Neonatal Insult to the Hippocampal Region and Schizophrenia: A Review and a Putative Animal Model

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Objective: *To review the mounting evidence implicating early hippocampal dysfunction in the pathogenesis and the pathophysiology of schizophrenia. An account is made of recent neurodevelopmental hypotheses indicating how an early dysfunction of the hippocampal region disrupts maturational events in brain systems connected to that structure, thus inducing dysfunctional connectional development. Finally, an animal model is presented.*

Method: *Socioemotional behaviour of monkeys (*Macaca mulatta*) with selective neonatal hippocampal lesions was assessed by analyzing their interactions with their age-matched controls at 2 months, 6 months, and 5 to 8 years of age and by comparing the social interactions at each age with those of normal controls paired together.*

Results: *At 2 months of age, monkeys with neonatal hippocampal lesions presented minor disturbances in initiation of social interactions. These subtle changes of behaviour were less evident at 6 months, although by that age, the operated monkeys displayed more withdrawals in response to an increase in aggressive responses from their unoperated peers. In adulthood, the amount of time spent by the hippocampectomized monkeys in social contacts with their normal peers decreased markedly. In addition, operated monkeys exhibited more locomotor stereotypies than normal controls.*

Conclusion: *These experimental findings indicate that the time-course and nature of the behavioural disturbances resulting from early trauma to the hippocampal region have some similarities with the clinical symptoms of schizophrenic patients and the typical time-course of the disease.*

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Key Words: *neonatal hippocampal lesion, social interactions, stereotypies, schizophrenia, monkeys*

During the last 2 decades, in keeping with Kraepelin's (1) original hypothesis, new developments in schizophrenia research have produced extensive evidence of an abnormal structure and function of the brain in schizophrenic patients (2–6). Two brain areas have especially been the targets of investigation: the prefrontal cortex and the medial temporal lobe limbic structures, in particular the hippocampal formation. As advances have been made in defining the type of neuropathology observed in these brain regions, a new theoretical framework has been elaborated (3,7,8). Thus, it has been proposed that this mental illness is a *neurodevelopmental* disorder in which a fixed brain dysfunction (presumably of the medial temporal region) occurring early in life interacts with normal brain maturational events that occur much later (presumably in the prefrontal cortex). So far, most animal models have used either pharmacological perturbations in the striato-limbic dopamine (DA) activity or primary prefrontal or hippocampal lesions in adult animals to modify subcortical DA activity (9–14) and reproduce the schizophrenic symptoms. None of these models, however, has addressed the hypothesis of a neurodevelopmental medial temporal lobe disorder in schizophrenia.

This paper first reviews empirical evidence suggesting an involvement of the prefrontal cortex and medial temporal lobe structures in the pathophysiology of schizophrenia. Then, the neurodevelopmental hypothesis of schizophrenia is des- cribed. Finally, to support this hypothesis, we present in the last section recent experimental findings in rodents and primates indicating that insult to the hippocampal region early

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in development results in behavioural changes that characterize the symptoms of schizophrenia as well as the typical course of this mental illness.

The Prefrontal Cortex and Schizophrenia

The prefrontal cortex, which comprises over 29% of the cortical mantle in humans (15), has been divided into 3 main regions: the dorsolateral cortex (including areas 9, 10, 44, and 46), the orbital frontal cortex (including areas 11, 12, and 47), and the frontal eye field (including portions of areas 8 and 9). Functionally, the prefrontal cortex is believed to be important in the generation and modulation of the highest integrative, adaptative, and executive functions, such as attention, volition, future-oriented planning, emotional expression, and social interactions (15,16). Studies of experimental lesions in animals and traumatic or disease-induced lesions in humans have indicated that injury to the prefrontal cortex leads to a number of affective, cognitive, and behavioural disorders. Thus, abnormalities in socioemotional behaviour, such as apathy, indifference, and loss of spontaneity and affective engagement, are associated with damage to the orbital portion of the prefrontal region (17–20). Moreover, disorders of cognitive function, such as difficulty abstracting or categorizing, impaired attention and memory for the temporal sequence of events, loss of the ability to selectively initiate, sustain, and monitor the results of ongoing behaviour or to anticipate consequences of self actions, decrease in voluntary motor behaviour, and irrelevant stereotyped acts, are typically seen with lesions to the dorsolateral portion of the prefrontal region (17–19). Several of these symptoms following frontal injuries closely resemble the negative symptoms (for example, affective flattening; alogia; anhedonia and asociality; and attentional impairment) observed in the majority of the individuals suffering from schizophrenia (21,22), suggesting that a prefrontal lobe dysfunction might be involved in the pathophysiology of this mental illness. Indeed, chronic negative symptoms are shared by many patients with prefrontal lobe lesions, and attentional deficits are among the anomalies most consistently found in schizophrenia.

Neuropathological Studies

A few abnormal prefrontal structural changes have been reported in neuropathological postmortem analyses of schizophrenic patients. Some of these morphometric studies have revealed an increase in neuronal density and a decrease in cortical thickness in cortical prefrontal area 9 (23,24). In contrast, another study has shown reduced neuronal densities in the dorsolateral prefrontal (DLPFC), anterior cingulate, and motor cortices (25). According to Benes and her associates (26), these reductions in neuronal densities could arise from losses of small inhibitory interneurons within intrinsic cortical circuits, perhaps as a result of a perturbation of normal ontogenetic events during the perinatal period. In this context, recent evidence (27) points to an altered distribution of neurons that are normally found in the subplate (for example, the transition zone between layer VI of the cortex and the white matter underlying it). These neuronal changes suggest a disorganized migration of neurons towards the cortical plate. Similarly, a recent study using ^{31}P nuclear magnetic resonance spectroscopy (28) indicated that, compared to control subjects, the cell bodies, processes, and terminals of neurons in the DLPFC of schizophrenic patients contained reduced levels of phosphomonoesters and increased levels of phosphodiesters, indicating an altered timing or abnormal enhancement of normal, programmed synaptic pruning during adolescence.

In addition to these morphometric studies, magnetic resonance imaging (MRI) investigations have demonstrated that, compared with healthy controls, schizophrenic patients have significantly smaller frontal lobes (29) and smaller prefrontal cortices (30). Several MRI volumetric studies, however, have failed to replicate these findings (31–34). Thus, while the existence of frontal structural abnormalities has not yet been demonstrated convincingly, the possibility cannot be ruled out that such abnormalities exist in a certain number of patients with schizophrenia.

Metabolic Studies

Two decades ago, Ingvar and Franzen (35) used xenon 133 to measure regional cerebral blood flow (rCBF) in normal and schizophrenic subjects. They reported that, during both resting state and performance on various cognitive tasks (Raven's Progressive Matrices and the auditory digit-span backward-test), there was a relatively greater rCBF to the prefrontal cortex than to the temporal or parietal cortex in control subjects. In patients suffering from chronic schizophrenia, however, this pattern of relative "hyperfrontality" was absent. Instead, schizophrenic subjects appeared to be "hypofrontal." Although there was no significant difference between schizophrenic patients and the controls in frontal flow rates, the postcentral flow rates were significantly greater in patients than in controls, resulting in a frontal to postcentral blood flow ratio significantly smaller in schizophrenic patients that in normal subjects. This accounts for the relative "hypofrontality"of schizophrenic patients.

In the last decade, this hypofrontality pattern of glucose metabolism during resting state has been fully or partially confirmed in several studies from different research groups utilizing xenon 133 rCBF and/or positron emission tomography (PET) with 18F-fluorodeoxyglucose (36–44). Other teams, however, have been unable to replicate this pattern (45,46). Moreover, Cleghorn and colleagues (47) have found increased frontal metabolism in schizophrenic patients during resting state. According to Weinberger and Berman (48), this divergent finding could be explained by the fact that frontal lobe metabolism may fluctuate as a function of behavioural and emotional states. "Hypofrontality" would then represent a pathophysiological correlate of an aspect of schizophrenic behaviour and not of schizophrenia itself.

In an elegant experiment designed to further understand the meaning of the frontal metabolic hypofunction, Weinberger and his colleagues (49) demonstrated that, when schizophrenic patients were administered the Wisconsin Card Sort-Test (WCS), a cognitive task known to measure function of the DLPFC, they did not show activation of this brain region, whereas normal controls given the same task did. The blood flow changes were regionally specific, involving only DLPFC. Furthermore, in schizophrenic patients, the DLPFC rCBF correlated positively with WCS cognitive performance, suggesting that the better the DLPFC was able to function, the better schizophrenic patients could perform on the task. These results have been duplicated by Rubin and colleagues (50) using the same task, and by Buchsbaum and others (51) using the Continuous Performance Test, another measure of prefrontal function. During the Tower of London task, designed to stimulate frontal cortex activity, Andreasen and associates (52) also observed a decreased activation in patients with chronic schizophrenia. Taken together, these data seem to plead in favour of a prefrontal cortex dysfunction in schizophrenic patients (48,53–58). In this context, Weinberger and his colleagues (49,57) have proposed that the metabolic "hypofrontality" could result from a hypofunction of the mesocortical ascending dopaminergic projections at the level of the DLPFC. This hypofunction would diminish schizophrenic patients' capacity to increase DLPFC metabolism when there is specific need for it and could, thus, account for some of the behavioural and cognitive impairments seen in schizophrenia (in particular, the negative symptoms associated with DLPFC dysfunction [17–19]).

Medial Temporal Lobe Structures and Schizophrenia

The medial temporal lobe structures include the hippocampal formation, the amygdaloid complex, and the adjacent medial temporal cortical areas. The hippocampal formation is composed of the dentate gyrus, the hippocampus proper (that is, the cornu Ammonis subfields CA_1 to CA_4), and the subicular complex (59). The amygdaloid complex includes several nuclei, divided into the basolateral and corticomedial nuclear groups (60). The medial temporal cortical areas comprise the parahippocampal cortex caudally and the peri and entorhinal cortex rostrally (61). These cortical areas link the hippocampal formation with diverse cortical association areas in the frontal, temporal, and parietal lobes, and also with subcortical targets such as the amygdala, ventral striatum, and hypothalamus. While the hippocampal formation is best known for its role in memory functions (62), it is also thought to be central in the processing and integration of drives and affective experiences with higher cognitive functions (63–65). In this context, it has been implicated in such processes as the formation of associations (66), comparison of actual with expected stimuli (67), stimulus encoding and active ignoring of irrelevant stimuli (68), analysis of contextual significance (69), and spatial cognitive mapping (70). In addition, the hippocampal formation has been postulated to be a cognitive system controlling goal-directed behaviour by doing a multidimensional analysis of the situation through the retrieval of the information appropriate to satisfying the motivational state of the moment (71). Thus, the hippocampal formation may be part of a neural circuit allowing highly processed environmental stimuli to be compared with pertinent information already stored in memory and associated with motivational and attentional states. Disruption of these important processing functions could well have large effects on the functioning of many brain systems and lead to marked and wide-ranging cognitive and affective disturbances that constitute the core of the schizophrenia syndrome (72,73). Indeed, organic lesions of the limbic structures (resulting from stroke, tumors, trauma, or infections, for example) and, in particular, of the hippocampus, are frequently associated with positive symptoms (perceptual distortions, hallucinations, irrational fears) (2,74). Finally, several neuropsychological studies have indicated that, besides a global cognitive impairment, schizophrenic patients exhibit basic verbal and visual recall deficits that are similar to the amnesic syndrome seen after a bilateral hippocampal insult (75–77).

Neuropathological Studies

In contrast to the prefrontal cortex, all volumetric studies of postmortem tissues of the medial temporal lobe structures of schizophrenic patients have reported numerous abnormal changes in this brain region. For instance, white matter reduction was found in the parahippocampal gyrus of patients with schizophrenia (78,79). Several investigators (80–85) have observed that the size of the hippocampal formation, parahippocampal gyrus, and amygdala was significantly smaller in schizophrenic subjects as compared with control cases. Likewise, Brown and associates (86) found a significant reduction of the thickness and width of the parahippocampal gyrus. In another morphometric study, Falkai and colleagues (87) demonstrated a marked reduction of the volume of the entorhinal cortex. In addition, this shrinkage of the entorhinal cortex was associated with reduced numbers of pyramidal cells in the areas CA_1 to CA_4, whereas cell numbers of the subicular complex were unchanged (88). There was also a trend toward loss of granular cells in the dentate gyrus. Similarly, Jeste and Lohr (84) reported that brain sections from schizophrenic patients had almost consistently the lowest sectorial volume and pyramidal-cell density in all areas of the hippocampus proper, the differences being greatest in CA_4.

In addition to these morphologic abnormalities of the medial temporal lobe structures, histological anomalies, such as disarray of hippocampal cell orientation (89–91) as well as alteration of these neurons, particularly in anterior and middle hippocampal regions (CA_1/prosubiculum and CA_1/CA_2 interfaces), were also displayed in patients with schizophrenia (92). Jakob and Beckmann (93) found a heterotopic displacement of single groups of neurons in the entorhinal region and, likewise, Arnold and colleagues (94,95) demonstrated entorhinal cytoarchitectonic disturbances, such as aberrant in-

vaginations of the cortical surface, disruption of cortical layers, and neuronal paucity in superficial layers, in schizophrenic subjects. More recently, Akbarian and colleagues (96) reported a distorted distribution of nicotinamide adenine dinucleotide phosphate diaphorase neurons in the hippocampal formation and the white matter underlying the lateral cortex of the temporal lobe. These changes, similar to those observed in the DLPFC (27), suggested developmental disturbances indicative of impaired neuronal migration or alteration in the death cycle of transitory subcortical neurons in the temporal lobe.

Finally, several MRI studies have revealed a significant reduction in the volume of the temporal lobes of schizophrenic patients as compared with normal controls (32,97–102) as well as reduced volume of medial temporal lobe structures, especially of the amygdala (30), hippocampus, and parahippocampal gyrus (30,32,81,103–105).

Metabolic Studies

In other respects, Wolkin and associates (45) reported a temporal lobe hypometabolism in schizophrenic patients under resting conditions, and Tamminga and colleagues (106) showed a lower regional glucose metabolic rate in the hippocampus, parahippocampus, and anterior cingulate cortex of schizophrenic subjects. Temporolimbic abnormalities have also been identified in patients with schizophrenia by examining spin-lattice (T1) magnetic resonance relaxation times (107). In contrast, DeLisi and collaborators (108) found a bilateral hypertemporality in similar subjects receiving forearm somatosensory stimulation. Since this stimulation was applied for the purpose of activating the prefrontal lobes, it is possible that the difference of metabolic pattern in this last study (hyper versus hypotemporality in the earlier studies) reflected the somatosensory activation process itself, rather than the intrinsic nonstate-dependent pathophysiological differences. Finally, a recent study using proton magnetic resonance spectroscopy (^{1}H-MRS) indicated a quantitative reduction of the N-acetyl aspartate in schizophrenic subjects, particularly in neurons of the right temporal lobe (109).

Electrophysiologic and Neurochemical Studies

In addition to neuropathologic and metabolic findings, neurophysiologic and biochemical studies have provided further evidence that a dysfunction of the hippocampal formation might be involved in schizophrenia. Abnormal electroencephalographic activity has been recorded during psychotic episodes in schizophrenic patients (110), and it has been shown that psychic experiences bearing great resemblance with the positive symptoms seen in this mental illness may be elicited by direct electrical stimulation of the hippocampal formation (111,112). Moreover, in postmortem neurochemical studies of the brains of schizophrenic patients, marked alterations in the concentrations of somatostatin, substance P, and cholecystokinin (113) and thyrotropin-releasing hormone receptors (114), selective loss of glutaminergic neurons (115), changes in serotonin uptake sites and serotonin receptors (116,117), and altered densities of cholecystokinin binding sites (118) have been observed in the hippocampal region.

A Neurodevelopmental Hypothesis of Schizophrenia

It has become apparent that the type of cytoarchitectonic abnormalities found in the medial temporal lobe region of schizophrenic patients has arisen through some failure of normal cerebral development very early in infancy, probably in fetal or neonatal life. This view of abnormal early development is also consistent with the increased frequency in schizophrenic subjects of normally rare congenital brain abnormalities, such as cavum septum pellucidum and agenesis of the corpus callosum (119,120), and with an excess of minor physical anomalies, particularly craniofacial and dermatoglyphic abnormalities (121). The causes of these developmental abnormalities are diverse. They might be heterogeneous; current models emphasize mostly genetic factors (122) or a perinatal insult that could be linked to anoxia, viruses, or toxins (92,123).

Several biological models for the etiology of schizophrenia have postulated abnormal prenatal or neonatal development of the central nervous system. In 1982, Feinberg (124) advanced the hypothesis that the typical pathogenesis of the disorder, namely its peripubertal onset, may be due to the role of late brain maturation. Thus, programmed synaptic elimination in early adolescence could be delayed or decreased (125). Schneider (126) propounded that schizophrenia may be a consequence of abnormal connectivity caused by early damage to temporal lobe structures. Finally, Jones and Murray (127) have proposed an abnormal control of cell proliferation in the hippocampal formation, while Kovelman and Scheibel (92) have suggested an aberrant migration of neuroblasts into the hippocampal formation, which would probably occur during the second trimester of gestation. According to these conceptualizations, the hippocampal insult would be constant, that is, not associated with a progressive neurodegenerative process. Indeed, there is little or no evidence of progressive structural changes in schizophrenic patients (72,128). Nevertheless, an early static morphological defect in the medial temporal lobe structures is difficult to reconcile with the characteristic time-course of the disease, namely, onset after puberty. Several attempts have been made to explain how an early medial temporal lobe insult might yield the protracted appearance of schizophrenic symptoms.

Based on animal studies indicating that early damage to the brain may remain quiescent until the animal reaches maturity (129), Weinberger (3) proposed that a similar process might explain the postpubertal appearance of the positive schizophrenic symptoms. A hippocampal dysfunction occurring early in life would disrupt maturational events in late-maturing brain systems connected to that structure, such as the prefrontal cortex, thus inducing dysfunctional

connectional development. Given the existence of direct pathways from the hippocampal formation to the prefrontal cortex (130), it is conceivable that the hypofrontality observed in schizophrenic patients and the negative symptoms traditionally associated with dysfunctional frontal lobes are secondary to a primary hippocampal pathology. Data from a study of discordant monozygotic twins provide more direct support for this possibility (131). In this investigation, the authors found differences on MRI in the size of the hippocampus, which was almost invariably smaller in the affected compared with the unaffected twin. Moreover, this morphological difference strongly predicted the difference within the pair in the WCS-related prefrontal activation, suggesting that the prefrontal abnormality is likely to be related to the structural hippocampal defect. Since the prefrontal cortex is a late-maturing brain region (132–134), immature prepubertally and continuing to develop into adulthood, the full-fledged neuropsychological symptoms of an early hippocampal dysfunction would not become apparent until the beginning of adulthood (52).

Alternatively, Bogerts (135) hypothesized that, because the medial temporal lobe structures are target areas of gonadosteroids and corticosteroids, the action of these hormones on the medial temporal lobe structures at puberty may yield to their dysfunction, leading to the emergence of psychotic factors. Experimental studies designed to test these premises are, therefore, clearly warranted.

Search for an Animal Model of Schizophrenia

Early attempts to model schizophrenia have predominantly used either pharmacologic perturbations in the striatolimbic DA activity or primary prefrontal lesions to modify subcortical DA activity (9–11). The recent findings of neuropathological changes in the hippocampal formation and cortical areas surrounding it, however, provided a fertile ground to explore hippocampectomized animals as a putative animal model of schizophrenia. As reviewed by Schmajuk (12), animals with hippocampectomy performed in adulthood exhibit attentional deficits, recognition memory deficits, and stereotyped behaviours. In addition, hippocampectomized animals are hyperactive and show poor habituation and resistance to extinction. Taken together, these data have led to the proposal that schizophrenia might be the result of hippocampal dysfunction and that adult animals with bilateral hippocampal lesions may provide an adequate model for several of the symptoms seen in this mental disorder (12,13).

Although these earlier models appear to mimic broadly the symptoms of schizophrenia, they have paid insufficient attention to the neurodevelopmental insult and the developmental time-course of the symptoms associated with schizophrenia. In keeping with the neurodevelopmental perspective discussed in the preceding section, a promising approach for future models of schizophrenia in animals will be to induce alterations of hippocampal development and then trace the time-course of behavioural changes from infancy through adulthood. To date there have been 2 such attempts: one is the study by Lipska and collaborators (136) on rodents and the other is our recently unveiled study of primates (137,138).

Rat Hippocampal Model

To determine the developmental sequelae of early hippocampal dysfunction, Lipska and colleagues (136) produced bilateral ibotenic acid lesions of the ventral hippocampal formation (VH) in rats on the seventh day after birth (PD 7). Motor activity in a novel environment, after saline injection, and after d-amphetamine administration was similar in control and operated rats at PD 35. In early adulthood, however, at PD 56, animals with the neonatal VH lesion were hyperactive in each of these conditions. The emergence of the hyperactivity at PD 56 could be prevented by pretreatment with the antipsychotic drug haloperidol. Moreover, rats operated on as neonates, in contrast to those operated on as adults, were also hyperresponsive to stress, evaluated with a swim test. This latter effect is analogous to that seen after adult lesions of the medial prefrontal cortex, rather than after adult lesions of VH, suggesting that the neonatal VH lesion may affect functional development of the medial prefrontal cortex. According to Lipska and her colleagues (136), these results demonstrate that, in rats with neonatally induced excitotoxic VH lesions, behavioural indices consistent with increased mesolimbic DA responsivity to stressful and to pharmacologic stimuli emerge only in early adulthood and suggest that homologous mechanisms may underlie certain aspects of the pathophysiology of schizophrenia.

This animal model demonstrates that the behavioural effects of an early lesion of the hippocampal formation may remain silent until puberty and supports the neurodevelopmental model of schizophrenia. It does not, however, provide an account for more recent findings indicating the presence of subtle cognitive, socioemotional, and neuromotor abnormalities during the premorbid developmental course of the disease. Neuromotor deficits and other socioemotional changes have been found during infancy and childhood in at-risk individuals (139,140). Furthermore, Walker and colleagues (141,142), examining childhood home movies of adult-onset schizophrenic patients, reported that, compared with their siblings, these patients had premorbid reduced responsiveness, eye contact, and positive affect, and poorer fine and gross motor coordination. Thus, as Walker (142) noted, "a comprehensive neurodevelopmental model of schizophrenia must encompass these early manifestations of dysfunction as well as the postmorbid period." Our recent studies of the long-term effects of early damage to the hippocampal region in monkeys appear to provide account not only for the types of behavioural changes seen in schizophrenic patients, but also for the typical time-course of the disease.

A Nonhuman Primate Hippocampal Model

Within the context of a long-term program designed to investigate the role of medial temporal lobe structures in the maturation of memory functions and in the genesis of socioemotional behaviour, we have followed the development of monkeys that had sustained bilateral aspiration lesions of the hippocampal region in infancy (137,138). Six animals had received hippocampal lesions neonatally (H/N) (at the age of 5 to 23 days), 6 were normal controls (N/H) reared together with the operated monkeys, and 6 were normal controls raised together (N/N). The hippocampal removals included both the dentate gyrus, all CA fields, the subicular complex, and the underlying parahippocampal gyrus lying medial to the occipitotemporal sulcus; the amygdaloid complex and the ento and perirhinal areas were spared. Histological or MRI examination of the extent of these early lesions revealed that the hippocampal removal was largely as intended, including most of the parahippocampal gyrus and all hippocampal formation except for the caudal-most 1 to 2.5 mm portion of the hippocampus unilaterally in 1 animal and bilaterally in 4. Encroachment to adjacent cortical areas was minor. In 5 of the 6 cases, the lesion included bilaterally the caudal-most portion (2% to 36%) of entorhinal cortex (area 28) lying adjacent to the parasubiculum, but perirhinal cortex (areas 35 and 36) was spared in all cases. In addition, the lesion encroached to anterior portion of inferior temporal cortex (area TE) unilaterally in 3 cases (1% to 18%) and bilaterally in 2 cases (2% to 4%), and to posterior portion of inferior temporal cortex (area TEO) unilaterally in 4 cases (20% to 75%) and bilaterally in one (18%).

The socioemotional behaviour of monkeys with selective neonatal hippocampal lesions was assessed by analyzing their interactions with their age-matched controls and by comparing these social interactions with those of the normal controls paired together. For this purpose, at 2 months, 6 months, and 5 to 8 years of age, 2 monkeys, either one operated (H/N) and its pair-reared control (N/H) or 2 pair-reared normal monkeys (N/N), were placed in a large enclosure while their activities were videorecorded for 2 periods of 5 minutes each, separated by a 5-minute interval, for 5 consecutive days. Behaviours on the videotapes were scored independently by 2 observers (one of whom was blind with respect to the lesion) who assigned them to one of 9 different behavioural categories: inactivity, manipulation, locomotion, locomotor stereotypies, self-directed activities, approach, social contact, hostility, and active withdrawal (Figure 1). Frequency and duration of all categories were recorded with a Tandy portable computer, and interobserver reliability averaged from 0.82 to 0.91.

Our data indicate that, at both 2 and 6 months of age, pairs of normal monkeys (N/N) spent most of their time in social contact, object manipulation, and locomotion. These animals did not display abnormal behaviours, such as active withdrawal, self-directed activities, or locomotor stereotypies, and showed very little passivity. By contrast, in the dyads

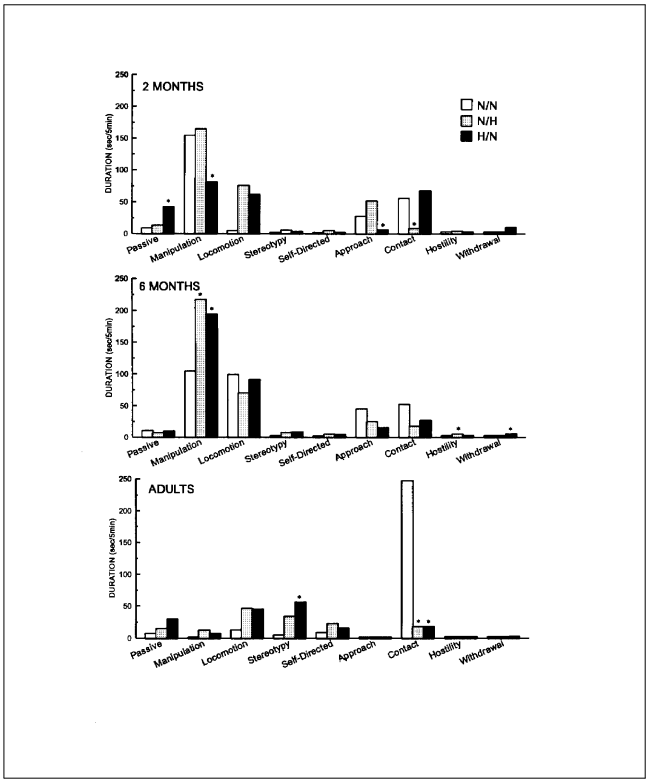

Figure 1. Bars represent average duration (seconds per 5 minutes) of each behavioural category across the 10 sessions in normal monkeys paired together (N/N) and in normal monkeys (N/H) paired with monkeys with early hippocampal lesions (H/N) at the ages of 2 months, 6 months, and 5 to 8 years (adults). *Passive:* Sleep or maintenance of stable, stationary position with no simultaneously scoreable behaviour; *Manipulation:* Any manual or oral manipulation of the physical surrounding, including handling, chewing, licking, or mouthing toys, parts of the cage, or droppings; *Locomotion:* Ambulation of one or more steps at any speed, including walking, running, climbing, jumping, dropping from ceiling, or swinging; *Stereotypy:* Motor behaviours repeated consecutively more than 3 times, including pacing, circling, hopping, rocking, or doing somersaults; *Self-directed:* Any activities directed towards self, including self-grooming, holding, clasping, biting, hugging head, pressing face with hands, clutching fists, and manipulating genitalia, and certain postures, such as prone or head on chest; *Approach:* Movement in the direction of the other monkey always accompanied by eye contacts; *Contact:* Monkeys are within an arms length of each other for at least one second, or animals' body parts are in contact for at least one second. Also includes picking and licking of partner's fur, following a partner closely, engaging in play and rough-and-tumble bouts, or chasing the other monkey; *Hostility:* Behavioural display directed at the partner, including mouth-threatening gestures, barking, lunging towards the other monkey, taking toy away from other or otherwise interfering with partner's occupation; *Withdrawal:* Monkey moves away or makes an active avoidance response after a partner attempts to initiate social contact. For each behavioural activity, MANOVA were performed at each age and across age groups. * indicates between-group differences at $P < 0.05$.

consisting of one normal control and one monkey with a neonatal hippocampal lesion, socioemotional disturbances emerged in the latter (see Figure 1). Thus, at 2 months, infants with neonatal hippocampal lesions exhibited subtle socioemotional disturbances, namely less initiation of approach than either unoperated controls (N/H) or normal controls (N/N). They also displayed more passivity and less manipulation than unoperated animals of both control groups. When these animals reached 6 months of age (see Figure 1, middle graph), although their social interactions with the pair-reared controls did not differ significantly from those recorded in the N/N dyads, they exhibited more active withdrawal than the unoperated controls of both groups (N/N and N/H). This withdrawal of social contact in animals with early hippocampal lesions was reciprocated by enhanced hostility in the normal controls. In addition, H/N and N/H monkeys spent more time manipulating toys and parts of the cage than animals in the N/N group.

The subtle effects of neonatal hippocampal lesions on socioemotional behaviour in early infancy became much more profound as the animals reached adulthood (see Figure 1, bottom graph). Indeed, the amount of time spent in social contact was nearly 3 times less in H/N dyads than in the N/N dyads (64 versus 268 seconds per period). Perhaps as a result of this loss of social interaction, both operated and control animals in the mixed dyads explored the environment through locomotion more frequently and for longer periods than did animals in the N/N dyads. In addition, the severe changes in social interactions were accompanied by an increase in stereotypy. Thus, monkeys with neonatal hippocampal lesions (H/N) exhibited more locomotor stereotypies than unoperated monkeys in groups N/H and N/N, averaging 55, 32, and 3 seconds per period, respectively.

As compared to the subtle behavioural changes observed in monkeys with early hippocampal lesions at 2 and 6 months of age, the dramatic behavioural changes seen in adulthood indicate that early damage to the hippocampal formation yields socioemotional disturbances that become more severe as the animals reach maturity. Also, animals with early hippocampal lesions exhibited locomotor stereotypies only when they reached adulthood. Thus, the findings point to a crucial role of the hippocampal formation in the establishment, expression, and maintenance of social and emotional behaviour in primates. In addition, the data demonstrate that the behavioural effects of neonatal hippocampal lesions remained relatively silent in infancy, though some minor changes were noticeable. By contrast, more severe disturbances emerged with further maturation of the animals, even though the exact period in development at which the profound changes occurred is still unknown. Finally, assessments of memory function in these same animals during infancy and adulthood have revealed that although these early hippocampal lesions did not affect the animals' ability to recognize objects after long delays of several minutes (143), they markedly diminished their ability to recognize objects when the context in which they are presented is modified (144). In addition, early damage to the hippocampal region significantly impaired the monkeys' ability to learn relationships among objects (145).

In summary, the developmental time-course and the nature of the behavioural disturbances seen in monkeys with early damage to the hippocampal region closely resemble some of the socioemotional, cognitive, and neuromotor abnormalities seen in schizophrenic patients, thus suggesting that a neonatal dysfunction of the hippocampal region may be involved in the pathogenesis of schizophrenia.

Conclusion

Evidence for involvement of the prefrontal cortex and the medial temporal lobe structures in schizophrenia and elaboration of neurodevelopmental models to account for the considerable delay between the onset of neuropathology and the onset of the disease were reviewed. Current theory proposes that static morphological changes in the hippocampal formation very early in infancy may impact on late-maturing brain areas, such as the prefrontal cortex. Early dysfunction of the hippocampal formation and its relationships to the formation of behavioural changes analogous to those found in schizophrenia were explored in nonhuman primates. The data suggest that neonatal hippocampal lesions in monkeys can induce behavioural disturbances that mimic some aspects of the symptoms encountered in schizophrenia. In addition, the time-course of behavioural changes observed in monkeys hippocampectomized early in infancy fits remarkably well with that of schizophrenic symptoms. Thus, monkeys with early hippocampal lesions had subtle changes in social interactions in infancy that resulted in a profound loss of social affiliation when they reached adulthood. Furthermore, they displayed selective deficits in memory functions and a marked increase in locomotor stereotypies in adulthood.

Although this primate model provides support for the neurodevelopmental hypothesis of schizophrenia, additional studies are clearly required to verify this conceptualization. Indeed, we recognize that there are major differences between nonhuman primates and humans; that modelling the symptoms of a highly complex human illness involving perception, emotion, and cognition is extremely difficult; that our model does not address the crucial question of the genetic basis of schizophrenia; that selective lesions of the hippocampal region might not have exactly the same behavioural consequences as a dysgenesis of the hippocampal region; and that the functional disturbances underlying schizophrenic symptoms are probably not confined to single anatomical loci, but rather involve extensively distributed neuronal networks. Nevertheless, we believe that the resemblance between the effects of neonatal damage to the hippocampal region in monkeys and the symptomatology of schizophrenia in humans is sufficiently close to encourage further study of this putative animal model. In conjunction with genetic or chemi-

cal manipulations aimed at creating early morphological disorganization of the hippocampal region, such a model would provide opportunities to study which factors could induce the early neural aberration in the hippocampal formation and how this restricted neuropathology in infancy might affect late-developing brain functions. Ultimately, the study of nonhuman primates raised with neonatal hippocampal dysgenesis might provide further understanding of the biological causes of this illness.

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Résumé

Objectif : *Examiner les preuves croissantes d'un dérèglement précoce de l'hippocampe dans la pathogénèse et la physiopathologie de la schizophrénie. Les auteurs présentent une hypothèse neurodéveloppementale récente montrant comment un dérèglement précoce de l'hippocampe bouleverse la maturation des systèmes cérébraux raccordés à cette structure, donc perturbe le développement des connexions. Suit la présentation d'un modèle animal.*

Méthode : *On a évalué le comportement socioaffectif de singes (Macaca mulatta) présentant une lésion néonatale sélective à l'hippocampe en étudiant leur socialisation avec des témoins du même âge à 2 mois, 6 mois et de 5 à 8 ans, et en comparant ces interactions à celles de paires de témoins normaux.*

Résultats : *À 2 mois, le singe atteint d'une lésion néonatale à l'hippocampe initie légèrement moins la socialisation. Ces changements subtils du comportement sont moins apparents à 6 mois, quoi qu'à cet âge, les singes ayant subi l'opération restent plus distants face à l'aggressivité accrue des témoins contemporains. À l'âge adulte, les singes ayant subi l'ablation de l'hippocampe consacrent sensiblement moins de temps aux contacts sociaux que leurs congénères normaux. Les singes traités affichent aussi plus de stéréotypes locomoteurs.*

Conclusions : *Les observations indiquent que la nature et l'évolution des perturbations comportementales découlant d'un traumatisme à l'hippocampe en bas âge présentent des similitudes avec les symptômes cliniques et l'évolution typique de la schizophrénie.*