critically assess selected aspects of the evidence that is often cited as supporting this hypothesis. The discussion will focus on the following questions: How conclusive is evidence of developmental neuropathology? Is there evidence from studies of brain function in adult patients with the disorder that add weight to the neurodevelopmental hypothesis? Is there reason to believe that the character of neuropathologic changes implicated in schizophrenia would account for the responsiveness of the clinical symptoms to antidopaminergic drugs? Would the clinical impact of this neuropathology likely be delayed for decades? The latter two questions address a broad concern about whether the neurodevelopmental hypothesis of schizophrenia is neurobiologically plausible. Ironically, as the following discussion will demonstrate, the more speculative aspects of the hypothesis, that is, those pertaining to the latter two questions, appear to be less impeachable than the empirical data. The principal weakness of the neurodevelopmental hypothesis at present is the clinical research database on which it rests.

HOW CONCLUSIVE IS EVIDENCE OF DEVELOPMENTAL NEUROPATHOLOGY?

There is no conclusive evidence of developmental neuropathology associated with schizophrenia. The data on which the assumption of such pathology is based are largely indirect and circumstantial and arise from several sources (see Table 1). The weakest data involve studies of what are called minor physical anomalies, such as low-set ears, tongue creases, palate height, facial muscle irregularities and so forth (Green et al. 1989). The assumption underlying these studies is that such physical characteristics are formed in utero, and disturbances in them must reflect abnormalities of intrauterine development. These studies are flawed in numerous respects, including that they are virtually impossible to perform blindly, that the impact of chronic illness and treatment on measurements of facial characteristics (including tongue creases) is uncertain, and that many of the characteristics reported in patients are not clearly qualitative developmental abnormalities as such, but rather variations in quantitative physical characteristics. Several studies have reported neurologic and neuropsychologic abnormalities of children with schizophrenic mothers (Fish 1977; Asarnow 1988; Erlenmeyer-Kimling 1987). These findings would be at least theoretically consistent with the possibility of neurodevelopmental deviance, but they address only a vague risk factor (genetic or otherwise), as the link between the findings reported and the subsequent diagnosis of schizophrenia is unclear.

Historic studies of premorbid educational and neuropsychologic function of patients with schizophrenia have suggested that they often perform more poorly then their siblings, implicating the presence of a deficit before the onset of the diagnostic syndrome (Aylward et al. 1984), but such data do not implicate an abnormality of brain development, per se. An interesting study of premorbid neurologic impairment was recently reported by Walker and Lewine (1990). They reviewed early childhood movies (even from the first year of postnatal life) of sibships containing an individual who eventually manifest schizophrenia. The affected sib reportedly had gross motor impairments even during the first few years of life, a finding difficult to explain except in terms of abnormal early brain development. However, the nature of the motor abnormalities is somewhat difficult to reconcile with the putative neuropathologic abnormalities implicated in schizophrenia. Moreover, the gross motor abnormalities would probably surprise most parents of patients with schizophrenia and most family physicians who saw these patients when they were children. Clearly, this potentially landmark study needs to be independently replicated.

The most incontrovertible evidence that patients with schizophrenia are neurologically and cognitively abnormal during childhood comes from two prospective epidemiological studies of British birth cohorts (Jones et al. 1994 and Done et al. 1994). Cognitive and social deficits as well as delayed neuromotor milestones during infancy and childhood were associated with the diagnosis of schizophrenia during adulthood. These studies, though clearly demonstrating that patients with schizophrenia have cognitive and neuromotor deficits long before the diagnosis is made, do not categorically implicate abnormal development of the brain. It is still conceivable, though admittedly improbable, that such deficits could reflect psychosocial adversity.

Another body of circumstantial evidence often cited as supporting the neurodevelopmental hypothesis comes from reports of obstetrical complications (OC) and from epidemiologic studies of viral exposure in utero, both of which are said to be associated with increased risk of subsequent schizophrenia. Although there are clearly

Table 1. Evidence for Developmental Neuropathology (from least to most incriminating)

1. Minor physical anomalies
2. Premorbid cognitive and neurologic deficits
3. History of obstetrical abnormalities
4. Potential prenatal viral exposure
5. Morphometric anatomic abnormalities
6. Cytoarchitectural abnormalities

negative reports, the majority of the OC literature supports a link between OC and schizophrenia (Weinberger 1995; McNeil 1988). It should be noted, however, that the increased risk, though significant, is small, on the order of less than 2% (Goodman 1988). A direct link between a history of OC and anatomic abnormalities on magnetic resonance imaging (MRI) scan have been found in some studies but not in others (Reveley et al. 1984; DeLisi et al 1988). The pathogenic implications of the OC association are unclear. One line of thinking holds that OCs cause developmental neuropathology (McNeil 1988; Cannon and Mednick 1991; Murray and Lewis 1987); the other suggests that it is caused by developmental neuropathology (Weinberger 1995b; McNeil 1988). Whereas either argument would be consistent with injury to the brain during its development, the potential mechanisms of injury are dramatically different if not mutually exclusive (Weinberger 1995a).

The prenatal viral exposure literature is especially provocative. Since the first report by Mednick et al (1988) of increased risk of schizophrenia associated with second trimester exposure to the Influenza A2 epidemic of 1957 in Helsinki, no less than seven additional studies have appeared—five of which have claimed to at least partially replicate the findings of Mednick et al (see Table 2). Unfortunately, as recently documented (Weinberger 1995a; Crow 1994), this is a remarkably confusing literature. No study has used the same methodology or approach to data analysis as another study. Reanalyses of earlier data have tended to produce inconsistent results (Adams et al. 1993). Only one study, a negative one, actually sought to document the occurrence of influenza in the mother (Crow and Done 1992). Overall, whereas potential intrauterine exposure to the 1957 epidemic in Europe has been associated with increased risk for schizophrenia in more than one study, the results are inconsistent and difficult to interpret. If the inconsistencies can be resolved, the data may add circumstantially to the notion that second trimester maldevelopment increases the risk for schizophrenia. However, exposure to influenza will likely account for at most a very small minority of cases.

The most consistent evidence that schizophrenia is a disorder of the brain comes from neuroimaging studies of cerebral anatomy. Numerous reports of enlarged cerebrospiral fluid (CSF) spaces and of reductions in cortical volume, whether focal or widespread, have appeared (for review, see Zigun and Weinberger [1992]). In most instances, the differences between patients and controls are very slight, indicating that the underlying process is a subtle one. Such findings, however, do not directly implicate any particular neuropathologic process. Reports that the morphometric abnormalities exist at the first diagnosis of the illness, that they do not progress in most patients over time, that they correlate with aspects of childhood premorbid adjustment (Breslin and Weinberger 1991), and that similar morphometric findings in postmortem tissue are not associated with gliosis (Roberts et al. 1986; Bruton et al. 1990) have been marshalled to support the conclusion that the findings are neurodevelopmentally based. Although it is reasonable to assert that such correlative results would be consistent with a neurodevelopmental process, they do not prove such causation. At most, they indicate that the process responsible for the morphometric findings is inconsistent, at least in most cases, with a

Table 2. Prenatal Influenza and Adult Schizophrenia

Study	Sample	Findings
Mednick et al. (1988)	Pregnancies coincident with Helsinki 1957 A-2 epidemic.	↑ schizophrenia in second trimester cohort, especially at 6th months' gestation.
Kendell and Kemp (1990)	Pregnancies coincident with Scottish 1918, 1919, and 1957 A-2 epidemics.	↑ in Edinburgh samples for 1957, second trimester. No ↑ association in entire sample.
Torrey et al. (1988)	43,814 schizophrenic births between 1950–1959 in USA.	No ↑ in association with 1957 A-2.
Barr et al. (1990)	Danish schizophrenic samples born between 1911 and 1950 (N = 7239).	↑ schizophrenia in 6–7 month gestational group coincident with high incidence of influenza compared to group coincident with low incidence.
O'Callaghan et al. (1991)	339 schizophrenic patients born around English 1957 A-2 epidemic.	Abnormal distribution of schizophrenia births in index year in women only, appearance of ↑ risk in 5th gestational month.
Sham et al. (1992)	British Hospital First Admission between 1970–1979 with schizophrenia, (*N* not specified).	Weak statistical association between frequency pattern of influenza deaths between 1939–1960 and second trimester of schizophrenic births.
Crow and Done (1992)	1620 pregnancies with history of 1957 A-2 influenza infection in Great Britain.	No ↑ risk of schizophrenia.
Adams et al. (1993)	Reanalysis of data from studies of Kendell and Kemp, Sham et al., and Barr et al.	↑ risk in all populations for 1957 A-2. No ↑ in association with other epidemics.

Upward arrow signifies an increase.

progressive and degenerative process of adult onset, analogous to Alzheimer's or Huntington's disease, and so forth.

Several studies have addressed cortical neurodevelopmental events having to do with the formation of normal cerebral asymmetries. Because the formation of the major cortical asymmetries is complete by the middle of the third trimester of gestation (Weinberger 1995a), abnormalities of such asymmetries would *directly* implicate a disruption of the normal developmental processes responsible. Initial studies of anomalous lateralization of the sylvian fissures (Falkai et al. 1992), planum temporale (Rossi et al. 1992), and other aspects of the posterior temporal cortex (Crow et al. 1989) have not been replicated (Bartley et al. 1993; Kulynych et al. 1995). One 3-D MRI study of identical twins discordant for schizophrenia found no abnormalities of gross gyral patterns (Noga et al. 1993), which also might have implicated directly a gross defect in cortical development. These studies indicate that if schizophrenia is associated with cortical maldevelopment, the process is sufficiently subtle as to not affect the formation of major gyri and asymmetries.

The most provocative evidence of brain maldevelopment in schizophrenia comes from a recent series of studies of cytoarchitecture in entorhinal, prefrontal, and lateral temporal cortices. These important studies merit especially careful review, because they describe a partially replicated result that, if valid, would be virtually conclusive evidence of developmental neuropathology. These studies stand in contrast to earlier reports of hippocampal pyramidal cell disarray (Kovelman and Scheibel 1984), which have not been independently replicated (Christison et al. 1989; Benes et al. 1991a). Jakob and Beckmann (1986) made a potentially landmark observation in the entorhinal cortex. In nissl-stained sections of 64 brains of patients with the diagnosis of schizophrenia and 10 controls, they described cytoarchitectural anomalies of laminar organization in the majority of all cases. Specifically, they reported attenuation of cellularity in superficial layers I and II, incomplete clustering of neurons into normal glomerular structures in layer II, and the inclusion of such clusters in deeper layers where they are not normally found. Unfortunately, there are several questions that must be answered before the results of this study can be understood: (1) are they artifacts of localization within entorhinal cortex? (2) are they related to schizophrenia per se? and (3) are they replicable? Other problems with the study included that it was not blind, that the controls were neurologically impaired in nine of the cases, and that the patient population was probably atypical (e.g., mean age of illness onset was 36).

Normal entorhinal cortex anatomy is characterized by remarkable regional variability. In fact, as one moves caudal in entorhinal cortex, the normal appearance looks increasingly like what Jakob and Beckmann reported in schizophrenia (Hyde and Saunders 1991). Therefore, it is critical that patients and controls be very carefully examined in the same cytoarchitectonic areas. The possibility that what Jakob and Beckmann observed may not be related to schizophrenia per se also must be considered. They subsequently reported the identical abnormalities in four patients with bipolar disorder, although two of these patients had originally been diagnosed with schizophrenia (Beckmann and Jakob 1991).

In spite of these questions, the basic findings of Jakob and Beckmann have been independently replicated using the same methods and further supported by other recent data from different approaches to cortical cytoarchitecture. Arnold et al. (1991) studied nissl-stained sections of six brains of patients with schizophrenia from the Yakovlev Collection and 16 controls. They observed essentially the same abnormalities as described by Jakob and Beckmann and in addition reported anomalous mesial temporal sulci in their specimens. They felt that all six cases were abnormal, but in five the abnormalities were dramatic and unequivocal. None of their controls had similar findings. The authors acknowledged the importance of location within entorhinal cortex and attempted to control for this. Moreover, they reported that as they moved caudally, the differences between patients and controls disappeared, an observation that corresponds to findings from the in vivo and postmortem morphometry literature. The authors believed that their findings indicated an abnormality of entorhinal cortex development, probably a migration failure, that would render normal neocortical-hippocampal communication impossible.

Akbarian and colleagues (1993a), taking a different approach to studying cytoarchitecture, found a similar phenomena to that of Jakob and Beckmann (1986) and Arnold et al. (1991). Using a histochemical stain for cortical neurons that express the enzyme, nicotinamide-adenine dinucleotide-diaphorase (NADPH-diaphorase), they studied the superior frontal gyrus region of dorsolateral prefrontal cortex in five brains of patients with schizophrenia and five controls matched for age, gender, and post mortem interval before fixation. They found reduced numbers of these neurons in superficial cortical layers I–III and increased numbers in deep layers, especially in subcortical white matter, which represents vestigial subplate neurons. In essence, they observed a qualitative shift in the representation of NADPH-diaphorase positive neurons, as if the younger neurons destined to migrate last from the subplate zone got held up and never made it to their superficial cortical targets. Their interpretations of the findings are remarkably similar to those of Jakob and Beckmann (1986) and Arnold et al. (1991).

It is also possible that the underlying defect reflected

in the findings of Akbarian and colleagues is the same as that of yet another recent report, a study of nissl sections of cingulate cortex by Benes et al. (1991b). They found decreased numbers of small, presumably GABAergic neurons in prefrontal cortex of patients with schizophrenia and larger numbers of pyramidal cells in deeper layers. This finding also might suggest a developmental failure of the normal inside-out neuronal migratory gradient. The potential coherence of these two studies may be underscored by the fact that NADPH-diaphorase positive neurons appear to be GABAergic. Unfortunately, there are some inconsistencies. Subsequent cell counts of small, neurons in nissl-stained sections of the samples of Akbarian et al. could not directly confirm the finding of Benes et al. of a reduction in the small neuron population (Bunney et al. 1993).

In a subsequent study of NADPH-diaphorase neurons of temporal lobe, including lateral temporal neocortex and mesial limbic cortex, Akbarian and colleagues (1993b) extended their abnormal findings to this region, suggesting a more widespread cortical developmental defect. This also would be consistent with the morphometric data. However, this second study presented some new inconsistencies. Athough they did find laminar gradient abnormalities in hippocampus and lateral temporal neocortex, entorhinal cortex was normal. It is conceivable that the abnormalities of entorhinal cortex observed by Jakob and Beckmann and by Arnold et al. did not involve the subset of neurons that express NADPH diaphorase. This might be consistent with the latter neurons being primarily GABAergic and the layer II entorhinal cortex neurons being primarily glutamatergic. On the other hand, the involvement of NADPH-diaphorase neurons in each of the other cortical areas examined by Akbarian et al. make this explanation seem a bit strained. Clearly, further studies of this type are needed before these uncertainties can be resolved.

The appeal of the cytoarchitecture results for the neurodevelopmental hypothesis is that, if valid, they are very hard to explain on the basis of anything that might happen to a brain after birth. In this respect they are potentially the most direct and ultimately incontrovertible evidence for the neurodevelopmental hypothesis. Nevertheless, they must be replicated in studies that control rigorously not just for illness, but for location in cortex, and for other potential confounds.

DOES EVIDENCE OF NEUROFUNCTIONAL ABNORMALITIES RELATE TO THE NEURODEVELOPMENTAL HYPOTHESIS?

The functional implications of the putative neuropathologic abnormalities are uncertain. Indeed, it might be reasonably argued that the subtle miswiring implicated by the slight cytoarchitectural abnormalities noted earlier would not be manifest as a cortical malfunction, let alone a clinical disorder as profound as schizophrenia. Sporadic cortical heterotopias are often seen at routine postmortem examination of tissue from presumably normal individuals. Therefore, conclusions about the neuropathologic origin of the functional abnormalities associated with schizophrenia must be viewed with skepticism.

Most studies of cortical function in patients with schizophrenia have involved either neuropsychologic testing or functional neuroimaging. The former studies for the most part indicate that cognitive deficits are a common if not near universal feature of the disorder, that they are reliable predictors of chronic disability and outcome, and that they tend to be independent of psychotic symptoms and of neuroleptic therapy (Goldberg et al. 1991). The nature of the cognitive deficits is somewhat controversial. Patients with schizophrenia are impaired on many cognitive tests, including IQ. Nevertheless, impairments of explicit memory, of attention, and of so-called executive functions appear to be the most characteristic deficits, suggesting that neural functions of the frontal and temporal cortices are especially impaired. The pattern in patients with schizophrenia, however, is difficult to localize to either of these specific cortical regions alone, and patients generally are differentiable in direct comparisons from patients with focal neuropathologies of these regions (Randolph et al. 1993; Gold et al. 1994). Taken together, the neuropsychologic data have been interpreted to suggest a breakdown in intracortical functional connectivity, at least conceptually consistent with what might be expected from a neurodevelopmental defect in the wiring of cortical architecture and connectivity (Goldberg et al. 1991; Randolph et al. 1993; Gold et al. 1994). This conclusion, however, is highly speculative. Neuropsychologic deficits and anatomic findings on neuroimaging correlate to a significant but small degree, at least consistent with the possibility that the underlying processes responsible for these datasets are related (Nestor et al. 1993; Seidman et al 1994).

The results of functional neuroimaging studies with techniques such as position emission tomography (PET) and single photon emission computed tomography (SPECT) also suggest that cortical function in schizophrenia is abnormal, but the nature of the abnormality is again controversial. Many regions of cortex have been noted to be hypoactive, in some cases depending on the conditions under which patients are studied (Berman and Weinberger 1991). The prefrontal cortex is the area most often identified. It is impossible to attribute this functional finding to a specific etiology, though it has been differentiated from the pattern of cortical hypofunction seen in neurodegenerative disorders (Weinberger et al. 1988; Goldberg et al. 1990). Also, prefrontal

hypofunction has been found in at least two studies to correlate with evidence of anatomic neuropathologic changes (Berman et al. 1987; Weinberger et al. (1992); thus, at least to some degree the anatomic and functional data are related, as would be predicted by the neurodevelopmental hypothesis.

The functional neuroimaging data, however, are much more complicated than simply focal areas of hypofunction. Whereas prefrontal cortex is often hypoactive, other areas, especially temporal cortex (Berman and Weinberger 1991), are often hyperfunctional. In a recent PET regional cerebral blood flow (CBF) study of monozygotic twins discordant for schizophrenia who were taking the Wisconsin Card Sorting Task during the PET rCBF scan, the affected twin of each pair had relatively decreased prefrontal rCBF compared with the well twin in all but one pair, whereas the hippocampus of the ill twin was invariably hyperactive (Weinberger et al. 1993). In other words, the patients had too little activity where it was supposed to be (i.e., for the appropriate behavioral response) and too much activity where it was not supposed to be. Analogous results have been reported in a study of singleton patients with schizophrenia during performance of a simple motor task (Guenther et al. 1986) and in a study of patients during a verbal fluency task (Frith 1995). These data raise the possibility that findings of hypofunction of specific cortical regions may actually be a reflection of a more general deficit in the physiologic mechanisms responsible for "focalizing" cortical activity. In other words, cortical function in patients with schizophrenia may lack appropriate "focality" in general, rather than lacking activity in any specific region. As the statistical methods typically used to analyze functional neuroimaging data (e.g., z maps, normalized t maps, normalized region of interest (ROI) analyses, covariance analyses) highlight relative changes in focal activity as referenced to either global or nonregional changes, a pattern that reflects "hypofocality" in general may tend to be overlooked by such analyses. If the behavioral task during which the PET scan is performed normally is associated with recruitment of a particularly robust focal response (e.g., prefrontal activation during the Wisconsin Card Sorting Task [Berman et al. 1995]), "hypofocality" might be interpreted during this condition as hypofrontality. Recent studies using the novel functional neuroimaging approach available with MRI (so-called fMRI), where cortical activation patterns can be appreciated in individual cases without grouping subjects as is standard procedure with nuclear medicine techniques, also suggest that "hypofocality" is a more general feature of the schizophrenic cortex. In two preliminary reports with fMRI, patients with schizophrenia tend to manifest similar unfocused overactivation of nonmotor cortex during simple finger movements (Wenz et al. 1993; Kotrla et al. 1994).

The implications for the neurodevelopmental hypothesis of viewing the pathophysiology of schizophrenic cortex in terms of a failure of more general mechanisms of focal activation rather than a restricted deficit of activation of a specific cortical region are unclear. For the most part, recent PET activation studies of normals have demonstrated that the more accurately an individual performs a cognitive task, the less area of cortex is activated (Haier et al. 1992). By the same token, the extent of cortical activation associated with a given task tends to diminish with practice as an individual becomes more skilled or proficient in performing it (Raichle et al. 1994). These observations suggest that efficiency of cortical processing correlates with focality of the physiologic response. Focality is in a sense a signal to noise phenomena, i.e. a regionally specific physiologic signal is recruited and regionally nonspecific "noise" is suppressed. The functional neuroimaging findings in patients with schizophrenia implicate inefficient or noisy cortical function. The mechanisms that might be responsible for such a deficit in cortical signal to noise are probably numerous. It is conceivable that they could involve subcortical diffuse activating systems, such as long projecting biogenic aminergic systems (Daniel et al. 1991), or that they could reflect disfunction in intracortical connections. Whereas either could conceivably result from brain maldevelopment, the cortical functional data do not by themselves argue strongly for or against the neurodevelopmental hypothesis. The data do, however, provide indirect support for involvement of neurodevelopmental processes in the delayed expression of the clinical manifestations. To the extent that the neurofunctional data implicate intracortical connectivity and/or prefrontal function, and to the extent that intracortical connectivity and prefrontal function are especially late maturing primate brain phenomena (Weinberger 1995a), these data are consistent with the possibility that the neuropathologic event(s) implicated in schizophrenia affect the function of later maturing neural systems and could have relatively obscure clinical effects until such neural systems reach functional maturation (Weinberger 1995b).

IS THE NEURODEVELOPMENTAL HYPOTHESIS NEUROBIOLOGICALLY PLAUSIBLE?

Even if developmental cortical pathology turns out to be a replicable correlate of schizophrenia, it will still be important to establish how such pathology accounts for the clinical syndrome. In particular, the responsiveness of the condition to antidopaminergic drugs and the delay from the occurrence of the pathology to the onset of the condition will have to be explained. Until recently, there has not been an experimental database demonstrating that this is a plausible possibility. It has long

been known that neonatal cortical damage produces a variety of behavioral effects in animals, depending on the location and extent of the damage and on the time of the injury (Kennard 1936; Kolb and Whishaw 1989). Moreover, the effects may vary as the animal ages; in most cases improvement occurs, but occasionally, functional deficits may actually worsen (Kennard 1936; Goldman 1971; Schneider 1981). Also, the emergence of some abnormal behaviors may be delayed until early adult life (Goldman 1971). It has been shown that cortical damage to adult animals can impact on regulation of subcortical dopaminergic activity (Thierry et al. 1986; Pycock et at. 1980), and prenatal perturbations also can lead to aberrations of dopaminergic function (Lyon and McClure 1992). All of these past observations, however, still begged the essential question posed by the neurodevelopmental hypothesis of schizophrenia: Can developmental cortical neuropathology analogous to what might be associated with schizophrenia have a *delayed* effect on the emergence of abnormal behaviors that would be ameliorated by antidopaminergic drugs?

A recent series of experiments in rats suggests that the scenario implicit in the question posed by the neurodevelopmental hypothesis is neurobiologically plausible. Lipska and colleagues (1993a,b) have described the effects of neonatal excitotoxic injury to the ventral hippocampus of the rat. The ibotenic acid lesion is produced on the seventh postnatal day, at a critical time in the development of intracortical connectivity in the rat. Studying exploratory behavior under a variety of conditions, these investigators have shown that 4 weeks after the lesion, on postnatal day 35 (PD35), shortly before puberty, the ibotenate lesioned animals do not differ from sham operates in terms of responsiveness to a variety of environmental stresses, amphetamine, apomorphine, or neuroleptics. Three weeks later, however, after puberty, the same animals now differ in response to each of these conditions. The animals with the neonatal hippocampal defect seem to grow into a condition of hyperresponsivity of their mesolimbic dopamine system to environmental and pharmacologic stresses. A similar pattern of postpubertal emergence of an abnormal prepulse inhibition of the acoustic startle response, analogous to what has been reported in patients with schizophrenia, has also been recently described in the neonatal lesioned animals (Lipska et al. 1995). Interestingly, animals with virtually identical lesions induced during early adulthood do not show the same severity or pattern of abnormalities and do not show a delay period in the appearance of the abnormalities (Lipska et al. 1992; Swerdlow et al. 1995). This indicates that the unique effects of the lesion are dependent on the fact that the injury occurs during brain development.

The neonatally lesioned animals also show interesting differential effects of antipsychotic drugs. Not surprisingly, the exaggerated exploratory behaviors of lesioned rats are ameliorated by antipsychotic drugs. After chronic treatment, these rats also appear to be at increased risk of some of the adverse effects of these drugs, in that they manifest enhanced dopamine-agonist induced stereotypies after haloperidol withdrawal compared with unlesioned animals (Lipska and Weinberger 1994a). What is particularly surprising is that they do not show this effect after withdrawal of clozapine. Moreover, the animals lesioned as neonates and tested as adults are uniquely responsive to the action of clozapine at suppressing exploratory behavior (Lipska and Weinberger 1994a). These data suggest that the lesion model highlights some mechanism of action of clozapine that is not shared with haloperidol and that may relate to its unique therapeutic effects as well as its decreased risk for both acute and chronic extrapyramidal toxicity.

To the extent that this animal model involves a developmental defect in temporal-limbic cortex and its prefrontal connectivity, an exaggeration of dopamine-related behaviors, and a delay between the occurrence of the anatomic pathology and the emergence in early adulthood of the behavioral abnormalities, it is isomorphic with several core features of schizophrenia and supports the neurobiologic plausibility of the neurodevelopmental hypothesis. However, this is at best a "model," as the rats do not have "schizophrenia," in the sense of a disorder of human perception, cognition, behavior, etc. Moreover, the cortical maldevelopment implicated in human schizophrenia is much more subtle, and the resulting behavioral and cognitive deficits are much more complex. Nevertheless, these rats appear to exemplify at their phylogenetic level analogous phenomena that may be useful in further elucidating relevant mechanisms and in searching for new treatments.

In future studies, it will be important to characterize the mechanisms responsible for the delayed emergence of the abnormal behavioral syndrome. This may provide clues to factors that facilitate clinical compensation and decompensation. Experiments in castrated male rats indicate that the peripubertal surge of gonadal hormones is not critical (Lipska and Weinberger 1994b). It also might be important to target some of the nondopaminergic abnormal behaviors manifest by these rats (e.g., cognitive and social abnormalities) as potential targets for pharmacologic compensation. Such targets may lead to the development of novel antischizophrenic treatments that would not be identified from traditional dopamine-related behavioral assays. Having demonstrated that neonatal hippocampal damage can account for certain neuropharmacologic aspects of schizophrenia, researchers can begin to modify the lesion, making it closer to the subtle changes implicated in the human illness. The plausibility of specific etiologic hypotheses may be testable in the context of this rat model. For example, the effects of prenatal viral expo-

sure can be compared with the standard lesion. Genetic factors also can be explored, both in terms of differential susceptibility of various genetically characterized rat or mice strains to excitotoxic injury and in terms of interactions of environmental injury (e.g., hippocampal damage) with genetic factors that determine the responsivity of neural systems (e.g., mesolimbic dopamine) that may be secondarily affected by the environmental injury. In a preliminary experiment aimed at the latter consideration, Lipska and Weinberger (1995) have shown that inbred rat strains differing in terms of their responsivity to environmental stresses show differential effects of the neonatal lesion. As might be expected, a strain (Fisher 344) that is hyperresponsive to stress, shows exaggerated effects of the lesion and can manifest the same behavioral abnormalities after a much smaller neonatal defect than an outbred strain (Sprague-Dawley). By the same token, a strain that is hyporesponsive to environmental stress (Lewis), appears to be able to compensate for many of the effects of the lesion. These preliminary observations may ultimately lead to insights about mechanisms of heterogeneity in schizophrenia, to explanations of how genetic liability factors may persist in the human genome despite the reduced fecundity of patients with schizophrenia, and perhaps, to identifying candidate genes that might be explored in human linkage studies.

CONCLUSION

The "neurodevelopmental hypothesis" has emerged over the past few years as a popular and heuristically useful approach to understanding and studying schizophrenia. It has generated a number of new lines of research involving developmental neurobiology and pathology and clinical epidemiology. As a useful hypothesis, it has posed more research questions than it has answered. It is also responsible for the development of the first high-fidelity animal model of a constellation of core neurobiologic aspects of the syndrome, a model that attests to the neurobiologic plausibility of the hypothesis. Nevertheless, the cornerstone of the hypothesis, that is, the evidence of pathologic brain development, is its "Achilles heel." The data implicating developmental neuropathology are either indirect or based on inconclusive studies. Nevertheless, if the preliminary evidence of cytoarchitectural abnormalities—the most qualitatively compelling evidence to date—can be replicated in a few methodologically rigorous efforts, then a neuropathologic substrate for at least some cases of schizophrenia will have been established. This effort has to be at the top of the list of research priorities.

Finally, an additional weakness of the neurodevelopmental hypothesis should be noted: In practical terms, the hypothesis is difficult to disprove. Lack of positive findings does not conclusively disprove it, because subtle findings are easily missed and may only be observed with highly selective probes. Ultimately, the decision to abandon the hypothesis will follow either more compelling evidence of an alternative explanation or repeatedly negative results from methodologically sophisticated and precise attempts to confirm it.

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