Neural Plasticity in Schizophrenia

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Abstract

No current biological hypothesis can assimilate the genetic, environmental, and clinical features of schizophrenia. If, as some authors contend, environmental factors have important effects on the course of schizophrenia, then a fruitful research concern may be the adaptation of neuronal circuitry to environmental changes. The plasticity of neuronal connections has been studied by subjecting animals to neurosurgical lesions, brain electrostimulation, and a variety of rearing environments. The present article approaches the schizophrenia research literature from a theoretical perspective which takes into account the plasticity of neuronal connections. In a speculative manner, it demonstrates how neural plasticity concepts can be invoked to explain the following seemingly disparate features of schizophrenia: the pharmacological support for the dopamine hypothesis, the delayed onset and offset of neuroleptic antipsychotic action, genetic and environmental influences in schizophrenia, the regional alterations in brain structure and function seen in chronic schizophrenic patients, and the various types of behavioral symptoms exhibited by schizophrenic patients. In view of the explanatory potential of neural plasticity concepts, a research program that focuses on these concepts seems warranted.

During the past decade, the dopamine (DA) hypothesis of schizophrenia has received wide attention as a theoretical framework for the biology of schizophrenia (Bowers 1980). The postulated dopaminergic hyperactivity provides an attractive explanation for the finding that positive symptoms of schizophrenia (i.e., hallucinations and delusions) are exacerbated by DA agonists and diminished by DA antagonists. However, this indirect pharmacological evidence has not been corroborated by compelling direct evidence of excess DA function in schizophrenia (reviewed by Haracz 1982). Schizophrenic and control subjects did not differ in their cerebrospinal fluid (CSF) or post-mortem brain levels of DA metabolites (Bowers 1973; Post et al. 1975; Crow et al. 1979; Winblad et al. 1979; Berger et al. 1980; Farley, Shannak, and Hornykiewicz 1980; Leckman, Bowers, and Sturges 1981; Wyatt et al. 1981). Elevated post-mortem brain concentrations of DA were found in deceased schizophrenic patients by some laboratories (Crow et al. 1979; Mackay et al. 1982), but not by others (Winblad et al. 1979; Farley, Shannak, and Hornykiewicz 1980; Wyatt et al. 1981). Schizophrenic patients reportedly have significant alterations in platelet monoamine oxidase (MAO) activity and in post-mortem brain neuroleptic binding, but antipsychotic drug treatment has not been ruled out as a cause of these findings (Mackay et al. 1980, 1982; Chojnacki et al. 1981; DeLisi et al. 1981; Sahai, Arora, and Meltzer 1981; Snyder 1981; Meltzer et al. 1982; Del Vecchio et al. 1983).

The DA hypothesis is not only deficient in direct support, but it is also restricted in theoretical scope. The hypothesis does not readily account for social aspects of schizophrenia (Wing 1978) or the biogenesis of specific behavioral symptoms. A fully developed biological hypothesis of schizophrenia must deal mechanistically with the complex clinical manifesta-
tions of the disorder, including the premorbid unfolding of maladaptive behavioral patterns (Kety 1972; Bowers 1980). In addition, environmental factors probably affect the schizophrenic process by acting on an, as yet, unidentified biological substrate (Denber 1970; Extein and Bowers 1979; MacCulloch and Waddington 1979). Currently, there is no comprehensive biological scheme that assimilates the genetic, environmental, and clinical features of schizophrenia.

In view of the potential etiological and/or modulatory significance of environmental factors in schizophrenia (Brown, Birley, and Wing 1972; Vaughn and Leff 1976; Kety 1978; Singer, Wynne, and Toohey 1978; Vaughn et al. 1982), a fruitful research concern may be the adaptation of neuronal circuitry to environmental changes. The plasticity of neuronal connections has been studied by subjecting animals to neurosurgical lesions, brain electrostimulation, and a variety of rearing environments. Each of these experimental paradigms has yielded morphological and biochemical evidence of synaptic reorganization. Neuroscientists have yet to define a precise role for neural plasticity in normal nervous system function (Lund 1978). However, some authors are already quite enthusiastic about the possibilities:

It appears that reactive synaptogenesis and other forms of plasticity provoked by denervation are not simply capacities reserved for repair, but may represent a display of an inherent brain plasticity. There are instances where it appears as if synapse formation can take place in the adult brain without denervation. It may turn out that synaptogenesis in the adult brain is an ongoing process which can be externally influenced by specific factors which mimic the effects of denervation... neuronal circuitry at all levels of the neuraxis is modifiable. It appears as if the structural plasticity of neuronal circuitry is a very powerful capability which we are only beginning to appreciate. [Cotman 1978, p. vi]

The present article briefly reviews the neural plasticity literature, particularly for the benefit of physicians and researchers in the field of biological psychiatry who are, perhaps, unfamiliar with these recent advances in basic neuroscience. The newly emerging principles of neural plasticity are then employed in an approach to the schizophrenia research literature. An attempt is made to gain a perspective that might be useful in the search for pathophysiological mechanisms underlying schizophrenia. It is anticipated that research in biological psychiatry may be facilitated by the adoption of a theoretical orientation which takes into account the plasticity of neuronal connections (see, also, Haracz 1984).

Brief Orientation to Neural Plasticity Research

Neural plasticity has been defined teleologically as an attempt of the nervous system to adjust the constraints imposed by the internal and external milieu (Vital-Durand 1975). In attempting to provide a phenomenological definition, it becomes obvious that the term subsumes a variety of phenomena. Most conveniently, these phenomena can be classified according to their temporal durations (i.e., short- or long-term). In general usage, short-term plasticity denotes the modulation of the transmission efficacy of existing synapses, whereas long-term plasticity might also include the formation or degeneration of synapses (Konorski 1968; Bloom 1970; Cotman and Nadler 1978; Lund 1978; Bliss 1979; Jones and Smith 1980). Thus, the term "neural plasticity" refers to the capacity of the nervous system to exhibit structural and functional adaptations to impinging stimuli.

Homosynaptic depression, presynaptic facilitation, and other types of short-term plasticity have been intensively studied with electrophysiological methods in simple invertebrate systems (Kandel 1979). The brains of humans (Babb 1982) and lower mammals (Alger and Teyler 1976; Teyler and Alger 1976; White, Nadler, and Cotman 1979) exhibit qualitatively similar forms of short-term response plasticity. These effects last for only a few milliseconds to several seconds following nonionizing electrostimulation. Due to its seemingly transient nature, short-term plasticity is not further considered in the present report.

Long-term neural plasticity typically has been induced by three kinds of experimental manipulations: (1) young animals are reared in different visual and general sensory environments; (2) discrete nerve tracts in the brain are lesioned; (3) electrostimulation is directly applied to the brain. Each of these procedures has characteristic neurobiological and behavioral consequences; thus they are described separately.

Environmentally Induced Plasticity. Environmental effects on the brains of young animals can, perhaps, be best appreciated when the normal events of brain development are kept in mind. Prenatal brain development proceeds almost exclusively according to genetic factors, and is interrupted only by severely noxious stimuli such as malnutrition, physical trauma, and the transplacental action of drugs (Reinis and Goldman 1980).
Most neuronal formation in rats is completed prenatally, although considerable postnatal neurogenesis occurs in the olfactory bulb, hippocampus, and cerebellum (Bayer and Altman 1975; Heineisen 1977; Bayer 1982; Bayer, Yackel, and Puri 1982). The nervous system appears to be genetically programmed to produce an excessive number of neurons and synapses (Purves and Lichtman 1980). Neuronal deaths vary from region to region, but as much as one half of the cells may be lost during development (Crouse and Cucinotta 1965; Cowan 1973; Crossland, Cowan, and Rogers 1975; Hamburger 1975). Synapse and cell survival depends on several factors: proper cell migration, the sending of axons to correct target zones, and successful competition for postsynaptic sites and/or trophic factors (Clarke and Cowan 1975, 1976; Hendry and Campbell 1976; Landmesser and Pilar 1976).

Associational, callosal, and thalamic fibers arrive at their target zones in monkey cerebral cortex during the last third of gestation (Goldman and Galkin 1978; Rakic 1979; Goldman-Rakic 1981, 1982). However, a great deal of synapse formation is delayed until the early postnatal period in monkeys and lower animals (Aghajanian and Bloom 1967; Cragg 1972, 1975b; Crain et al. 1973; Tennyson et al. 1973; Lauder and Bloom 1975; Wise and Jones 1976; Lund, Boothe, and Lund 1977; Lund and Mustari 1977; Vrensen, De Groot, and Nunes-Cardozo 1977; Boothe et al. 1979; Buchwald et al. 1981). These studies indicate that the maximum synaptic density and number of synapses per neuron is reached postnatally in cortical and subcortical areas. Dendritic spine frequency in monkey visual cortex peaks in infancy and then declines until adulthood (Lund, Boothe, and Lund 1977; Boothe et al. 1979).

In agreement with the animal studies, human neonates have many morphologically immature synapses in layer III of frontal cortex (Huttenlocher 1979). In a post-mortem study of normal human brains, frontal cortical synaptic density increased during infancy and peaked at 1 to 2 years of age (Huttenlocher 1979). Thereafter, frontal synaptic and neuronal density declined until the adult condition was reached at 16 years of age. In human visual cortex, the decline to the adult level of synaptic density is completed earlier (at about age 11 years) than in frontal cortex (Huttenlocher et al. 1982). Huttenlocher (1979) concluded that human cerebral cortex is one of a number of neuronal systems in which loss of neurons and synapses appears to occur as a late developmental event. Noting the frequency of schizophrenic onset in adolescence, Feinberg (1982, 1982/1983) proposed that schizophrenia may result from a defect in the synaptic elimination programmed to occur during adolescence.

Since the brain undergoes much postnatal maturation, recent theorization has implicated the organism's postnatal environment as a regulator of brain development. Altman (1967) and Jacobson (1974) proposed that Golgi II neurons, which are greatly modified after birth, could be especially susceptible to environmental influences. With regard to specific mechanisms, Lund (1978) and Singer (1979) suggested that environmentally activated pathways may form more synapses or undergo a consolidation of transmission efficiency while inactive pathways may lose synapses or efficiency. The proposals of Lund and Singer derive some support from a study of long-term monocularly deprived monkeys (Hubel, Wiesel, and LeVay 1977). When monkeys are raised with one eyelid sutured shut, a marked imbalance develops in the afferents from the lateral geniculate nucleus to the visual cortex. Autoradiographic labeling of axonally transported protein reveals that the geniculocortical projection corresponding to the open eye predominates over that of the closed eye.

Both monocular and binocular visual deprivation produces deficits in the density of visual cortical synapses and dendritic spines (Cragg 1969, 1975a; Ruiz-Marcos and Valverde 1969; Fifkova 1970c; Creutzfeldt and Yinon 1978; Rothblat and Schwartz 1979; Pecci-Saavedra et al. 1982). Accompanying the neural changes are aberrations in visual acuity and visuomotor behavior (von Noorden 1973; Regal et al. 1976; Tees 1976; van Hof-Van Duin 1976; Schwartz and Rothblat 1980; Emerson et al. 1982; Mower, Caplan, and Letsou 1982). Physiological, anatomical, and behavioral studies indicate that the neuronal connectivity of the visual system is highly susceptible to deprivation effects only during a critical period in development (Dews and Wiesel 1970; Hubel and Wiesel 1970; Yinon 1978; Rothblat and Schwartz 1979). Even in adulthood, though, visual deprivation can induce gross decreases in the volume of the lateral geniculate nucleus and the thickness of the visual cortex, as well as alterations in the physiological responsiveness of visual cortical cells (Fifkova 1970c; Creutzfeldt and Heggelund 1975; Singer 1979).

Different levels of general sensory stimulation can also have striking effects on brain development. In order to control the complexity of the general sensory environment, rats are raised under so-called "enriched" (EC), "impoverished" (IC), or "standard" conditions (SC) (Rosen-
From birth through old age, the later the EC/IC separation is begun, the less the brain responds to the differential environments (Malkasian and Diamond 1971; Riege 1971; Diamond et al. 1972; Fiala, Joyce, and Greenough 1978). However, environmental separation begun in adulthood can still lead to significant differences in cerebral cortical weight and thickness, dendritic length and spine density, total dendritic material per neuron, acetylcholinesterase activity, RNA/DNA ratio, and maze-learning ability (Bennett et al. 1964; Riege 1971; Diamond et al. 1972; Cummins et al. 1973; Uylings et al. 1978; Uylings, Kuypers, and Veltman 1978; Connor and Diamond 1981; Connor et al. 1981, 1982; Green, Schlumpf, and Greenough 1981; Chang and Greenough 1982; Connor, Wang, and Diamond 1982). These results suggest that some brain neurons retain a significant degree of structural plasticity well into adulthood (Green, Schlumpf, and Greenough 1981).

Underlying mechanisms are still unclear, but the EC/IC findings have been interpreted to suggest that IC rats exhibit delayed development of environment-dependent neurons (Jorgensen and Bock 1979) and an enhancement of the normal post-weaning reduction in neuronal number (Cummins, Livesey, and Evans 1977; Cummins and Livesey 1979). EC rats might benefit from a prolonged neurological activation that stimulates a number of metabolic processes (Walsh and Cummins 1975; Walsh 1981). Whatever the mechanisms may be, it seems evident that both visual experience and general environmental complexity can influence brain development:

after birth, the inborn developmental capacity can only be fully realized in a favorable external environment. Both adequate sensory stimulation and some level of participatory involvement in activities are necessary conditions for satisfactory brain development. [Reinis and Goldman 1980, p. 293]

The sensitivity of brain development to environmental conditions is noted below in a discussion of some developmental theories of schizophrenia.

Lesion-Induced Plasticity. The plasticity of the adult mammalian nervous system has been studied using lesioning techniques. In this paradigm, a portion of the neuronal input to a target zone is destroyed neurosurgically. Anatomical, biochemical, and electrophysiological methods are then used to seek evidence for reinnervation of the target zone by neighboring, uninjured afferents. This response (known as "postlesional plasticity," "axonal sprouting," or "reactive synaptogenesis") has been elicited in a number of regions in the mature central nervous system (CNS), including the ventral cochlear nucleus (Gentschev and Sotelo 1973), nucleus gracilis (Rustioni and Sotelo 1974), superior colliculus (Lund and Lund 1971), lateral geniculate nucleus (Stenevi, Bjorklund, and Moore 1972), cerebral cortex (Rutledge 1978), cerebellum (Chen and Hillman 1982), hippocampus (Lynch, Deadwyler, and Cotman 1973), red nucleus (Nakamura et al. 1974), and septal nuclei (Raisman 1969; Moore, Bjorklund, and Stenevi 1971). Chemically induced lesions, such as those produced by the injection of kainic acid or 6-hydroxydopamine, also appear to evoke postlesional plasticity (Cotman 1979; Acheson, Zigmond, and Stricker 1980).

The noncommittal term "postlesional plasticity" is used here because it has not yet been possible to determine if this form of plasticity occurs by collateral sprouting,
paraterminal sprouting, contact synaptogenesis, or some other theoretically possible mechanism (Cotman and Nadler 1978). What seems clear is that unlesioned afferent fibers can reinnervate a zone that has lost another convergent input. For example, the septal nuclei receive a catecholaminergic input from the medial forebrain bundle and a noncatecholaminergic input from the hippocampus via the fimbria. Following destruction of the hippocampal input, electron microscopy and fluorescence histochemistry reveal that the medial forebrain bundle increases its innervation of the septal nuclei (Raisman 1969; Moore, Bjorklund, and Stenevi 1971; Raisman and Field 1973; Moore 1974). Thus, it appears that postlesional plasticity need not be neurotransmitter-specific since catecholaminergic fibers might be innervating postsynaptic elements that had formerly received cholinergic contacts (Raisman and Field 1973). In this case it is not clear if the reinnervating presynaptic fibers come to occupy vacated postsynaptic sites or if entirely new synapses are generated.

A few recently uncovered principles of postlesional plasticity are outlined in the succeeding paragraphs. Especially important is the principle that postlesional plasticity does not represent a generalized growth response by all nearby surviving fibers. Instead, reinnervation is accomplished by selected afferents. The selectivity may be influenced by axonally transported trophic factors as well as the proximity and growth rates of surviving afferents. Additionally, it is shown below that synaptogenesis in the mature brain (1) is not dependent upon the destruction of neuronal elements and (2) results in functional synapses.

Unilateral fimbriectomy demonstrates that lesioned afferents may be preferentially replaced by a particular surviving input (Field, Coldham, and Raisman 1980). When one fimbria is cut, the septum is reinnervated only by the contralateral fimbria even though nonfimbrial fibers are capable of reinnervating the septum after bilateral fimbriectomy. Selective postlesional plasticity has also been observed in the hippocampal formation. After an afferent to a dentate granule cell is lesioned, reinnervation is accomplished only by normally existing inputs to the cell (Cotman 1979). The reinnervating presynaptic fibers may grow outside their normal dendritic field, but they do not innervate a new cell type. Proximity to the denervated zone influences the selection of reinnervating afferents since sprouting fibers usually travel less than 250 μm (Steward, Cotman, and Lynch 1976; Jacobson 1978). However, proximity is not a sufficient condition for reactive growth inasmuch as all nearby afferents do not respond (Cotman and Nadler 1978). The selectivity of reinnervation may also be due to a temporal preference based on the relative rates of response of the different afferents (Field, Coldham, and Raisman 1980). Finally, the analysis of hippocampal extracts (Crutcher and Collins 1982) and colchicine-induced synaptogenesis (Goldowitz and Cotman 1980) suggests that trophic or growth factors may help ensure the specificity of postlesional plasticity. The latter observation also indicates that the degeneration of neuronal elements is not a prerequisite for synaptogenesis in the mature brain.

Evidence for synaptic reorganization in the absence of neuronal degeneration has also been found in the red nucleus of adult cats. Red nucleus cells are characterized by the discrete lamination of their two major synaptic inputs. The cerebellar afferent terminates on the somatic portion of the cell membrane, while the input from the sensorimotor cortex forms synapses on the distal dendrites. After the cerebellar afferent is surgically lesioned, anatomical and electrophysiological evidence suggests the formation of new axosomatic synapses by the corticorubral fibers (Nakamura et al. 1974; Hanaway and Smith 1978; Nakamura, Mizuno, and Konishi 1978; Tsukahara 1978, 1981; Murakami et al. 1982; Tolbert, Marshall, and Murphy 1982). Ten or more days following surgery, electrostimulation of the sensorimotor cortex reveals that the corticorubral pathway has become more effective in producing excitatory postsynaptic potentials (EPSPs) in red nucleus cells. Tsukahara (1978, 1981) concluded that this elevated transsynaptic drive could be best explained by the formation of new corticorubral synapses on the denervated somas of red nucleus neurons.

A similar postoperative increased corticorubral drive was found after the cross-innervation of peripheral nerves (Tsukahara and Fujito 1976; Tsukahara 1978, 1981; Fujito et al. 1982; Tsukahara et al. 1982). In these studies, the forelimb nerves of cats were cut and resutured so that formerly flexor and extensor nerves were innervating the opposite type of muscle. Electrophysiological evidence of corticorubral synaptic reorganization was found even though it is unlikely that the cross-innervation caused any large-scale degeneration of the cerebellorubral pathway. It seems that a disorganization in the physiological activity of the cerebellorubral afferent was sufficient to induce corticorubral plasticity. In addition, the elevated corticorubral...
drive after cross-innervation or cerebellar lesioning provides evidence that newly formed corticorubral synapses are functionally effective.

Functional postlesional plasticity has also been reported following the lesioning of specific afferents to the hippocampal formation. Microscopically, new synapses appear at 5 days after lesioning, but the most rapid phase of synaptogenesis occurs between 9 and 30 days (Cotman and Nadler 1978). Electrophysiological studies show that the nascent synapses first become functional at 9 days postoperatively, and nearly all are functional at 15 days (Lynch, Deadwyler, and Cotman 1973; Cotman and Nadler 1978).

The functional effectiveness of the newly formed synapses hints at a role for postlesional plasticity in the recovery of behavioral function after brain injury. Following entorhinal cortex lesions, correlations have been reported between hippocampal reinnervation and the reversal of performance deficits (Loesche and Steward 1977; Schell and Cotman 1977; Steward, Loesche, and Horten 1977). As an organism ages, there is a decline in the capacity for both postlesional plasticity and postinjury behavioral recovery (Cotman and Schell 1979; Schell, Benardo, and Cotman 1980; Gall and Lynch 1981).

On the other hand, postlesional plasticity has occasionally seemed more likely to impede the recovery of function (Raisman 1969; see discussion by Jacobson 1978). Thus, some authors suggest that the mechanisms underlying postlesional plasticity may have some primary purpose other than the repair of lesions (Moore, Björklund, and Stenevi 1971; Cotman, Nieto-Sampedro, and Harris 1981). According to this view, there may be a continuous turnover of synaptic elements in the intact mature brain.

This proposal receives some support from observations of altered, and possibly regenerating, axon terminals in normal animal brains (Clemente 1964; Hashimoto and Palay 1965; Sotelo and Palay 1971; Van Houten and Brawer 1978; Jones 1982). Spontaneously degenerating dopaminergic nerve fibers were found in neostriatal brain regions of control rats that had only received subcutaneous saline injections (Lorez 1981). Furthermore, adult male canaries exhibit seasonal differences in the volume of two telencephalic song control nuclei, suggesting an annual cycle of synaptic degeneration and regeneration (Nottebohm 1981). Ongoing synaptic regeneration may potentially be related to learned behaviors (Nottebohm 1981). However, synaptogenesis has yet to be conclusively demonstrated in the unmanipulated mature brain (Cotman, Nieto-Sampedro, and Harris 1981). Recent ultrastructural evidence is suggestive of cyclical synaptogenesis in the supraoptic nucleus in correspondence with the rat reproductive cycle (Theodosius and Poulain 1984).

The brain's capacity to exhibit postlesional plasticity is also addressed in a later section which discusses theories relating schizophrenia to early developmental brain lesions.

Electrostimulation-Induced Plasticity. The mature mammalian brain also exhibits long-term neural plasticity following repetitive electrostimulation. A series of neurophysiological and behavioral events develop when certain brain sites are stimulated once daily with a brief train of electrical impulses. Initially, there is a marked potentiation of the postsynaptic electrophysiological response to a single test pulse. This phenomenon, referred to as "long-term potentiation" (LTP), is frequently discussed as an experimental model of long-term memory (Goddard and Douglas 1975; Bliss 1979; Eccles 1979; Levy and Steward 1979; Lynch, Browning, and Bennett 1979; Teylew and Discenna 1984). If the same daily electrostimulation regimen is continued, the animal eventually develops generalized motor seizures. This so-called "kindling" phenomenon has been cited as a possible model of epilepsy (Wada, Sato, and Corcoran 1974; Pinel and Van Oot 1975; Goddard 1980; McNamara et al. 1980; Girgis 1981; Kalichman 1982). Thus, the repetitive electrostimulation paradigm is purported to have relevance to both physiological and pathological brain function.

A chronic electrostimulation experiment is carried out with stimulation and recording electrodes implanted extracellulary in the brains of freely moving animals. Recording electrodes are placed in brain sites that are postsynaptic to the stimulated region. Mapping studies indicate that the LTP and kindling phenomena are especially demonstrable in limbic regions (Goddard, McIntyre, and Leech 1969; Racine, Milgram, and Hafner 1983). Hippocampal pathways show the strongest and longest-lasting LTP effects, although a number of pathways throughout the limbic forebrain also exhibit LTP (Racine, Milgram, and Hafner 1983).

Repetitive electrostimulation typically consists of a single daily pulse train lasting one to two seconds (methodological details are reported by Goddard, McIntyre, and Leech 1969; Racine 1972a, 1972b; Teylew and Discenna 1984). Low-intensity current is applied such that the first day's kindling train generally does not produce any behavioral response (Goddard, McIntyre, and Leech...
LTP is tested for by applying a single electrical pulse through the same stimulation electrode before and after the kindling trains. Douglas and Goddard (1975) found a potentiated postsynaptic response when a test pulse was applied 24 hours after the first kindling train (i.e., just before the next train). Additional daily kindling trains led to further potentiation of the hippocampal extracellular EPSPs and population action potentials (APs) evoked by test pulses. This type of potentiation may develop simultaneously in several neural pathways. For example, daily stimulation of the amygdala resulted in an enhancement of transmission through all amygdalofugal pathways tested (Racine, Gartner, and Burnham 1972). Potentiated evoked responses were recorded in the frontal cortex, hippocampus, preoptic area, and ventromedial nucleus of the hypothalamus.

The enduring nature of LTP is revealed by reapplying a test pulse long after kindling stimulation has ceased. In this way, potentiation of the hippocampal population EPSP was shown to last at least 2 months after the cessation of daily entorhinal cortex stimulation (Douglas and Goddard 1975). On the other hand, continuation of the daily pulse trains eventually results in the triggering of a sustained after-discharge (AD) (Racine 1972a). An AD is a prolonged epileptiform potential that may be accompanied by the firing of APs for many seconds after the applied pulse train is stopped (Racine, Gartner, and Burnham 1972). At this point it is apparent that the AD threshold of the stimulated structure has been reduced since a previously subthreshold stimulus intensity is now capable of firing an AD. As is discussed below, the AD threshold reduction, or "partial kindling," of a limbic region can be attended with long-lasting changes in animal behavior. After kindling stimulation is stopped, the AD threshold remains at the same decreased level for at least 100 days (Racine 1972a).

Maintaining daily stimulation past the point of partial kindling causes a change in the waveform of the AD, as well as an increased AD duration and amplitude (Racine 1972b). Brief behavioral automatons appear and then grow in severity with each successive stimulation until electrographic and behavioral seizures are elicited. Completion of the kindling procedure grants the animal an apparently permanent elevation in seizure susceptibility. Epileptic seizures can still be triggered when baboons are restimulated over 2 years after the last kindling stimulus (Wada 1980). Alternatively, animals can be made to develop spontaneous seizures if the kindling process is continued after stimulation-induced seizures have appeared (Wada, Sato, and Corcoran 1974; Pinel, Mucha, and Phillips 1975). This state of "kindling-induced epileptogenesis" has been offered as an animal model of human epileptic conditions (Pinel and Van Oot 1975; Wada, Osawa, and Mizoguchi 1975).

It seems clear that the LTP and kindling phenomena are associated with an elevated efficiency of transmission across the synapses of the stimulated pathways (Racine, Okujava, and Chipashvili 1972; Bliss and Lomo 1973; Douglas and Goddard 1975; Lynch, Browning, and Bennett 1979; Goddard 1980). However, information on the mechanism of this transsynaptic potentiation has only recently begun to accumulate. Experiments using radiolabeled neurotransmitters indicate that the development of hippocampal LTP is correlated with an increased electrically evoked presynaptic release of neurotransmitter (Skrede and Malthe-Sorensen 1981; Dolphin, Errington, and Bliss 1982) and an elevated postsynaptic binding of neurotransmitter (Baudry and Lynch 1979; Baudry et al. 1980; Lynch, Halpain, and Baudry 1982).

Two laboratories have reported that the calcium-dependent phosphorylation of a synaptic membrane protein may be involved in hippocampal LTP production (Browning et al. 1979; Dunwiddie and Lynch 1979; Lynch, Browning, and Bennett 1979; Bar et al. 1980, 1982). LTP has also been correlated with an increased synthesis of synaptic proteins (Duffy, Teyler, and Shashoua 1981; Shashoua and Teyler 1982). Morphological studies of hippocampal LTP demonstrate a swelling of dendritic spines (Van Harreveld and Fifkova 1975; Fifkova and Van Harreveld 1977; Fifkova and Anderson 1982; Fifkova et al. 1982) and an elevated number of synaptic contacts on dendritic shafts (Lee et al. 1979a, 1979b, 1980; Chang and Greenough 1984). Repetitive stimulation of the cerebral cortex produced a number of changes in pyramidal cells, including an enhancement of apical dendritic branching and increased numbers of dendritic spines (Rutledge, Wright, and Duncan 1974). Continued application of the LTP paradigm should help to elucidate the neurobiological mechanisms of synaptic potentiation.

Although repetitive stimulation ultimately produces seizures, the mechanism underlying the synaptic potentiation is not dependent on epileptic activity. Both LTP and partial kindling can be induced by repetitive stimulation which does not elicit AD or seizures (Racine 1972a; Douglas and Goddard 1975). Thus, it is conceivable that the physiological repetitive firing of neurons could...
trigger a natural LTP-like process. Lynch, Gall, and Dunwiddie (1978) noted that the experimental stimulation parameters are not unlike events encountered in the behaving animal. Hippocampal recordings show that many cells do discharge at high frequencies for nearly a second when a rat is in the process of learning various behaviors.

A hypothetical link between learning and LTP-like processes is supported by reports of learning-dependent changes in hippocampal cell-firing patterns (Berger and Thompson 1978a, 1978b; Deadwyler, West, and Lynch 1979a, 1979b; Patterson, Berger, and Thompson 1979; Berger, Laham, and Thompson 1980; Berger 1982; Berger and Thompson 1982; Thompson 1982b). For example, hippocampal cells begin to respond differentially to rewarding and nonrewarding stimuli following the acquisition of a discrimination task (Lynch, Gall, and Dunwiddie 1978). Transmission across hippocampal synapses is potentiated during behavioral conditioning (Jaffard and Jeantet 1981; Ruthrich, Matthies, and Ott 1982; Thompson 1982a). Furthermore, repetitive electrostimulation of the hippocampus facilitates the acquisition and retention of behavioral tasks (Campbell and Milgram 1980; Soumireu-Mourat et al. 1980; Gauthier, Soumireu-Mourat, and Destrade 1980). Aged, memory-deficient rats are also deficient in the production of synaptic potentiation following hippocampal stimulation (Landfield, McGaugh, and Lynch 1978; Barnes 1979). In addition to the above observations, the rapid onset and extreme persistence of LTP make it an attractive model of long-term memory (Goddard and Douglas 1975; Bliss 1979; Eccles 1979; Levy and Steward 1979; Lynch, Browning, and Bennett 1979; Teyler and Discenna 1984).

Other studies have shown that the kindling procedure can produce long-lasting changes in behavior. In humans, nonepileptogenic repetitive stimulation of the amygdala yielded enduring alterations in affective behavior (Stevens et al. 1969). Complete kindling of the amygdala or hippocampus increased escape behaviors in rats (Pinel, Treit, and Rovner 1977). Lasting increases in the defensive behaviors of cats were found after the partial kindling (i.e., AD threshold reduction) of the basolateral amygdala (Adamec 1975a) and hippocampus (Adamec and Stark-Adamec 1983a, 1983b). An analysis of electrically evoked potentials suggested that the behavioral changes were mediated by a lasting synaptic potentiation in specific limbic pathways (Adamec 1975a; Adamec and Stark-Adamec 1983b).

Since the electrostimulation-induced potentiation of pathways appears capable of mediating lasting behavioral changes, it seems possible that physiological potentiating mechanisms may underlie natural behavioral differences in animals. In support of this notion, the natural transmission efficiencies of limbic pathways were found to vary systematically with what might be described as "personality" characteristics of cats (Adamec 1975a, 1975b; Adamec and Stark-Adamec 1983c). Upon single-pulse stimulation of the amygdala, the most defensive cats exhibited the greatest evoked synaptic responses in the ventromedial hypothalamus and relatively small responses in the ventral hippocampus. Perforant path stimulation also evoked relatively low ventral hippocampal synaptic responses in defensive cats. Aggressive cats showed the opposite pattern of evoked potentials in each of the three limbic pathways. These data are in logical agreement with previous electrostimulation and lesioning experiments which indicated that an amygdalo-hypothalamic pathway tonically inhibits feline aggressive behavior, while the ventral hippocampus facilitates aggression (Egger and Flynn 1967; Flynn et al. 1970; Adamec 1974). Thus, it appears that aggressive cats have a naturally enhanced transmission efficiency in pathways that facilitate aggression. Adamec and Stark-Adamec (1983c, p. 279) concluded that "it is likely that some form of LTP underlies naturally occurring behavioral differences between aggressive and defensive cats." The following section discusses potential links between LTP-like mechanisms and the development of pathological behaviors in animals and man.

Neural Plasticity and Schizophrenia: Convergent Hypotheses

Since a rigorous study of neural plasticity has only recently begun, the limitations of the involved mechanisms are yet to be established. However, the preceding paragraphs illustrate how neural plasticity might be invoked to explain the enduring behavioral effects of environmental and experiential factors. The present section evaluates the explanatory potential of neural plasticity concepts in relation to human psychopathology, particularly schizophrenia. Various aspects of the schizophrenia research literature are approached in a necessarily speculative fashion.

Pharmacological and Biochemical Studies. The introduction to this article briefly summarized the major pharmacological and biochemical findings pertaining to the DA hypothesis of schizophrenia; viz. the
pharmacological evidence for a dopaminergic hyperactivity has not been compellingly borne out by studies of DA function in schizophrenic subjects (reviewed by Haracz 1982). If compelling biochemical evidence for a dopaminergic dysfunction is not forthcoming, then the disparity between the pharmacological and biochemical data will require explanation. One possible resolution could be provided by the occurrence of potentiating mechanisms at dopaminergic synapses. LTP-like processes might allow a functional dopaminergic hyperactivity in the face of a relatively normal DA turnover. Post and his associates have suggested that catecholaminergic pathways in the limbic system may become potentiated following their repetitive activation by stressful events (Post and Kopanda 1976; Post, Kopanda, and Black 1976; Post 1977). It was further proposed that this type of potentiation provided a possible mechanism by which repeated psychological stresses in man could become associated with progressive increases in psychopathology and potentially in the development of psychosis. Similarly, van Kammen, Docherty, and Bunney (1982) suggested that excessive aversive stimuli could lead to increased dopaminergic activity in man and subsequently to psychotic decompensation in vulnerable individuals.

The above suggestions are consistent with the following four types of experimental evidence:

1. Subjecting animals to electric foot-shocks demonstrates that mesolimbic and mesocortical dopaminergic neurons are activated by stress (Thierry et al. 1977; Blanc et al. 1980; Reinhard, Bannon, and Roth 1982). (2) The repetitive administration of DA agonists induces a progressive disruption of behavior in animals and man: Animals develop increasingly severe “stereotypic” behaviors, such as sniffing, rearing, and purposeless searching movements (Segal and Mandell 1974; Klawans and Margolin 1975; Borison, Havdala, and Diamond 1977; Kilbey and Ellinwood 1977; Smith et al. 1977; Antelman et al. 1980; Akiyama, Sato, and Otsuki 1982); normal human volunteers receiving amphetamines develop a psychosis that closely resembles the acute paranoid type of schizophrenia (Angrist et al. 1974, 1977).

2. Repetitive electrostimulation of mesolimbic dopaminergic neurons in cats leads to the progressive onset of a behavioral syndrome that includes fearfulness, hiding, staring, and loss of social behavior (Stevens and Livermore 1978).

3. Repetitive stressful experience and amphetamine can each induce a long-lasting behavioral sensitization to the other, regardless of the order of administration (Eichler and Antelman 1979; Antelman et al. 1980; MacLennan and Maier 1983). Thus, it seems possible that the repetitive activation of dopaminergic systems by either electrostimulation, pharmacological agents, or stressful events could trigger potentiating mechanisms that lead to a gradual deterioration of behavior. This kindling model for progressive behavioral change emphasizes a correlation between behavior and synaptic connectivity. Just as differentially aggressive cats differed naturally in the transmission efficiencies of limbic pathways (Adamec 1975a, 1975b), humans with psychopathology may also have alterations in the functional connectivities of some nerve tracts.

According to Post's (1977) model, various psychotic symptoms may be related to potentiated pathways in different neuroanatomical areas subserving globally different functions. For example, auditory and visual hallucinations might, respectively, be associated with pathologically facilitated pathways in the temporal and occipital lobes. Motor and postural changes, such as stereotypies, waxy flexibility, and catatonia, may indicate the involvement of neostriatal pathways. In this way, a wide variety of clinical phenomena potentially could be accounted for:

Thus a kindling model for the development of pathological behavior is capable of dealing with a changing symptomatology which may be manifest over time in the functional psychoses and does not require a given, discrete neuroanatomical lesion to explain a variety of symptoms and syndromes. [Post 1977, p. 37]

Other authors have proposed that a catecholaminergic hyperactivity in schizophrenia may be produced by an abnormally increased density of catecholaminergic nerve terminals in some brain areas (Hokfelt et al. 1974; Coyle and Johnston 1980). Each of these articles held that such a catecholaminergic hyperinnervation could have developed after a primary lesion in a nearby noncatecholaminergic system. A number of animal studies demonstrating this type of postlesional plasticity have been reviewed above (see text under Lesion-Induced Plasticity). The hyperinnervation hypothesis receives some support from reports of elevated norepinephrine concentrations in CSF and post-mortem brain samples from schizophrenic patients, especially those patients with paranoid features (Lake et al. 1980; for reviews, see Wyatt et al. 1981; van Kammen and Antelman 1984). However, preliminary studies indicated that schizophrenic and control samples did not differ in the post-mortem fluorescence histochem-
istry of catecholamine neurons in cortical and subcortical regions (Olson, Nystrom, and Seiger 1973a, 1973b; Olson 1974). Future tests of the hyperinnervation hypothesis may do well to include a post-mortem examination of the brains of paranoid schizophrenic patients with the fluorescence histochemistry technique.

Studies of Regional Brain Structure and Function. Long-term neural plasticity has been defined earlier as the capacity of the nervous system to exhibit enduring structural and functional adaptations to impinging stimuli. Various experimental approaches have revealed that the structural and functional manifestations of long-term plasticity are neuroanatomically specific. For example, the structural and biochemical effects of altered rearing environments are most readily found in the visual cortices of young rats (Bennett et al. 1964; Diamond et al. 1972). Neurosurgical lesions induce reactive growth only in specific nearby afferent fibers (Cotman and Nadler 1978; Field, Coldham, and Raisman 1980). Repetitive electro-stimulation in the hippocampal formation yields structural and functional changes that are restricted to the synapses of the stimulated pathway. Electrophysiological potentiation (Andersen et al. 1977; Lynch, Dunwiddie, and Gribkoff 1977; McNaughton and Barnes 1977; Dunwiddie and Lynch 1978), enhanced protein synthesis (Duffy, Teyler, and Shashoua 1981), and enlarged dendritic spines (Van Harreveld and Fifkova 1975; Fifkova and Van Harreveld 1977) are all found only at the synaptic sites of the stimulated pathway and not at the synapses of nearby unstimulated afferents. Thus, several workers have concluded that the neurophysiological mechanism underlying LTP is localized at the synapses of the potentiated pathway (Douglas and Goddard 1975; Lynch, Browning, and Bennett 1979).

The findings reviewed above indicate that the structural and functional manifestations of neural plasticity can develop at restricted neuroanatomical sites without any widespread changes over extended brain regions. This property, referred to herein as the "neuroanatomical specificity" of neural plasticity, allows a prediction to be made on the basis of the hypothesis that neural plasticity is involved in the pathophysiology of schizophrenia. Such a hypothesis would seem to require the existence of regional alterations in brain structure and function in schizophrenic patients. This prediction is now addressed in a review of schizophrenia research findings that relate to regional brain structure and function.

Regional neuronal function in human brain has been estimated by examining some of the physiological processes that are coupled to neuronal activity. In animal brains, good correlations have been found between cerebral blood flow, oxygen consumption, and glucose utilization on the one hand, and neuronal activity on the other (Sokoloff 1981a, 1981b, 1981c; Yarovsky and Ingvar 1981). Each of these indices of cerebral energy metabolism is now measurable in the brains of awake humans.

Cerebral blood flow (CBF) and oxygen consumption were first measured in humans with the use of the nitrous oxide method of Kety and Schmidt (1948). This method allowed only an overall estimate of CBF and the cerebral metabolic rate for oxygen (CMRox) without the possibility of regional measurements. Three early studies did not find significant differences in overall CBF between schizophrenic and normal control subjects (Gordan et al. 1955; Sokoloff et al. 1957; Della Porta et al. 1964). Two of these studies also reported that the global CMRox of the schizophrenic subjects was within normal limits (Sokoloff et al. 1957; Della Porta et al. 1964), but Gordan et al. (1955) found a significantly decreased CMRox in a group of 24 chronic schizophrenic subjects.

Hoyer and Oesterreich (1975, 1977) recently applied the nitrous oxide technique to a group of schizophrenic patients who were subtyped according to clinical symptomatology, a strategy not employed in the earlier studies. Compared to 15 normal subjects, overall CBF and CMRox were both nearly doubled and CMRglucose was more than doubled in a group of 16 acutely psychotic schizophrenic subjects with "productive" symptoms such as hallucinations, apprehension, catatonic excitement, and catatonic stupor. Each of the three aforementioned parameters was significantly decreased in 16 patients with "nonproductive schizophrenia" (i.e., patients with "hebephrenia or schizophrenic defects"). Patients with "paranoia or schizophrenia simplex" did not differ from controls in the indices of cerebral metabolism. According to these findings, it appears that global cerebral function can be greatly altered in opposite directions in schizophrenics with predominately "productive" or "nonproductive" symptoms (also referred to, respectively, as "positive" or "negative" symptoms by Crow 1980).

The determination of regional CBF has recently become possible with the development of the intra-arterial
Mathew’s patients maintained the background of this diffuse deficit, normal relatively hyperfrontal regions in the patients. Against the frontal and postcentral cortical deficit present throughout widespread recent studies disclosed a diffuse CBF pattern in Ingvar’s (1980) patients, the more "hypofrontal" CBF pattern in schizophrenia. In contrast to the with subchronic to chronic schizophrenic patients were (i.e., the more negative symptoms), the lower was the flow in the frontal regions of their brains. Elevated flow in postcentral regions was significantly related to cognitive disturbances including hallucinatory activity (i.e., positive symptoms). Each of these CBF patterns differed from the typical “hyperfrontal” circulation found in normal human subjects (Ingvar 1979). Confirming a relationship between CBF and neural activity, the “hypofrontal” CBF pattern in schizophrenic patients was associated with increased slow (delta-wave) electroencephalographic (EEG) activity frontally (Buchsbaum and Ingvar 1982). Ingvar (1980) hypothesized that the CBF abnormalities in schizophrenia are secondary to one or several defects in certain subcortical-cortical projection systems, possibly including the catecholaminergic projections to the cortex.

Using the \(^{133}\)Xenon inhalation technique, Mathew et al. (1981, 1982) and Ariel et al. (1983) measured resting regional CBF in normal controls and a total of 58 patients with subchronic to chronic schizophrenia. In contrast to the “hypofrontal” CBF pattern in Ingvar’s (1980) patients, the more recent studies disclosed a diffuse CBF deficit present throughout widespread frontal and postcentral cortical regions in the patients. Against the background of this diffuse deficit, Mathew’s patients maintained the normal relatively hyperfrontal pattern while Ariel’s patients showed a diminished hyperfrontality (decreased anterior/posterior CBF ratio). Ariel et al. (1983) found that the largest schizophrenic-normal differences in gray-matter CBF were in the anterior (largely frontal) regions. The report by Mathew et al. (1982) of an inverse correlation between postcentral regional CBF and hallucinatory behavior was at variance with the previous finding of increased postcentral blood flow in hallucinating patients (Ingvar 1980). The contrasting results in the above studies might be explained on the basis of differing patient populations: many of Ingvar’s (1980) patients were permanently institutionalized and had been ill for 35 or more years, whereas the patient groups of Mathew et al. (1982) and Ariel et al. (1983) had mean ages of only 26.9 ± 8.9 (SD) and 29.7 ± 10.6 years, respectively.

Differing from the above three research groups (Ingvar 1980; Mathew et al. 1981, 1982; Ariel et al. 1983), Gur et al. (1983) and Berman et al. (1984) found that schizophrenic and normal control subjects did not significantly differ in resting regional CBF. However, the patients of Gur et al. (1983) showed significantly altered hemispheric activation patterns during the performance of cognitive tasks. Control subjects showed asymmetric increases in regional CBF during task performance with larger left hemispheric increases for the verbal task and larger right hemispheric increases for the spatial task. In contrast, schizophrenic subjects displayed symmetric increases in regional CBF for the verbal task and relative left hemispheric increases for the spatial task. The schizophrenic patients of Berman et al. (1984) showed diminished elevations in frontal CBF during a card-sorting task in comparison with normal subjects.

Regional cerebral glucose utilization measurements are now achievable with the use of positron emission computed tomography (PECT) coupled with the \(^{18}\)F-fluorodeoxyglucose technique of Sokoloff (1981a, 1981b, 1981c). Buchsbaum et al. (1981, 1982) recently applied this method to six normal control subjects and eight schizophrenic patients who had not received neuroleptics for at least 2 weeks. The patients exhibited significantly decreased glucose utilization in the frontal cortex and left subcortical central gray matter. Using \(^{11}\)C-labeled glucose, Widen et al. (1981) found significantly decreased frontal-to-temporal cortical ratios of glucose utilization in nine schizophrenic patients compared to two control subjects. Similarly, a comparison with 11 normal controls revealed that 13 schizophrenic patients had significantly lower glucose use in the frontal lobes relative to posterior regions (Farkas et al. 1984). A longitudinal study of one chronic schizophrenic patient suggests that cerebral glucose utilization can covary over time with behavioral symptoms (Farkas et al. 1980). Before neuroleptic therapy, the studied patient had intense auditory and somesthetic hallucinations and difficulty in communicating with others. Compared to normal controls, there was a 40-percent depression in the patient’s regional \(\text{CMR}_{\text{glucose}}\) in the frontal cortex and a higher than normal value in the right temporal and somatomotor cortices. After 4 months of neuroleptic treatment, the patient underwent a moderate recovery and showed increased communication while the regional \(\text{CMR}_{\text{glucose}}\) returned to within 25 percent of normal in the frontal cortex. Following neuroleptic withdrawal, the patient relapsed and
the frontal CMR_{glucose} reverted to the depressed level observed before drug therapy. Thus, both Farkas et al. (1980, 1984) and Buchsbaum et al. (1981, 1982) found low frontal cortical glucose utilization in unmedicated schizophrenic patients, indicating that neuroleptics are not a likely cause of these findings.

Computerized tomographic (CT) scans can also provide information on the density of brain structures. Golden et al. (1980a, 1981) reported that 23 chronic schizophrenic patients showed a significantly decreased overall brain density on CT scans in comparison with 24 normal controls. When regional density was examined, it was found that the density deficit was concentrated primarily in the left frontal lobe of the schizophrenic patients (Golden et al. 1981). This deficit was especially apparent in patients with "process" schizophrenia who showed a poor response to neuroleptic treatment. The density changes in the left frontal lobe were not correlated with age or lifetime neuroleptic usage (Golden et al. 1981; Lyon et al. 1981). The authors speculated that the decreased brain density in schizophrenic patients might be accounted for by atrophied cell bodies or dendritic processes, fewer cell bodies, enlarged sulci, decreased myelination, or decreased glial cells (Golden et al. 1981). The method of Golden et al. (1980a, 1981) might not accurately reveal the density of brain parenchyma since their measurements were influenced by the density of brain ventricles and sulci as well as parenchyma. Using a method that excluded ventricles and sulci, Kanba et al. (1984) reported significantly lower CT brain density in the bilateral frontal and occipital areas of 40 chronic schizophrenic patients as compared to 40 controls. Again, there were no correlations between CT density and age, drug dosage, or duration of illness (Kanba et al. 1984). In contrast to the above reports, Largen et al. (1983) failed to find any CT brain density differences between 19 normal controls and 25 schizophrenic or schizoaffective patients. However, the patient group exhibited significantly more left-right density asymmetries than did the control group. Within the patient group, but not in controls, there were significantly lower densities of both gray and white matter in the left hemisphere than in the right.

The results reviewed above have begun to coalesce into a pattern which suggests that chronic schizophrenia is associated with regional alterations in brain structure and function. Deficits in CBF, glucose utilization, and brain density were found in the frontal cortices of schizophrenics (Farkas et al. 1980, 1984; Ingvar 1980; Golden et al. 1981; Buchsbaum et al. 1981, 1982; Buchsbaum and Ingvar 1982; Mathew et al. 1982; Ariel et al. 1983; Kanba et al. 1984). CBF alterations were also reported in postcentral cortical regions (Ingvar 1980; Mathew et al. 1982; Ariel et al. 1983). Theoretically, these changes could be secondary to regional degenerative pathology, a neuroanatomically specific viral infection, or the regional expression of an inherited biochemical defect among other possibilities. However, regional changes in structure and function might also be derived from an inherent plasticity of mammalian brain. The latter possibility seems to be worth considering since the structural and functional manifestations of neural plasticity can develop at restricted neuroanatomical sites (see the above discussion of the "neuro-anatomical specificity" of neural plasticity).

In addition to the brain density deficits described earlier, controlled CT studies have uncovered four other types of structural abnormalities in subgroups of patients with chronic schizophrenia: enlargement of the lateral cerebral ventricles, enlargement of cerebral cortical sulci, reversal of normal neuroanatomical asymmetries, and atrophy of the cerebellar vermis (Johnstone et al. 1976, 1978; Golden et al. 1980b; Weinberger and Wyatt 1980, 1982; Wyatt et al. 1981; Andreasen et al. 1982; Heath et al. 1982; Luchins, Weinberger, and Wyatt 1982; Nasrallah et al. 1982); however, see Jernigan et al. (1982a, 1982b) and Boronow et al. (1983) for discussions of negative findings. The possible functional significance of these CT findings was examined by clinically comparing subgroups of schizophrenic patients with clear abnormalities to subgroups with normal CT scans. In this way, it was found that the patients with CT evidence of cerebrocerebral atrophy had significantly more neuropsychological deficits than those without such findings. Weinberger and Wyatt (1980, 1982), as well as altered visual and auditory evoked responses in frontal regions (Morihisa and McAnulty 1985). It was also clinically apparent that CT deficits were most prevalent among schizophrenic patients who responded poorly to neuroleptic therapy (Weinberger and Wyatt 1980, 1982; Luchins, Lewine, and Meltzer 1983, 1984; Schulz et al. 1983).

Weinberger and Wyatt (1980) felt that the four different types of CT abnormalities probably involved multiple etiologies since the presence of one of the alterations did not correlate well with the presence of the others. Treatment factors did not seem to be etiologically involved because (1) neither ventricular nor sulcal size appeared related to the
duration of hospitalization or drug treatment (Weinberger and Wyatt 1980, 1982) and (2) significant ventricular enlargement was found in a group of young patients with first-episode schizophreniform disorder (Weinberger et al. 1982). From an etiological standpoint, it is interesting that the CT abnormalities seemed to correlate with premorbid adjustment. Compared to schizophrenic patients with normal CT scans, 21 patients with cerebral atrophy had significantly poorer school and social premorbid adjustment, especially during childhood (Weinberger et al. 1980). This finding led the authors to suggest that the brain structural abnormalities may be the result of early developmental defects (Weinberger and Wyatt 1980, 1982). In the present context, it is tempting to recall that the early development of mammalian brains can be altered by environmental factors (see text under Environmentally Induced Plasticity). The early developmental occurrence of unusual patterns of neural plasticity might be considered, especially in view of the regional nature of the brain structural and functional deficits in schizophrenia as well as the correlation between the structural changes and poor premorbid adjustment. Developmental theories of schizophrenia are further examined in the section that follows.

Developmental Theories of Schizophrenia. The earlier section on environmentally induced plasticity pointed out that the structural and functional development of the brain can be environmentally modified. These effects have been extensively studied in the developing visual system, but are less well studied in the maturing limbic system. Postnatal hippocampal development appears to be influenced by the environment (Jones and Smith 1980), but little is known about environmental effects on other limbic areas that are, perhaps, more directly concerned with the emotional state of the organism (Papez 1937; MacLean 1949; O'Keefe and Nadel 1978).

Some studies of limbic system development are reviewed in the present section and the data are related to certain developmental theories of schizophrenia. A concluding discussion focuses on the hypothesis that psychopathology may be derived from either of two types of aberrations in brain development: (1) alterations in the development of dopaminergic neurons or (2) activation of LTP-like mechanisms during development.

Developmental theories of schizophrenia place special emphasis on an evolution of psychopathology that follows general rules of personality development and learning. A developmental theorist would claim that the main prognostic variables in schizophrenia are not characteristics exclusive to that disorder, but are common human traits with important developmental roots that can reach back into earliest childhood (Strauss et al. 1978). Such prognostic indicators would include family characteristics, psychodynamic conflicts, premorbid social functioning, work history, and social class (Vaughn and Leff 1976; Lidz 1978; Strauss and Carpenter 1981).

These types of developmental variables would be not only prognostic indicators, but also etiological agents according to developmental theory. In this view, adverse environmental factors leave the potential schizophrenic with a psychosocial deficit that eventually leads to a schizophrenic break when heightened developmental demands cannot be met. The evolution of schizophrenia could be further described as follows:

The genetic components of vulnerability to schizophrenia are inevitably shaped from conception onward throughout development as the result of transactions of the individual with the psychosocial and physical environment. . . . Constitutional and experiential influences recombine in each developmental phase to create new biologic and behavioral potentials which then help determine the next phase. [Wynne 1978, p. 704]

In a similar vein:

A working hypothesis for the mechanism of the impairment in the functions of the cerebral hemispheres of patients with schizophrenia may be suggested. Neuronal excitation and alterations in the patterns of neuronal activity during faulty adaptation [to the environment], if sustained could lead to persistent disorganization of neural patterns . . . prolonged disorganization of neural patterns would further interfere with proper interaction [with the environment] and perpetuate a cycle that could lead to long-lasting impairment. [Chapman, Hinkle, and Wolff 1960, p. 201]

The above quotes demonstrate that developmental theories leave considerable room for biological influences in schizophrenia, although little attempt is made to postulate specific biological mechanisms. More recently, the postnatal development of the brain has been described as a biological issue that has great relevance to a developmental view of schizophrenia. Some authors have suggested that emotionally stressful experiences during early development could leave a lasting impression on CNS circuitry and, thereby, predispose the person to future psychopathology (Post 1977; Hubel 1978; Brody 1981; Schefflen 1981). In this manner, Brody (1981) and Schefflen (1981) speculated that the mother-infant
relationship might have an especially significant impact on vulnerability to schizophrenia. With the use of general systems theory, Schefflen (1981) has eloquently argued that postnatal brain development could ultimately be affected by events at the societal, familial, interpersonal, and intrapersonal (psychological) levels. This complex web of mutually interacting factors was proposed to be capable of altering postnatal dendritic proliferation and synaptogenesis, with the result being an enhanced vulnerability to schizophrenia. Kafka et al. (1980) also suggested that patterns of synapse formation, including the extent and location of axonal and dendritic terminal arborizations, may have been altered in schizophrenia by the actions of environmental stressors. Thus, a biological foundation for developmental theories of schizophrenia might be derived from the environmental sensitivity of postnatal brain development.

Alterations in the development of dopaminergic neurons. The postulated developmental brain defect in schizophrenia could be specified even further by theoretically linking it with the DA hypothesis of schizophrenia. In this view, the dopaminergic projections would be considered as potential sites of developmental defects.

The genesis of catecholaminergic neurons occurs early in the prenatal development of animals and man (Olson and Seiger 1972; Cochard, Goldstein, and Black 1978; Levitt and Rakic 1979, 1982; Pearson, Brandeis, and Goldstein 1980). However, animal studies demonstrate that these neurons undergo extensive postnatal maturation. Histofluorescence microscopy and measurements of regional catecholamine content, uptake, and receptor binding all reflect the postnatal proliferation of catecholaminergic terminals in cortical and subcortical areas of catecholaminergic innervation (Loizou and Salt 1970; Loizou 1972; Porcher and Heller 1972; Tennyson et al. 1973; Nomura, Naitoh, and Segawa 1976; Coyle 1977, 1982; Goldman-Rakic and Brown 1982). Several biochemical indices of dopaminergic innervation in the rat striatum do not approach adult levels until 3 to 4 weeks of age (Coyle 1977). Ultramicroscopic observation of the formation of synapses onto catecholaminergic cells reveals that most of this synaptogenesis occurs postnatally and continues into adulthood in the rat (Lauder and Bloom 1975). Lesioning experiments suggest that intact mesolimbic dopaminergic neurons are essential for the normal ontogeny of social, locomotor, and consummatory behaviors (Smith, Cooper, and Breese 1973; Burt et al. 1981; Heller et al. 1981). Therefore, an altered postnatal development of dopaminergic neurons might be expected to have important behavioral consequences.

It recently was concluded that brain dopaminergic systems also mature relatively late in humans (Leckman et al. 1980). CSF levels of homovanillic acid (HVA), a DA metabolite, were negatively correlated with age in a large heterogeneous group of child and adult psychiatric patients. The authors suggested that the maturation of brain DA centers occurs during late childhood or adolescence, and is associated with falling rates of DA turnover that eventually plateau in early adulthood (Leckman et al. 1980). It was further hypothesized that critical brain DA systems never fully mature in some schizophrenic patients (Leckman, Bowers, and Sturges 1981). This proposal was supported by the finding that schizophrenic patients with poor premorbid sexual adjustment had significantly higher CSF HVA levels than better adjusted schizophrenic patients.

Thus, an aberration in the postnatal development of dopaminergic neurons may be related to the elevated DA turnover rates and poor sexual adjustment in some schizophrenic patients (Leckman, Bowers, and Sturges 1981).

Activation of LTP-like mechanisms during development. Postnatal brain development could also be modified, at least hypothetically, by the occurrence of LTP-like processes. Early experiential factors might repetitively activate and, eventually, potentiate certain behaviorally important neural pathways. Some credibility can be ascribed to this notion on the basis of studies related to the development of feline predatory behavior. The neural correlates of adult feline predatory behavior were previously reviewed (see Electrostimulation-Induced Plasticity). Compared to rat-killers, adult non-rat-killing cats demonstrated a naturally enhanced efficacy of transmission in pathways that inhibit predatory behavior (Adamec 1975a, 1975b; Adamec and Stark-Adamec 1983c). This differential transmission efficacy may have originated during early development since it was found that the development of feline predatory behavior could be modified by early experience (Adamec, Stark-Adamec, and Livingston 1980a, 1980b). In this study, the level of predatory behavior exhibited by individual adults was apparently determined by such early experiential factors as exposure to dead prey and competition from littermates. Unfortunately, these differentially behaving adult cats were not studied electrophysiologically to determine whether they also exhibited differential limbic transmission efficacies as in the
dopaminergic systems may be a stress-induced potentiation of Preussler (1984), it follows that the al., 1977; Blanc et al. 1980; Reinhard, mesolimbic DA neurons (Thierry et this implies that differences in early experience could account for the various levels of predatory behavior and neural excitability seen in adults. The adult behavioral and neural effects might be generated by the potentiation of specific pathways during development.

In a similar manner, Post proposed that repetitive stressful experiences during early development may potentiate limbic catecholaminergic pathways and, thus, predispose an individual to future psychopathology (Post and Kopanda 1976; Post, Kopanda, and Black 1976; Post 1977). Stressful events later in life might trigger a psychopathological episode by reactivating the potentiated pathways—albeit that the same stressors may be innocuous for nonpredisposed individuals. Such a view is consistent with the subjective reports of overwhelming stress that appear in studies of experiential phenomena associated with the onset of schizophrenia (Bowers 1965, 1968; Docherty et al. 1978). Bowers (1968) reported that patients frequently described their helplessness in the face of an insoluble psychological impasse in such terms as “I had no where to turn” and “There was no way out.” Since animal studies indicate that stress activates mesolimbic DA neurons (Thierry et al. 1977; Blanc et al. 1980; Reinhard, Bannon, and Roth 1982; Trulson and Preussler 1984), it follows that the stress-induced potentiation of dopaminergic systems may be a biological mechanism that is relevant to a developmental view of schizophrenia.

Genetic Factors in Schizophrenia. Studies of schizophrenic adoptees provide strong evidence for a genetic influence in schizophrenia, but the 50-per cent concordance rate for schizophrenia among monozygotic twins suggests that environmental factors must also be important (Gottesman and Shields 1972, 1982; Kety 1978). There is no consensus on the precise mode of genetic transmission, although the complex familial patterns of schizophrenia seem to favor a nonstraightforward form of transmission, perhaps involving multiple genes or genetic heterogeneity (Gottesman and Shields 1967; Matthyse and Kidd 1976; Rosenthal 1977; Tsuang, Bucher, and Fleming 1982). Returning to the subject of neural plasticity, polygenetic factors also conceivably affect both the establishment of neuronal connections during development and the plasticity of neuronal connectivity in the later life of an organism. Studies of animal genetic variants suggest that genetic factors affect such developmental processes as neuronal migration and axonal outgrowth (Lund 1978). Neural plasticity induced by both environmental and electrophysiological means is associated with enhanced protein synthesis and is, therefore, potentially influenced by genetic factors (Bennett and Rosenzweig 1971; Geller 1971; Levitan, Mushynski, and Ramirez 1972; Rosenzweig, Bennett, and Diamond 1972a; Hydén and Ronnback 1979; Duffy, Teyler, and Shashoua 1981). Since the development and plasticity of neural connections may be genetically influenced, the present section addresses the hypothesis that polygenetic influences in schizophrenia achieve their pathogenetic effects by altering the connectivity of neurons.

Animal studies indicate that genetic factors can alter the connectivity of neurons in behaviorally important ways. Strain-related differences have been reported in the size and distribution of several neural pathways including the corpus callosum (Wahlsten 1974, 1982), fornix, anterior commissure (Wahlsten 1974), central retinal projections (Lund 1975), and the mossy fiber path of the hippocampal formation (Barber et al. 1974; Schwegler and Lipp 1981). These genetically induced changes may be functionally important since strain-related behavioral and neurophysiological differences were also found in the same animals (for reviews, see Wahlsten 1974; Lund 1978; Lipp and Schwegler 1982). Of interest in the present context are the reported alterations in the size of the corpus callosum in post-mortem brain samples from schizophrenic patients (Rosenthal and Bigelow 1972; Nasrallah 1982a, 1982b). In comparison with nonpsychotic (Rosenthal and Bigelow 1972) and affectively ill controls (Nasrallah 1982a, 1982b), greater corpus callosum thickness was especially evident in patients with nonparanoid schizophrenia. The relatedness of this finding to genetic and behavioral factors is presently unknown, although it has been interpreted as possible evidence for interhemispheric dysfunction in schizophrenia (Nasrallah 1982a, 1982b).

Neuronal connectivity can also be altered by genetic variations in the numbers of neurons. Inbred strains of mice were shown to differ in the number of midbrain dopaminergic cell bodies (Ross et al. 1976; Baker, Joh, and Reis 1980; Fink and Reis 1981). The presence of increased numbers of DA terminals in one of
the strains was suggested by the increased gross size of the caudate nucleus and the elevations in DA receptor numbers and DA-synthesizing enzyme activity in DA-terminal regions (Baker, Joh, and Reis 1980, 1982; Fink and Reis 1981). These genetically induced alterations in the mesolimbic and nigrostriatal dopaminergic projections were correlated with strain-related differences in DA-mediated behaviors. The strain with elevated numbers of dopaminergic neurons and terminals showed increased locomotion when placed in an open field and increased stereotypic behavior after D-amphetamine administration (Fink and Reis 1981).

Genetic variations in the orientation of dendrites would presumably affect neuronal connectivity. Bereiter and Jeanrenaud (1980) found that genetically obese (ob/ob) mice differed from a lean strain of mice in the orientation of hypothalamic dendrites. The two mouse strains differed significantly in the dorsal-ventral and medial-lateral orientations of dendrites in the ventromedial nucleus (VMN) and lateral hypothalamic area (LHA). These dendritic changes could potentially influence behavior since both the VMN and LHA have been implicated in the regulation of feeding behavior (Powley 1977).

Studies of brain development indicate that profound behavioral effects can be produced by genetic mutations which lead to a failure of neuronal migration. Homozygous weaver (wv/wv) mutant mice show extreme aberrations in the numbers and distribution of cerebellar granule cells (Rezai and Yoon 1972; Rakic and Sidman 1973a, 1973b, 1973c; Sotelo and Changeux 1974).

Available evidence suggests that massive granule cell degenerations occur as a result of the failure of the cells to migrate to their mature positions in the internal granular layer (reviewed by Landis and Landis 1978; Lund 1978). This developmental defect is manifested behaviorally in the form of cerebellar ataxia and hypotonia in young mutant mice.

It is conceivable that genetically altered receptor sensitivities may affect behavior. Segal, Geyer, and Weiner (1975) reported that two rat strains which differed with respect to spontaneous behavioral activity and norepinephrine-elicited accumulation of adenosine 3',5'-monophosphate also exhibited differential behavioral responsiveness during the intraventricular infusion of norepinephrine. These results were interpreted as reflecting genetic variations in catecholamine receptor sensitivity. The authors speculated that genetic or experientially induced differences in receptor sensitivity may influence proneness to psychiatric disorders. More recently, DA systems have been subjected to studies of genetically altered receptor sensitivity. Compared to the DBA/2J strain, the AKR/J mouse strain exhibited significantly greater climbing behavior after apomorphine or bromocriptine administration and increased stereotypy after apomorphine (Kendler and Davis 1983, 1984). These behavioral differences seem to be mediated by genetically altered receptor populations since the AKR/J strain also has greater numbers of DA receptors in mesolimbic and striatal areas (Boehme and Ciaranello 1981). Kendler and Davis (1983, 1984) proposed that these results may usefully model the interaction of genetic and environmental variables that are potentially involved in the production of schizophrenia.

Genetic factors might also influence the plasticity of neurons and, hence, the responsivity of neuronal connections to changes in the environment. Jacobson (1978) has suggested that the postnatal development of the brain in altricial animals is more susceptible to environmental conditions than that in precocial animals. It was also inferred that the human brain has attained a comparatively greater responsivity to the environment at the risk of an increased vulnerability to unfavorable conditions during the neonatal period. Jacobson (1978) further proposed that the responsivity of neurons to the environment could show genetic variation within a given species. Thus, different human genotypes may respond to environmental changes with different degrees of alterations in neuronal connectivity and behavior (figure 1). This emphasis on an interplay between genetic and environmental factors fits well with the diathesis-stress (Rosenthal 1970), general systems (Scheflen 1981), and vulnerability (Zubin 1980) models of schizophrenia. These models postulate that overt illness results from complex interactions between environmental stressors and an inherited predisposition or vulnerability. What is inherited may be an enhanced sensitivity of neuronal connectivity to environmental stressors.

In summary, it seems that behaviorally important changes in neuronal connectivity can be produced by genetic variations in at least six parameters: (1) the migration of neurons, (2) the distribution of neural pathways, (3) the number of neurons, (4) the orientation of dendrites, (5) the sensitivity of receptors, and (6) the plasticity of neuronal connections in response to environmental changes. With the present state of knowledge, only speculative answers can be given to the question of whether these types of genetic alterations could influence the vulnerability to psychopathology.
Figure 1. Neural responsivity to environmental conditions for three hypothetical genotypes, either of the same or of different species

Among the depicted cases neural responsivity would be ranked as follows: Genotype C > B > A. Neural response may be measured in such terms as biochemical changes in the brain, alterations in brain weight or size of individual neurons, changes in physiological connectivity, or variations in behavior. Modified from Jacobson, M. Developmental Neurobiology. 2nd ed. New York: Plenum Press, 1978. p. 432.

However, the results of a controlled, quantitative study of post-mortem brain samples suggest that some schizophrenic patients may have a genetic defect in neuronal connectivity (Scheibel and Kovelman 1981; Kovelman 1983; Kovelman and Scheibel 1984). Hippocampal samples from 10 chronic schizophrenic patients showed a significant disorganization relative to the normal alignment of pyramidal cells. The resultant disorientation of dendrite systems was proposed as profoundly affecting synaptic patterns in the areas involved. It was further concluded that the pyramidal cell disorganization must have been generated at the stage of fetal development in which neuroblasts migrate into the hippocampal primordium. The authors suggested that such a developmental defect could be secondary to either (1) defective genetic expression or (2) a highly specific infectious attack on a specific cell species at a critical time in development. These findings are discussed further in the following section.

Proposed Directions for Future Research

In a frankly speculative manner, this essay has shown how neural plasticity concepts can be invoked as potentially explanatory of the following seemingly disparate features of schizophrenia: the pharmacological support for the DA hypothesis, the various types of behavioral symptoms exhibited by schizophrenics (e.g., hallucinations and motor disorders), the regional alterations in brain structure and function seen in chronic schizophrenia, genetic influences in schizophrenia, and those aspects of schizophrenia that are suggestive of a developmental disorder. However, the data that now exist are, at best, only consistent with, and not directly supportive of, a role for neural plasticity in the pathophysiology of schizophrenia. It is presently difficult to evaluate most hypotheses that relate neural plasticity to schizophrenia since few, if any, studies have been designed with such a relationship in mind. In view of the explanatory potential of neural plasticity concepts, a research program which focuses on these concepts seems warranted. Both animal and human studies could be employed in an attempt to more directly assess the putative relationship between neural plasticity and schizophrenia, or psychopathology in general. The research program outlined below amounts to an extension and elaboration of the program proposed by van Praag (1981) under the rubric of "socio-biological psychiatry."
Animal Studies. Several animal models of schizophrenia have been proposed (reviewed by McKinney and Moran 1981), any one of which may be employed in a search for evidence linking neural plasticity and schizophrenia. Experimental models which involve social isolation may be particularly relevant to developmental theories of schizophrenia. The method of raising monkeys in isolation has been discussed as a model of both human depression (McKinney and Bunney 1969; Katz, 1981) and schizophrenia (Kornetsky and Markowitz 1978; McKinney and Moran 1981). An alternative, simpler hypothesis would propose that the social isolation of animals is a model of socially induced psychopathology in humans, without attempting to specify exactly which diagnostic category is being modeled.

Socially isolated animals could serve as subjects in experiments that make use of the neuroanatomical and electrophysiological techniques typically employed in studies of neural plasticity. In this way, structural evidence of altered innervation patterns or electrophysiological evidence of LTP-like mechanisms could be sought. Some evidence for each of these manifestations of neural plasticity has already been found in the brains of socially isolated monkeys.

Monkeys raised in social isolation develop a variety of abnormal behaviors including self-clasping and -biting, retarded motor activity, avoidance of social contact, fearfulness, and a lack of appropriate sexual behavior (Seay, Hansen, and Harlow 1962; Heath 1972; McKinney 1977; Riesen, Dickerson, and Struble 1977; Floeter and Greenough 1979; Sonnier 1981). Light microscopic examination of the brains of isolated monkeys reveals dendritic branching deficits in cells of the cerebral and cerebellar cortices (Riesen, Dickerson, and Struble 1977; Struble and Riesen 1978; Floeter and Greenough 1979; Sonnier 1981; Riesen et al., in press). Compared to socially raised controls, 6- to 8-month-old deprived monkeys show a significant decrease in the dendritic branching of cerebellar Purkinje cells (Floeter and Greenough 1979) and layer-IV cerebral cortical stellate cells (Riesen, Dickerson, and Struble 1977; Struble and Riesen 1978; Sonnier 1981; Riesen et al., in press). Since the dendrites of these cell types normally receive a rich innervation, it is quite possible that the altered dendritic branching reflects altered innervation patterns.

It also seems possible that the decreased dendritic branching was a response to the relatively diminished opportunity for motor activity, general somatosensory stimulation, and social interaction (or any combination of these factors) provided by the rearing environment of the isolated monkeys. Although it is difficult to determine which aspects of the isolation environment are related to the dendritic changes, recent studies are beginning to distinguish between the effects of social and sensorimotor deprivation (Sonnier 1981; Riesen et al., in press). This distinction was made by raising some monkeys in the usual social isolation condition, but with the added presence of a trapeze, ladders, and play objects. Such sensorimotor enrichment did not prevent the development of typical isolation syndrome behaviors. At an anatomical level, the additional sensorimotor stimulation prevented the dendritic branching deficits in layer-IV stellate cells of the primary somatosensory and motor cortices, but not the secondary motor cortex (M-II). Dendritic branching indices in the visual, frontal, and secondary somatosensory cortices were minimally affected by social deprivation with or without sensorimotor enrichment. Thus, it appears that monkey isolation syndrome behaviors are specifically a consequence of social isolation, and are correlated with dendritic branching deficits in M-II, also referred to as the "supplementary motor area" (Penfield and Welch 1949; Woolsey et al. 1952).

M-II has been proposed to function in the programming of voluntary motor behaviors (Brinkman and Porter 1979; Orgogozo and Larsen 1979; Roland et al. 1980). Based on the monkey isolation studies, M-II might also facilitate the development of normal social behaviors. Interestingly, Buchsbaum et al. (1982) noted that the deficits in cerebral blood flow and glucose utilization exhibited by schizophrenic patients are often focused in the vicinity of M-II. Thus, it can be hypothesized that an M-II dysfunction underlies the deficits in social behaviors seen in human and animal pathological behavior syndromes. It is possible, however, that socially isolated monkeys also exhibit behaviorally relevant anatomical changes in other unexamined brain areas, most notably the limbic system (Riesen, Dickerson, and Struble 1977).

Heath (1972) made electrophysiological recordings from electrodes implanted in various limbic regions in the brains of monkeys raised in isolation. These bizarrely behaving monkeys exhibited electrographic abnormalities such as sharp spiking and high-amplitude spindling in the anterior septum, hippocampus, and somatosensory thalamic nuclei. Such electrographic changes were not apparent in recordings obtained from control monkeys.

Four research groups have also
recorded abnormal limbic electrical activity, including spiking, from electrodes implanted in the brains of schizophrenic patients (reviewed by Torrey and Peterson 1974). Electrographic abnormalities in the septum, hippocampus, amygdala, and frontal lobes were occasionally reported to correspond precisely with the patients' ongoing psychotic behavior.

Limbic spike discharges also developed in baboons subjected to repetitive electrostimulation of the amygdala (Wada, Osawa, and Mizoguchi 1975; Wada and Osawa 1976). As daily kindling stimulation was administered, interictal spike discharges gradually developed in the amygdala, hippocampus, mesencephalic reticular formation, and orbitofrontal cortex. The chronology and distribution of spike discharges suggested to the authors a "trans-synaptic nature of functional reorganization of the brain associated with kindling." Thus, a potentiating process seems to be involved in the spread of abnormal electrical activity during repetitive electrostimulation. The presence of abnormal limbic spiking in kindled animals, isolated monkeys, and schizophrenic patients suggests that LTP-like mechanisms may be operative in each of these conditions. To investigate further this possibility, specific limbic pathways in the brains of isolated animals could be monitored for changes in transmission efficacy. The after-discharge thresholds of various limbic structures could also be measured as in Adamec's (1975a, 1975b) study of feline predatory behavior. Such studies, together with neuroanatomical data, could begin to answer the question of whether altered innervation patterns or LTP-like mechanisms are involved in the production of socially induced psychopathology.

Animal models could also be used to test the hypothesis that neural plasticity plays a role in the antipsychotic effect of neuroleptic drugs. Meltzer, Goode, and Fang (1978) have proposed that the relatively slow onset of the therapeutic response to neuroleptics and the persistence of the therapeutic effect after neuroleptic withdrawal are both consistent with the hypothesis that neuroleptics initiate a biological process with a relatively long half-life which, in turn, initiates and maintains the antipsychotic effect. Axonal sprouting was cited as a possible example of such a process (Meltzer, Goode, and Fang 1978). A recent quantitative electron microscopic study revealed that rats chronically treated with haloperidol exhibited significantly increased numbers of axon terminals per dendrite cross-section in the substantia nigra, suggesting neuroleptic-induced axonal sprouting (Benes, Paskevich, and Domesick 1983). This type of anatomical evidence might best be interpreted functionally by studying electrophysiological adaptations in various synaptic populations during neuroleptic administration. For example, neuroleptics block the development of hippocampal LTP (Finch, Browning, and Lynch 1980; Turner, Baimbridge, and Miller 1982). If neuroleptics can be shown to reverse already-established LTP, then these results would be consistent with a role for an LTP-like mechanism in the development of psychosis (Post and Kopanda 1976; Post, Kopanda, and Black 1976; Post 1977).

Human Studies. Theories proposing an altered neural connectivity in schizophrenia could be directly tested by the analysis of human post-mortem material. The neuropathological studies done to date are generally considered to be inconclusive (see reviews by David 1957; Dastur 1959; Correllis 1976; Matthysse and Williams 1982; Weinberger, Wagner, and Wyatt 1983). Some histologic changes have been reported, but these findings are usually regarded as nonspecific for schizophrenia and are more likely to be related to normal variation, aging effects, technical artifacts, or complicating terminal illness. Using a glial stain, Stevens (1982a, 1982b) recently found that some schizophrenic patients exhibit a subcortical gliosis that may be evidence of past brain injury. The absence of a universal neuropathology of schizophrenia has helped to motivate a trend, in recent decades, toward biochemical explanations of the disorder (Correllis 1976).

However, Hubel (1978) has intimated that the connectivity of brain structures can be highly abnormal despite the absence of abnormalities when the tissue is stained and examined according to classic neuropathological methods. This point may carry considerable significance since the early neuropathological studies did not provide controlled, quantitative data on dendritic structure in the brains of schizophrenic patients. Animal studies show that cerebral cortical dendrites remain quite sensitive to environmental changes well into adulthood (Uylings, Kuypers, and Veltman 1978; Connor et al. 1981, 1982; Green, Schlumpf, and Greenough 1981; Chang and Greenough 1982; Connor, Wang, and Diamond 1982). Post-mortem brain specimens from nonschizophrenic humans have shown age-related changes in dendritic structure and synaptic density in neocortex and allocortex (Scheibel and Scheibel 1975; Scheibel et al. 1975, 1976; Buell and Coleman 1979;...
the relatively parallel alignment of pyramidal cells seen in material from eight nonpsychotic controls, the cells of the schizophrenic patients were highly disorganized in relation to each other. This finding was apparent even without computer assistance: the dendritic domains extended in a variety of directions and were occasionally completely reversed, i.e., upside down relative to normal position. The authors felt that such a lack of orientation must profoundly affect synaptic patterns in the areas involved. A failure to replicate the findings of Scheibel’s laboratory was recently reported, although quantitative data were not presented (Weinberger, Wagner, and Wyatt 1983). In the latter study, pyramidal cell dendritic disarray was found as frequently in controls as in the brains of schizophrenic patients. The results of Kovelman and Scheibel (1984) clearly deserve attempts at quantitative replication as well as extension into unexamined brain regions. Early neuropathological studies of the cerebral cortices of schizophrenic patients did not include quantitative analyses of cell orientation and dendritic branching patterns.

Another drawback of the early neuropathological studies was their adherence to an oversimplified theoretical orientation. The research was generally motivated by the notion that some specific neuroanatomical defect(s) must underlie the drastic behavioral changes exhibited by schizophrenic patients. Research in this area almost ground to a halt when no consistent defect was revealed by the conventional neuropathological methods. This failure does not preclude the possibility that defects exist at a finer structural level (i.e., the orientation, branching pattern, and spine density of dendrites) could be aided by the techniques already employed in neural plasticity research. As theories of brain plasticity continue to evolve, further guideposts for the direction of neuropathological research should become available. As outlined above, the emerging principles of neural plasticity could also aid in the design of animal studies concerned with environmentally induced psychopathology. In conclusion, the design of both animal and human studies may benefit from a theoretical orientation which takes into account the plasticity of neuronal connections (see also Haracz 1984).

Tests of Specific Hypotheses. Summarized below are some specific, testable hypotheses that are derived from a general theory relating neural plasticity to animal and human pathological behaviors.

Hypothesis 1. Psychopathology results from the potentiation of catecholaminergic pathways in the limbic system following their repetitive activation by stressful events (Post and Kopanda 1976; Post, Kopanda, and Black 1976; Post 1977). Animals subjected to repetitive stress could be tested for the potentiation of potentials evoked by the electrostimulation of catecholaminergic pathways. The experimental procedure could be similar to that employed in studies of hippocampal potentiation during behavioral conditioning (Jaffard and Jeanet 1981; Rüthrich, Matthies, and Ott 1982; Thompson 1982a). In addition, evoked single-unit activity may contribute to the analysis (Morris et al. 1979; Buchwald et al. 1981; Fisher et al. 1982; Yin and Mogenson 1982). Potentiation of limbic pathways might also be
manifested as an increased propagation of electrically evoked after-discharge (Adamec 1975a, 1975b). Post's hypothesis could be generalized to allow a search for potentiation throughout the brain, especially in view of the growing number of pathways known to support LTP (Racine, Milgram, and Hafner 1983; Teyle and Discenna 1984) and the relatively widespread distribution of abnormal electrical activity recorded from depth electrodes in kindled baboons (Wada, Osawa, and Mizoguchi 1975; Wada and Osawa 1976), isolated monkeys (Heath 1972), and schizophrenic patients (reviewed by Torrey and Peterson 1974).

Hypothesis 2. Adaptive changes in neuronal structure contribute to the generation of animal and human pathological behaviors. Stated in terms of structure rather than function, this hypothesis is otherwise analogous to the general version of Hypothesis 1, which proposed that neurophysiological adaptations underlie psychopathology. Altered dendritic structure has already been found in the cerebral and cerebellar cortices of isolated monkeys (Riesen, Dickerson, and Struble 1977; Struble and Riesen 1978; Floeter and Greenough 1979; Sonnier 1981; Riesen et al., in press), although limbic areas have yet to be examined (Riesen, Dickerson, and Struble 1977). Quantitative studies of post-mortem tissue from schizophrenics might be directed at the orbitofrontal and secondary motor (M–II) cortices. A preliminary post-mortem study suggests that schizophrenics have an increased dendritic spine density on orbitofrontal pyramidal cells (Senitz and Winkelmann 1981), while in vivo studies are suggestive of M–II deficits in glucose utilization and blood flow (Buchsbaum et al. 1982). Dendritic structural deficits in M–II were found to correlate with the presence of monkey isolation syndrome behaviors (Sonnier 1981).

Hypothesis 3. The density of catecholaminergic nerve terminals is abnormally increased in some schizophrenic patients (Hökfelt et al. 1974; Coyle and Johnston 1980). This specified version of Hypothesis 2 could be tested by applying the post-mortem fluorescence histochemistry technique (Olson, Nystrom, and Seiger 1973a, 1973b; Olson 1974). Tissue from patients with paranoid schizophrenia may be of special interest since members of this subtype exhibit elevated post-mortem brain norepinephrine levels (Wyatt et al. 1981).

Hypothesis 4. The relationship between the CT evidence of cerebral atrophy and poor premorbid school and social adjustment led to the proposal that brain structural abnormalities in schizophrenia may be the result of early developmental defects (Weinberger and Wyatt 1980, 1982). Since early brain development can be altered by environmental factors (see text under Environmentally Induced Plasticity), it could be further hypothesized that specific environmental factors, one example being familial communication patterns (Singer, Wynne, and Toohey 1978), are etiologically related to the brain structural alterations depicted on the CT scans of some schizophrenic patients. This hypothesis could be tested by correlating objective indices of familial communication with CT scan results, especially those obtained from young first-episode patients (Weinberger et al. 1982). These young patients have already been found to exhibit a positive relationship between cerebroventricular size and poor premorbid social adjustment (Delisi et al. 1983). Since ventricular enlargement is confined to schizophrenic patients without a known genetic predisposition (Reveley, Reveley, and Murray 1983, 1984), it can be hypothesized that an aversive familial environment is predictive of both increased ventricular size and poor premorbid social function.

Hypothesis 5. Structural and/or functional adaptations are involved in the antipsychotic effect of neuroleptics. Neuroleptics block the development of hippocampal LTP (Finn, Browning, and Lynch 1980; Turner, Baimbridge, and Miller 1982), but it is not known if neuroleptics can reverse already-established LTP, particularly in extra-hippocampal regions. An LTP-reversing capability would allow neuroleptics to negate the pathological potentiating mechanisms postulated in Hypothesis 1. Especially interesting would be the time course of LTP reversal vis-à-vis the time course of clinical antipsychotic activity.

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Acknowledgments

The author thanks Dr. R. Harper for the use of computer facilities and Dr. E. Zimmermann for editorial assistance.

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