Cortical Development and Thalamic Pathology in Schizophrenia

by Edward G. Jones

Abstract

In this article, morphological data suggesting that brain development may be altered in schizophrenia are reviewed in relation to the major events in neural development. In the absence of severe defects in brain structure in individuals with schizophrenia, developmental processes governing the establishment, refinement, and maintenance of connections are potential sites of pathological involvement. Alterations in connectional patterns are likely to result in activity-dependent changes in gene expression for molecules involved in the neurotransmission process, with functional consequences. Loss of cells in the thalamus may be primary or secondary to cortical or other subcortical pathology. Loss of thalamic cells and/or corticothalamic inputs could lead to disintegration of thought processes by a failure in functional brain states dependent on collective oscillation of large ensembles of cortical and thalamic neurons.


Many theories have suggested that brain development is affected in schizophrenia and that the psychopathology of schizophrenia may derive from alterations of brain organization secondary to defective ontogenesis. The developmental hypothesis of schizophrenia has its origins in studies of psychomotor and neuropsychological development in individuals with schizophrenia and in children genetically at risk for schizophrenia (Bender 1947; Bender and Freedman 1952; Fish 1957; O’Neal and Robins 1958; Sobel 1961); it has received support from more recent prospective studies (Fish et al. 1992). Because those who will develop schizophrenia tend to show alterations in the normal pattern of psychomotor and intellectual development during their early postnatal years, the development and maturation of the cerebral cortex and related structures are likely to be compromised in the disease. However, ascertaining the nature of a putative developmental insult and then finding evidence of its effects in the brains of individuals with schizophrenia are challenges of considerable magnitude.

Several observations made in recent years hold out the hope that some breakthrough may be imminent at the histological level: Defective migration of young neurons during the latter stages of cerebral cortical development has been invoked as a potential cause of putatively disturbed patterns of cytoarchitecture in the hippocampus and entorhinal cortex of brains of individuals with schizophrenia (Scheibel and Kovelman 1981; Jakob and Beckmann 1986, 1989; Kovelman and Scheibel 1986; Arnold et al. 1991a), and alterations in the distribution of interstitial neurons of the white matter of the temporal and frontal lobes have been ascribed to either defective migration or altered programmed cell death (Akbarian et al. 1993a, 1993c, 1994). At a grosser level, the significant increase in the volume of the lateral and third ventricles that has been reported fairly consistently in individuals with schizophrenia may also reflect altered brain development since it is present from the early stages and does not progress (Johnstone et al. 1976, 1989; Hyde and Weinberger 1990; Roberts and Bruton 1990; Pfefferbaum and Zipursky 1991). Other macroscopic alterations, such as partial agenesis of the corpus callosum (Swayze et al. 1990; Degreef et al. 1992) and aberrant gyration of the insular and temporal cortex (Jakob and Beckmann 1986), are inconsistently present. These macroscopic observations, together with the lack of gliosis and of other major signs of neuronal degeneration in the forebrains of individuals with schizophrenia (Benes et al. 1986, 1991; Roberts et al. 1987), make it difficult to view the pathology of schizophrenia as a primarily neurodegenerative process. Indeed, the rather modest anatomical changes that have been described, although suggestive, do not nec-

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essarily imply that brain development is compromised in schizophrenia or that they are phenomena that occur secondary to a developmental or degenerative insult.

Support for a causal relationship between disturbed brain ontogenesis and schizophrenia comes from epidemiological studies that have identified several risk factors acting during pregnancy that increase the incidence of schizophrenia in offspring. Studies of the incidence after maternal infection with influenza virus in the second trimester, although the numbers of cases involved are small, have had a major influence (Mednick et al. 1988; Mednick and Cannon 1991; Mednick and Hollister 1994). Even in the absence of an imposed risk factor of this type, the proven genetic influence in schizophrenia could exert its effect upon brain development.

Much of the emphasis in the search for a neuropathology of schizophrenia has focused on the cerebral cortex as the obvious site in which a pathological insult is likely to disrupt cognitive function. Cortical function is, however, dependent on connections with such subcortical structures as the thalamus and the basal ganglia, with the former providing many re-entrant loops that serve to cement the relationships among multiple cortical areas upon which cognitive function depends. Pathology, developmental or otherwise, in one of these structures is not only likely to have anterograde, retrograde, and activity-dependent effects on the others, but potentially may spread throughout the cortico-thalamic-basal ganglia network and beyond. This possible spread must always be borne in mind when assessing the significance of many of the observations made to date in the neuropathology of schizophrenia.

In this article, I review the major events in the development of the forebrain in relation to what is known of the neuropathology of schizophrenia, attempting to point out the likelihood of that pathology being produced by a disturbance of one or more of the developmental processes. The focus is on the development of the primate brain for obvious reasons and on the circuitry linking cerebral cortex, thalamus, and basal ganglia, the dysfunction of which appears to be of fundamental importance in the pathophysiology of schizophrenia.

Proliferation

The first major step in the development of the forebrain is the generation of huge numbers of neurons in the neuroepithelium, a process that in primates occurs mainly during the first trimester (Rakic 1975). Any interference with this proliferative process should result in changes in the absolute number of forebrain neurons unless compensated for by reduced programmed cell death, and a major perturbation should result in major cytoarchitectural anomalies. Experimental disturbances in the proliferative process, which can be engendered by exposure to ionizing radiation (Rakic 1988) or by the administration of cytotoxic drugs to animal fetuses (Jones et al. 1982; Yurkiewicz et al. 1984), cause severe reductions in the extent of whole cortical areas, disruption of cortical lamination, and islands of ectopic neurons. These changes undoubtedly result from the destruction of neuronal precursor cells, as well as of neuroglial precursor cells whose progeny provide processes along which young neurons migrate to the cerebral cortex. Where changes are least evident in the experimental brains, they consist primarily of disrupted lamination patterns, but even these alterations are more severe than anything that has ever been described in the brains of individuals with schizophrenia. A less substantial interference with neuronal proliferation, if it occurs in the disease, might only be revealed by a reduction in the total number of neurons in cerebral cortex, basal ganglia, or thalamus, possibly with concomitant regional reductions in brain volume. A decrease in the total number of neurons was reported in the mediodorsal nucleus of the thalamus (Pakkenberg 1990, 1992) and in the entorhinal cortex (Falkai et al. 1988) of schizophrenia subjects. However, it is not clear whether these decreases stem from reduced neuronal proliferation in the fetus or whether they represent degeneration of neurons secondary to primary pathology elsewhere; for example, the prefrontal cortex or basal forebrain. No changes in neuronal number were found in the hippocampal formation (Heckers et al. 1991), which is closely related to the entorhinal cortex (Rosene and Van Hoesen 1987) and might be expected to show transneuronal degeneration secondary to cell loss in the entorhinal cortex.

If there were a substantial alteration in the number of cortical, thalamic, or other forebrain neurons in individuals with schizophrenia, it would be expected to result in changes in the volume of gray matter from which cells were lost and of the white matter through which the axons of cells in these regions project. Several volumetric studies based on magnetic resonance imaging (MRI) or post-mortem analysis have focused upon the above regions, but the changes that have been described tend to be rather small and inconsistent. However, small reductions in cortical gyri are reported commonly (e.g., Weinberger et al. 1992), and a reduction in the overall volume of the thalamus or of the white matter around it seems to rest on solid ground (Andreasen et al. 1994). Where neurons have been counted in the prefrontal cortex of schizophrenia subjects, the results have also been inconsistent, possibly reflecting differences in the clinical samples and...
particularly in the methods of preparing brains for analysis. Decreased neuronal density was reported in the prefrontal cortex of schizophrenia subjects by Colon (1970) and Benes et al. (1986, 1991), but in other studies neuronal density was either increased (Daviss and Lewis 1993;Selemon et al. 1993) or unchanged (Akbarian et al. 1993b, 1995a; Bunney et al. 1993; Pakkenberg 1993). There is still no compelling reason to believe that the proliferative phase of forebrain ontogenesis is compromised in any major way in schizophrenia.

Migration

Virtually all newly born neurons migrate from the ventricular neuroepithelium toward their definitive positions elsewhere. Those destined for the cerebral cortex, thalamus, and basal ganglia migrate over considerable distances, following guides provided by neuroglial fibers (Rakic 1975, 1988). This process, from work on cerebellar cells in vitro, appears to depend upon N-methyl-D-aspartate (NMDA) receptors and N-type calcium channels (Komuro and Rakic 1992, 1993), a potential point of attack for a perturbing influence. In the monkey cerebral cortex, most of the migratory activity occurs during the middle third of pregnancy (Rakic 1972, 1974). Neuronal migration in the forebrain can be compromised by genetic mutations (Caviness et al. 1988) and exposure to environmental factors such as alcohol (Shetty and Phillips 1992; Miller 1993) and ionizing radiation (Rakic 1988). All of these usually result in grossly abnormal brains, commonly with lissencephaly and microgyria and accompanying disruptions of cytoarchitecture. Humans, for example, with the Miller-Diecker form of inherited lissencephaly have cerebral cortex from which layers II, III, and IV are absent, the young neurons originally destined for these layers having apparently come to rest in an abnormal position beneath the cortical plate (Richman et al. 1975; Caviness and Williams 1979). Microgyria in humans in which there is usually a greater-than-normal cell density in lissencephalic patients in layer II and III has also been attributed to defective neuronal migration (Richman et al. 1975; Caviness and Williams 1979). Changes of this magnitude are not typical of the brain of individuals with schizophrenia, and there is really no conclusive evidence for a disturbance of neuronal migration in schizophrenia.

However, impaired neuronal migration has been suggested as a cause of certain cytoarchitectonic anomalies described in the medial temporal cortex and hippocampal formation of brains of some schizophrenia subjects. The evidence upon which this interpretation is based is, admittedly, conjectural. Abnormal positioning and dendritic orientation of neurons were described in the cortex intervening between the presubiculum and the hippocampal formation in some (Scheibel and Kovelman 1981; Kovelman and Scheibel 1986; Altschuler et al. 1987; Conrad et al. 1991) but not all (Christison et al. 1989) brains of schizophrenia subjects. In the anterior entorhinal cortex, poorly developed lamination in the superficial cortical layers and displacement of islands of nerve cells, normally found in layer II downward into layer III were described in approximately 50 percent of the brains of schizophrenia subjects (Jakob and Beckmann 1986, 1989; Arnold et al. 1991a), were more common in brains of nonparanoid schizophrenia subjects, and tended to be more prominent on the left side (Jakob and Beckmann 1986). The feature that most strongly suggests a migratory disturbance is the displacement of layer II cells into layer III. This change could reflect arrested migration of the layer II cells since they normally migrate through the deeper layers en route to their definitive positions following the well-known "inside-out" sequence (Rakic 1974). The cytoarchitectonic anomalies, when present, were accompanied by reductions in cell numbers in all layers, although the details of the cell-counting procedures were not given. Nor is it clear in these studies that the sampling frequency was sufficiently close to ensure that the rather dramatic changes in the cellular organization of layer II in the several areas of the normal human entorhinal cortex (Beall and Lewis 1992) were taken into account. In the insular cortex (Jakob and Beckmann 1986), cytoarchitectonic changes were reported in less than half of the brains examined. These alterations consisted of reduced numbers of neurons in layers II and III and were found mainly in the ventral insular regions adjacent to the entorhinal areas. There was also an abnormal gyral pattern in the lateral aspect of the temporal lobe in these brains (Jakob and Beckmann 1989). There is no particular reason for believing that these or the changes reported in the entorhinal cortex represent migratory disturbances, and this issue requires detailed reexamination.

The cytoarchitecture of the prefrontal cortex, a region whose function seems to be particularly compromised in schizophrenia, is within normal limits in the brains of schizophrenia subjects (Benes et al. 1991; Akbarian et al. 1993a, 1995b). In the cingulate cortex of such brains, layer II shows large gaps between neuronal clusters (Benes and Bird 1987), but there is no reason yet to believe that this finding indicates defective migration.

Despite the lack of conclusive evidence for disturbances of neuronal migration in schizophrenia such disturbances remain an attractive hypothesis. Proving the hypothesis is likely to be a major problem.
Cortical Subplate

One of the key structures involved in setting up the complex pattern of cortical connectivity, both intrinsic and with subcortical centers such as the thalamus, is a temporally regulated set of early generated neurons that form a transitional zone immediately beneath the cortical plate, referred to as the subplate (Shatz et al. 1990). The primordial cerebral cortex is laid down at the surface of the cerebral hemisphere near the beginnings of the second trimester of pregnancy (Marin-Padilla 1988; Kostovic and Rakic 1990; Shatz et al. 1990). It is made up of the earliest generated neurons of the cerebral cortex. It is later split into a superficial or marginal zone and a deep or subplate zone by later arriving and progressively accumulating cells that form the definitive cortex.

The subplate is particularly thick in the brains of human fetuses and comprises both neurons and a synaptic neuropil. Through it grow all axons entering the cortex from subcortical sites such as the thalamus, and all axons leaving the cortex for other sites pass through it. The neurons of the subplate appear to form functional contacts with arriving thalamic afferents, with neurons in the overlying cortex, and probably with one another (Marin-Padilla 1988; Friauf et al. 1990; Shatz et al. 1990). The subplate is important in helping establish the normal pattern of afferent connectivity in the overlying cortex, and if it is damaged experimentally, these patterns are disrupted (Shatz et al. 1990; Ghosh and Shatz 1992). The processes of subplate cells that extend down into the internal capsule may guide cortical efferent axons to their targets, particularly the thalamus (Shatz et al. 1990; O’Leary and Koester 1993). Once these tasks are complete, the majority of subplate neurons undergo a program of physiological cell death (Chun and Shatz 1989), which occurs during late pregnancy and early postnatal life in humans (Kostovic and Rakic 1990). However, substantial numbers are spared in all primates and remain as interstitial neurons of the white matter. These neurons continue to maintain synaptic contact with the overlying cortex (Hendry et al. 1984), and those of the prefrontal region are reported to remain connected with the mediodorsal (MD) thalamic nucleus as well (Giguere and Goldman-Rakic 1988).

Many surviving interstitial neurons of the white matter and a small additional subpopulation in the overlying cortex stain positively for several neuropeptides (Jones et al. 1988) and for the enzyme nicotinamide adenine dinucleotide phosphate-diaphorase (NADPH-d) (Akbarian et al. 1993a, 1993b, 1993c), which is the same as nitric oxide synthase. These neurons are normally concentrated in layer II of the cortex and in the white matter immediately deep to layer VI. Other interstitial neurons can be identified by immunostaining for structural proteins (Akbarian et al. 1993b) or by expression of a variety of neuronal genes (Jones et al. 1994).

A disturbance of the cortical subplate, perhaps involving altered migration of subplate neurons or an alteration in their pattern of programmed cell death, could account for a distorted distribution of the NADPH-d neurons found in the cerebral cortex and white matter of individuals with schizophrenia (Akbarian et al. 1993a, 1993c, 1995c). In the prefrontal and lateral temporal areas of schizophrenia subjects, the number of these neurons is decreased in the cortex and in the superficial white matter (less than 2 mm deep to the cortex), but is increased in deeper white matter up to 8 mm beneath the cortex (Akbarian et al. 1993a, 1993b, 1993c). In the hip- pocampus and entorhinal cortex, the number of neurons is reduced in the gray matter, but the white matter in these regions is thin, which makes it impossible to identify a deep displacement in the white matter comparable to that beneath the neocortical areas (Akbarian et al. 1993c). Other populations of interstitial neurons of the white matter are also displaced deeply in the white matter beneath the prefrontal cortex of many (but not all) schizophrenia subjects. These include neurons identified by immunoreactivity for neurofilament protein epitopes and by immunoreactivity for microtubule associated protein 2 (Akbarian et al. 1993b, 1994).

This change in the distribution of interstitial neurons of the white matter for several millimeters beneath the prefrontal and lateral temporal cortex appears to affect a region corresponding to the territory of the former subplate. A perturbation of the original subplate may therefore account for this modified distribution pattern. However, it is not clear whether the change results from an alteration in the original migration of subplate neurons, from a change in the timing of their program of cell death, or indeed from some other mechanism unrelated to the development of the subplate. Furthermore, it may not be present in all schizophrenia subjects (Akbarian et al. 1993b, 1994a). If this change does reflect a subplate disturbance, it could have consequences for the organization and function of the overlying cerebral cortex. The redistribution of interstitial white matter neurons does not seem to indicate an interference with migration of all neurons to the cerebral cortex in individuals with schizophrenia, although this originally seemed possible. It is now clear that the number and density of neurons in the prefrontal cortex of the brains studied are not substantially altered in schizophrenia subjects in comparison with matched controls (Bunney et al. 1993; Akbarian et al. 1993b, 1995b). A small increase in neuronal density
has been reported by other investigators, although in material prepared by different methods (Selemon et al. 1993).

Axon Elimination

Large numbers of commissural, cortico-cortical, and subcortically directed axons grow out of the cerebral cortex in the course of its development, but many are eliminated in the early postnatal phase, either because they grow toward inappropriate targets (O'Leary and Koester 1993) or are less successful than their fellows in the competition for synaptic space (Chalupa and Killackey 1989; Meissirel et al. 1991; Webster et al. 1991). In primates, most cortical connections are established prenatally (Chalupa et al. 1989; Schwartz and Goldman-Rakic 1990, 1991), but axon elimination extends into the first few months after birth (LaMantia and Rakic 1990; Meissirel et al. 1991; Webster et al. 1991) elimination of an initial large excess of synapses formed by the remaining axons and the reduction of related receptors continue into early adulthood (Rakic et al. 1986; Lidow et al. 1991). In the establishment, stabilization, and maintenance of the connections of the cerebral cortex, many factors are involved. Two that may be among the most important are neurotrophic factors and neural activity, including sensory input from the periphery via the thalamus. Nerve growth factor (NGF) receptors are present early in the cortical subplate of primates (Meinecke and Rakic 1993), and their disappearance coincides with the time at which extensive cell death occurs in the subplate (Allendoerfer et al. 1990; Meinecke and Rakic 1993). This timing suggests the involvement of NGF in the early phases of axon growth into and out of the cortex. A second neurotrophin, brain-derived neurotrophic factor (BDNF), is expressed more widely than NGF in the adult brain, and its expression is increased when motoneurons are induced to regrow severed axons (Oppenheim et al. 1992; Sendtner et al. 1992; Yan et al. 1992). BDNF is first expressed in the fetal monkey frontal cortex on the 121st day of gestation, at a time when afferent connectivity is being established (Huntley et al. 1992), and in rodents all the known neurotrophins found in the central nervous system show high expression only at about birth (Maisonpierre et al. 1990; Scarisbrick et al. 1993) when cortical connections are being established.

Although it is not yet possible to determine whether any of the factors involved in the formation of cortical connections have been compromised in brains of individuals with schizophrenia, several observations warrant thinking in those terms. For example, the increased volume of the corpus callosum described in some brains of schizophrenia patients (Nasrallah et al. 1986; Raine et al. 1990) could indicate incomplete elimination of the huge excess of callosal axons (LaMantia and Rakic 1990). The abnormalities described in the corpora callosa of schizophrenia patients, however, variable (Casanova et al. 1990; Coger and Serafetinides 1990; Gunther et al. 1991), and decreased callosal volume (Hauser et al. 1989; Rossi et al. 1989; Woodruff et al. 1993) and even partial callosal agenesis (Swayze et al. 1990; Degreel et al. 1992) have been described in schizophrenia. These conditions would reflect excess elimination, if they do not reflect later degeneration of parent cells, for which there is no evidence.

Axonal loss in the white matter surrounding the inferior horns of the lateral ventricles might account for the consistently reported increase in ventricular volume in schizophrenia, but it has not been directly demonstrated and whether it could reflect an altered pattern of developmentally regulated axon elimination is not known. Whether axonal loss is in any way related to the redistribution of interstitial neurons has not been explored.

Synaptic Pruning

Synaptogenesis in the cerebral cortex continues well beyond the period during which the basic connections of the cortex are established and synaptic stabilization and pruning are major features of early postnatal development. In the human brain, the density of cortical synapses increases markedly during the first year of life, but then progressively decreases, becoming relatively stable by approximately the 15th year. A further decline occurs in old age (Huttenlocher 1979, 1990; Huttenlocher and De Courten 1987). In the frontal and occipital cortex of humans and in nonhuman primates, overabundant synapses are eliminated, starting early in postnatal life and ending around the time of puberty (Rakic et al. 1986; Zecevic et al. 1989; Huttenlocher 1990; Missler et al. 1993). The process of synaptic pruning is associated with contemporaneous changes in the densities of most neurotransmitter receptors (Lidow et al. 1991), and in the prefrontal cortex, at least, its terminal phases are contemporaneous with the functional maturation of the prefrontal areas as assessed by neuropsychological methods (Goldman-Rakic 1987). This period is also the time in which the overt symptoms of schizophrenia usually appear (Kraepelin 1919/1971). There is no convincing evidence that the process of synaptic pruning is affected in brains of schizophrenia subjects, although this has been proposed (Feinberg 1982). It is clearly an area that requires further attention since large changes in synaptic density could exist in the absence of overt light microscopic pathology. Any evidence of a reduction in the cor-
tical neuropil would be particularly important in assessing the possibility of loss of synaptic terminals. Moreover, changes in synaptic stabilization and maintenance, resulting in a loss of synapses, may be anticipated under conditions in which connection formation is compromised, as discussed in the next section.

Activity-Dependent Phenomena in Cortical Development

The genesis of membrane conductance and polarization changes in neurons and the initiation and propagation of action potentials are major factors that influence the establishment of patterns of connectivity during cortical development (Shatz 1990) and the maintenance and stabilization of synaptic connections into adulthood (Jones 1990). When thalamocortical axons first enter the subplate and before they penetrate the cortex, they are capable of conducting action potentials and of generating excitatory postsynaptic potentials in subplate cells (Friauf et al. 1990), presumably via transient synapses. These may be the first afferent signals that influence cortical development since they may induce changes in gene expression in the cells by which the axons, when they later invade the cortex, may be able to recognize appropriate target cells.

The establishment of domains of axonal terminal ramification in the developing nervous system is also profoundly influenced by afferent activity and may represent the next step whereby axon distributions are restricted in the cortex. In the tectum of the frog, regenerating retinotectal axons are capable of growing to the optic tectum in the absence of action potentials, but when axon potential propagation is blocked their terminal ramifications are more widespread than usual and fail to establish the normal pattern of retinotopy (Schmidt 1985). The establishment of the normal pattern is normally dependent upon activation of NMDA receptors on the postsynaptic cells (Cline et al. 1987). There are potential parallels in the establishment of connectivity in the mammalian cerebral cortex because, in many areas, the initial pattern of ingrowth of afferent axons is relatively diffuse and is refined only later into a topographic map based upon restricted terminations of groups of axons arising from localized clusters of thalamic cells.

One of the best known examples is in the visual cortex of cats and monkeys in which the ocular dominance columns, which are zones of alternating input of thalamocortical fibers carrying information from the left and right eyes, segregate out of an initially overlapping pattern (Hubel et al. 1977; LeVay et al. 1978). This segregation begins in utero, but is strongly affected by sensory influences during a critical period in early postnatal life. During this critical period, the segregation of thalamocortical fibers into ocular dominance columns occurs under the influence of correlated patterns of input from the two eyes. If the correlation is disturbed by depriving one eye of pattern vision or by blocking impulse activity in one optic nerve, the more active fibers from the unaffected eye are at a competitive advantage in the cortex and acquire more synaptic space in the cortex. This competitive advantage is manifested anatomically by widening of the ocular dominance columns related to the undeprived eye and by a greater number of neurons than normal being preferentially driven by this eye (LeVay et al. 1980). Any change in the balance of inputs from the two eyes during the critical period can alter the degree of ocular dominance segregation. Similar activity-dependent influences also affect the topographic segregation of thalamic fibers in the somatosensory cortex of rodents (Van der Loos and Woolsey 1973; Killackey et al. 1976). This process of segregation also depends upon the activation of NMDA receptors (Schlagger et al. 1993), and it is likely that it is a general phenomenon of cortical development.

Once connections are made in the cerebral cortex, synapses must be stabilized. As elsewhere, this process involves the induction of membrane events (Singer et al. 1977; Wilson et al. 1977; Shaw and Cynader 1984; Reiter and Stryker 1988) and the expression of transmitter, receptor, and many other genes involved in the transmission process in the postsynaptic cells (reviewed in Jones 1990). The same kinds of activity-dependent phenomena appear to remain part of the maintenance of functional cortical connectivity throughout the lifetime of the individual. For example, in the somatic sensory, auditory, and visual cortices of mature animals including primates, large shifts in the position and extent of a portion of the cortex representing a particular part of the receptive field can be induced by reducing or enhancing correlated neural activity emanating from the peripheral receptors (Kaas et al. 1983, 1990; Wall et al. 1986; Clark et al. 1988; Robertson and Irvine 1989; Jenkins et al. 1990; Allard et al. 1991; Gilbert and Wiesel 1992).

The mechanisms involved in inducing shifts of several millimeters in a representational map are not completely understood. They may involve the silencing of certain synapses and the enhancement of others that were previously silent, resulting in changes in the balance of excitation and inhibition. These changes may or may not be accompanied by formation of new synapses, but they lead to up- and downregulation of gene expression for transmitter, receptor, and other neuroactive molecules. Short periods of monocular visual deprivation in adult monkeys, for example, will cause large decreases in gene expression.
expression in the inhibitory transmitter, decreases in gamma-aminobutyric acid (GABA) and its ionotropic receptors, and parallel increases in alpha type II calcium/calmodulin-dependent protein kinase, a protein associated with excitatory synapses and synaptic learning (Hendry and Jones 1986, 1988; Hendry and Kennedy 1986; Hendry et al. 1990; Benson et al. 1991a, 1991b, 1994; Huntsman et al. 1994).

The crucial importance of neuronal activity in the development and maintenance of cortical circuitry raises the question of its relevance to schizophrenia and whether a defect of the cortical subplate or some other element of the developing cortex—leading to alteration in the distribution of afferent axons, in the degree of axonal pruning, or in the efficacy of connection formation—could compromise the circuitry to the extent that interactions with other cortical and subcortical regions would be compromised when stressed by life events, with the ensuing onset of psychotic symptoms. The disintegration of thought in schizophrenia may then be likened to a functional disconnection syndrome.

If there is a compromised circuitry in the frontal cortex of schizophrenia patients, it should be manifested by changes in the levels and distributions of neurotransmitter and receptor-related molecules whose expression is activity-dependent. Several observations suggest, indirectly, that neural circuitry is compromised in the brains of individuals with schizophrenia. Whether this changed circuitry has activity-dependent consequences is still difficult to evaluate, but certain observations point in that direction. Functional imaging studies in adult schizophrenia patients demonstrate hypoactivity in the forebrain, particularly in the prefrontal cortex, but changes have also been reported in the striatum and medial temporal lobe (Buchbaum et al. 1992; Weinberger et al. 1992). These regions are highly interconnected among themselves and with the medioventral nucleus of the thalamus. The overall circuitry has an important function in representational memory (Goldman-Rakic 1987) and is the essential psychosis circuitry of virtually every circuit-based theory of schizophrenia. The cause of the hypoactivity is still unclear, but it is interesting to speculate whether any associated effects are potentially attributable to activity-dependent downregulation of neurotransmitter function. The inhibitory GABAergic system provides some clues to suggest that this may be true. GABA is the transmitter of 25 to 30 percent of all neurons of the primate cerebral cortex (Jones 1993), and its ionotropic or GABA_A receptors are expressed by virtually every cortical cell (Huntsman et al. 1994). In the brains of schizophrenia patients, GABA function appears to be severely compromised, as manifested by decreased GABA uptake in the temporal cortex (Simpson et al. 1992), by increased radioligand binding to GABA_A receptors in superficial layers of the cingulate cortex (Benes et al. 1992), and by reduced gene expression for glutamic acid decarboxylase (GAD), the enzyme necessary for synthesis of GABA, in the prefrontal cortex (Bunney et al. 1993; Akbarian et al. 1995b). Downregulation of GAD messenger RNA (mRNA) levels is of particular interest since there was no loss of neurons in the prefrontal areas of the brains examined. The effect is therefore probably best explained as an activity-dependent reduction based upon hypoactivity. It has parallels with the downregulation of GAD gene expression demonstrated by monocural deprivation in the visual cortex (see above). Upregulation of dopamine D_4 receptors also observed in the the brains of schizophrenia patients (Seeman et al. 1993), downregulation of D_3 receptor mRNA in parietal and motor cortices (Schmauss et al. 1993), reduced immunoreactivity for structural proteins in the hippocampus (Arnold et al. 1991b), and changes in the relative proportions of different NMDA receptor subunit mRNAs (Akbarian et al. 1995a) may be other examples of activity-dependent effects based on hypoactive circuitry. What we now need to do is to determine whether the functional hypoactivity indeed stems from altered circuitry and if it is developmentally based.

Involvement of the Thalamus

Several theories have implicated the thalamus in schizophrenia. Most have a functional slant, mainly relating to the potential role of the thalamus in "gating," and do not involve a specific thalamic neuropathology. They nevertheless serve to highlight the importance of the thalamus as a relay to the cerebral cortex and as a structure whose function cannot be divorced from that of the cortex in consciousness, perception, and the integration of thought processes.

Apart from the recent description of overall volume changes in the thalamus or in the white matter surrounding it (Andreasen et al. 1994), the only pathology that has been demonstrated in the thalamus of schizophrenia patients involves the MD nucleus. This finding is interesting in view of the connections that link MD to the prefrontal cortex, medial temporal cortex, and basal forebrain, all of which have been implicated in the dysfunction of schizophrenia and in all of which some evidence of schizophrenia pathology has been presented. The primary defect described in the MD nucleus (Pakkenberg 1990, 1992) is one of substantial cell loss—at least 40 percent of the neurons disappear in comparison with the MD nucleus of control thalami. This loss is accompanied by a 22 to 31...
percent reduction in volume of the nucleus; the severity of this loss is apparently unrelated to whether the subjects had been medicated or not. Neuronal density is reduced only slightly, and there is a parallel loss of neuroglial cells. Similar cell loss was found in the nucleus accumbens, but not in other basal forebrain nuclei. Other thalamic nuclei were not examined so it is uncertain whether the more recently reported reductions in thalamic or in perithalamic white matter volume seen in MRI scans of schizophrenia patients stem from the loss of MD neurons or of neurons in all thalamic nuclei.

We need to ask whether the neuronal loss in MD has occurred secondary to a lesion elsewhere, whether it is a primary degeneration of MD neurons occurring in the adult, or whether its origins lie in a disruption of normal thalamic or cortical development. At present, none of these questions can be answered.

Neuronal loss in the thalamus is commonly a retrograde degeneration ensuing from pathology in the cerebral cortex that affects the axon terminations of thalamocortical relay cells. When it occurs in adulthood, retrograde degeneration is typically accompanied by severe gliosis (i.e., a true proliferation of neuroglial cells), although this condition may be less severe if the pathological process occurs slowly over a protracted period. Retrograde degeneration occurring as the result of cortical damage in the developing or immature brain is typically unaccompanied by gliosis. Another potential cause of cell loss in the thalamus customarily occurring without gliosis is a transneuronal degeneration consequent upon destruction of afferent fibers, although this condition has only consistently been described in the lateral geniculate nucleus (Cowan 1970).

Apart from the thalamocortical relay neurons that die in retrograde degeneration, or shrink and may eventually die in transneuronal degeneration, 25 to 30 percent of the neurons in the thalamic nuclei of primates are GABAergic local circuit neurons (Montero and Zempel 1986; Hunt et al. 1991) that are only secondarily affected, if at all, by death of the relay neurons.

Based on the above information, these questions arise from the described pathology in the MD nuclei in schizophrenia: Is it primary? Is it secondary to cortical pathology occurring in adult life or during the development of the cortex? Is it confined to the MD nucleus, or is the whole thalamus affected? Does it affect relay neurons, interneurons, or both? There are no data available to answer any of these questions. The cell loss is unlikely to be a direct effect of chronic drug treatment since the thalamus, the MD included, does not receive a dopaminergic innervation and is thus unlikely to be a target of neuroleptics that act at dopamine synapses. It has to be remembered, however, that dopamine receptors are expressed in the thalamus, unrelated to any obvious dopaminergic fiber system (G.W. Huntley, personal communication, 1993), and that the MD nucleus has strong interconnections with most of the other forebrain areas, such as the nucleus accumbens, that have been implicated in schizophrenia. Most of these forebrain areas receive a heavy dopaminergic innervation, primarily from the ventral tegmental area of the midbrain (reviewed in Bjorklund and Lindvall 1984; Alheid et al. 1990).

The possibility that neurons in MD in schizophrenia may die from a primary pathology affecting this nucleus or the thalamus generally has not been explored. In the absence of evidence of lesions indicative of a cytotoxic pathology elsewhere in the brain of the schizophrenia patient, it is difficult to view a toxic degeneration as a likely possibility. Miller (1989) has raised the interesting suggestion that in schizophrenia patients there may occur a kind of intrinsic toxicity due to the excitotoxic effects of acidic amino acid transmitters such as glutamate, which are released in excess under conditions of heightened neural activity. The weakness of this proposal is that the evidence for enhanced neural activity is rather slight, being mostly confined to electroencephalographic observations; even more, the evidence supporting an imbalance in excitatory amino acid-based transmission is lacking. Finally, the hypothesis requires that the homeostatic mechanisms that should normally compensate for change in levels of excitatory amino acid transmitters and their receptors should be inactivated or defective. For this, we have no evidence.

There is nothing obvious about the development of the thalamus that would lead us to suspect that the MD nucleus should be uniquely vulnerable to a developmental insult. By analogy with experimental animals (McAllister and Das 1977), cells of the MD nucleus should be among the last generated in the neuroepithelium of the third ventricle. From there, they migrate over a short distance into an immediately adjacent region, which should be complete in humans by the 15th week of gestation (see Rakic and Sidman 1969).

The timing is right for a second-trimester insult to perturb this developmental process, but at present we have no way of relating the reported cell loss in the adult MD to a developmental pathology. A defect of neuronal migration or of cell-settling patterns in the thalamus as the result of a developmental insult occurring in the second trimester might be expected mostly to affect the organization of the pulvinar—in humans, unlike all other primates that have been examined, a substantial number of neurons that contribute to the pulvinar arise between the 18th and 22nd weeks from a proliferative zone, the ganglionic eminence, in the wall of the lateral ventricle and...
migrate into the thalamus over the 16th to 34th week (Rakic and Sidman 1969). No evidence of pulvinar pathology has been reported in schizophrenia patients, although it is doubtful that it seriously has been examined. The only indications of pathology in the cortical target regions of pulvinar projection—the occipital, posterior parietal, and posterior temporal association cortex—in individuals with schizophrenia, are the abnormal gyral patterns reported by Jakob and Beckmann (1986) and an alteration in the distribution of interstitial neurons of the white matter similar to that found in the frontal lobe (Akbarian et al. 1993b). Although it is relatively easy to attribute many of the cognitive defects of schizophrenia and especially many of the positive symptoms to disordered integration between pulvinar and the parieto-temporo-occipital association cortex, we are on dangerous ground if we attempt at this time to attribute these symptoms to a primary thalamic pathology, especially to one arising from a developmental disturbance.

If we can accept, at least for argument’s sake, that neural circuit formation is compromised in the prefrontal cortex of schizophrenia patients as the result of earlier occurring subplate pathology, then the thalamic innervation from the MD nucleus should be among the fiber systems affected. Could this lead to death of MD cells because their axons were not able to establish or maintain effective synapses in the prefrontal cortex? We do not know, but a 40 percent loss of cells in MD probably means a 40 percent reduction in thalamocortical axons entering the prefrontal cortex, unless there is compensatory sprouting of those that remain, for which there is no evidence. Let us assume, however, that thalamic input to the prefrontal cortex is substantially reduced in schizophrenia. What does this reduction imply? To attempt to answer this question, we must first look at the overall connections of MD.

The MD nucleus of all mammals is not a single entity, but rather a complex of at least three nuclei, all with different patterns of input-output connections. It is incorrect to consider the MD as a single entity related only or specifically to “the” limbic cortex. The human MD is perhaps the most highly differentiated of all, with clear-cut medial or magnocellular, lateral or parvocellular (fascicular), and posterior or multiform divisions. A further paralamellar division may be regarded more properly as part of the intralaminar system of nuclei (Jones 1985). It is a pity that studies reporting cell loss in the MD in schizophrenia have paid scant attention to these nuclear subdivisions. So far as is known, the connections of the three primary subnuclei of MD are as follows (Velayos and Reinoso-Suarez 1982; Price and Slotnick 1983; Aggleton and Mishkin 1984; Goldman-Rakic and Porrino 1985; Russchen et al. 1987; Cornwall and Phillipson 1988; Giguere and Goldman-Rakic 1988; Groenewegen 1988; Steriade et al. 1988; Kuroda and Price 1991; Siwek and Pandya 1991; Ray and Price 1992, 1993): The magnocellular division receives input from the lateral nuclei of the amygdala and olfactory and entorhinal cortex and projects mainly to areas on the orbital and medial surface of the frontal lobe, including at least cytoarchitectonic areas 11, 12, 13, and the agranular insular area. A large component of this projection is olfactory-related (Benjamin and Jackson 1974; Tanabe et al. 1974, 1975a, 1975b; Takagi 1980; Yarita et al. 1980). The parvocellular and multiform divisions receive input from the superior colliculus and other midbrain structures and project mainly to dorsal and lateral areas of the prefrontal cortex, including areas 14, 24, and 32.

All divisions also receive GABAergic inputs from the so-called ventral pallidum and the pars reticulata of the substantia nigra. The ventral pallidum occupies a key position in that it receives the apparently GABAergic outflow of the nucleus accumbens. This so-called limbic part of the striatum is the target of the presumed glutamatergic inputs from the hippocampus and adjacent cortical areas, such as the entorhinal, retrosplenial, and posterior cingulate areas, and of dopaminergic inputs from the ventral tegmental area of the midbrain (Swerdlow and Koob 1987; Alheid et al. 1990). Other inputs to MD are presumed to be excitatory and glutamatergic. A large population of these afferents arises in the cortical areas to which MD nuclei projects (Ray and Price 1992). They exert their effects in the thalamus via a combination of ionotropic and metabotropic glutamate receptors (McCormick and von Krosigk 1992). Also distributing diffusely throughout MD are cholinergic, noradrenergic, and serotonergic fibers from the brainstem and GABAergic fibers from the thalamic reticular nucleus. The thalamic reticular nucleus is itself under the control of the same brainstem and corticothalamic inputs as MD and is influenced by collaterals of MD axons projecting to the cerebral cortex (reviewed in Steriade et al. 1990).

Much effort has been expended in attempting to calculate how a defect at one point in this complex interconnected circuitry could explain the symptoms of schizophrenia, commonly with an emphasis on the nucleus accumbens, which, unlike MD, receives a substantial dopaminergic input. Apart from the fact that theories based on circuit analysis tend to treat MD as a single entity and to see its sole subcortical input as the GABAergic one from the ventral pallidum—an emphasis perhaps too highly driven by rat rather than by primate anatomy—these theories tend to characterize the various excitatory and inhibitory inputs in absolute terms. I have
serious reservations about whether the functions of a neural circuit, and especially its dysfunction in disease, can be determined simply by adding up the pluses and minuses to arrive at an overall excitatory or inhibitory effect. The thalamus just does not work that way.

In circuit-based theories of schizophrenia, breakdown of the strong cortico-cortical connections between the prefrontal and parietotemporal cortex is commonly thought of as preeminent. The typical inability of the individual with schizophrenia to keep a goal or concept in mind has been argued as a prefrontal defect, whereas symptoms, especially positive ones, which seem to betray defective access to information about the outside world and to long-term memory stores, may indicate a functional disconnection of prefrontal cortex from the parietotemporal cortex and hippocampus. The thalamus, if considered at all, is usually relegated to a role as a source of external information. This betrays the traditional attitude about the thalamus as a simple relay station. A full decade of recent work, however, has revived interest in the thalamus as a center whose activities are intrinsically bound up with the regulation of the state of consciousness and with the manner in which the cerebral cortex gains access to and processes information.

Much of this new awareness of thalamic function has come from reinvestigation from a modern physiological perspective of the propensity for large populations of thalamic neurons to be thrown into repetitive patterns of discharge that oscillate at relatively constant frequencies (Steriade et al. 1990, 1993). Low-frequency oscillations in the range of 2 to 4 hertz (Hz), commonly called spindles, are correlated with drowsy inattentiveness and the phases of sleep characterized by a synchronized electroencephalogram (EEG). Higher frequency oscillations in the range of about 40 Hz occur mainly during phases of sleep characterized by dreaming and a desynchronized EEG. They may reflect events occurring in the awake state when attention is focused (Llinás and Ribary 1993). The capacity for thalamic neurons to oscillate depends on a particular set of intrinsic membrane conductances that ensure that a cell will discharge repetitive action potentials when recovering from inhibition-imposed hyperpolarization that takes the membrane potential below about –60 millivolts (mV) (reviewed in Steriade et al. 1990). In the case of low-frequency oscillations, a pacemaker in the reticular nucleus of the thalamus sets the GABAergic reticular cells to discharge repetitively at low frequency, thus setting up a repetitive series of inhibitory postsynaptic potentials in the cortically projecting cells of the underlying dorsal thalamus. As these cells rebound from inhibition, they fire repetitive action potentials that reexcite the reticular cells, and so the cycle repeats itself, recruiting more thalamic cells to fire series of spindle bursts that eventually wane as reticular nucleus and dorsal thalamic cells get out of synchrony. Under these conditions, the dorsal thalamic cells are thought to be less effective in transferring information from the periphery to the cerebral cortex, and the thalamus is in a sense decoupled from its sources of input.

In the waking state, when the thalamus is functionally coupled to its extrinsic sources of input, the reticular nucleus cells, possibly under the influence of corticofugal influences, discharge tonically at high frequency and serve to dampen background discharge in dorsal thalamic cells, thus increasing the signal-to-noise ratio of excitatory inputs arriving over the afferent pathways. Under these conditions, the thalamus is a more effective transmitter of information to the cerebral cortex. It now seems evident that in brain states involving the collective activities of large populations of neurons, such as in the acts of perception, cognition, and planning of motor strategies, in which large neuronal collections are functionally recruited in the service of a particular performance, cells of the cortico-reticulo-thalamo-cortical loop are thrown into oscillations in the range of 40 Hz. These oscillations may serve to bind together the neural populations of the relevant thalamic nuclei and the cortical territories to which they project (Singer 1993). When demanded, it is assumed that a rapid switching can occur to recruit a different constellation of nuclei and cortical areas.

One of the key aspects of schizophrenia symptomatology—the inability to maintain focus, especially on what is relevant, in order to ensure the appropriate contextual interactions and a cognitively or behaviorally relevant response—could be associated with or even determined by an inability to recruit cortex and thalamus into collective action. The fragmentation of thought processes in schizophrenia seems to be a result of both a failure to bind together the large thalamic and cortical cell collectives necessary for higher order processing and a difficulty in switching between collectives. If we consider the possible implications in the prefrontal cortex, a failure to integrate the activities of the large neuronal populations of prefrontal cortex and MD nucleus should have the effect of making the prefrontal cortex less effective in holding spatial and nonspatial representations in mind while a response strategy is planned and a response initiated.

One could envisage a situation in which a sequence of thought processes initiated by an external stimulus and requiring an integrated response would depend upon the sequential or parallel recruitment into sequential oscillation of large neuronal ensembles in sensory thalamic nuclei and primary sensory cortices, in pulvinar and parietotemporal cortex, in anterior thalamic nuclei and limbic cortex, and in MD nucleus and prefrontal cortex. Failure of any or all of the thalamic components of each collec-
tive would therefore be associated with fragmentation of thought such as exhibited in schizophrenia.

Although it is tempting to focus on the substantial loss of neurons in the MD nucleus as a prime cause of failure of the kind of thalamocortical integration outlined here, its involvement is by no means certain. Other mechanisms may be involved, including the incapacity of the corticothalamic population of cells, mainly located in layer VI of the cortex, to oscillate at the frequency required to maintain 40-Hz oscillations in the thalamus. They could also include changes in the balance of subcortical inputs to the MD nucleus or to the reticular nucleus, both of which would alter the functional state of the thalamic cells, as well as alterations in the intrinsic membrane properties of MD or reticular nucleus cells that would render them less likely to be recruited into cooperative behavior.

Grace (1991) has proposed that prolonged hypoactivity of the prefrontal cortex as exhibited by schizophrenia patients, should be associated with chronically reduced cortico- striatal (glutamatergic)-induced, tonic, nonsynaptic release of dopamine from dopaminergic terminals in the ventral striatum. This release would activate homeostatic mechanisms, resulting in upregulation of dopamine receptors and other dopaminergic synaptic mechanisms in the ventral striatum. Hence, when behaviorally relevant stimuli activated dopaminergic neurons projecting to the striatum, the spike-mediated phasic release of dopamine (which is not subject to homeostatic control) would produce unusually large dopamine responses, with consequent effects throughout the circuitry downstream from the ventral striatum, including the thalamus (Lavin and Grace 1994).

Reduction in prefrontal cortical activity sufficient to reduce corticostriatal activation is also likely to reduce corticothalamic activation. Thus, the capacity of the corticothalamic projection to reinforce thalamocortical oscillations in the 40-Hz range may be compromised, with severe consequences for cognition. This finding might lead us back to the cortex as the location of an effective lesion in schizophrenia. On the other hand, a 40-percent loss of thalamic neurons that are one of the main sources of afferent drive to the cortex could be the cause of the reduction in cortical activity. At this point, our argument becomes circular and we are forced to conclude with a plea for further studies to determine the relationship between thalamic and cortical pathology and the nature of schizophrenia symptom complexes.

Summary

Morphological data of a variety of types provide suggestive evidence that cortical ontogenesis may be affected in schizophrenia. Reductions in thalamic cell numbers especially in the MD nucleus may or may not be secondary to cortical pathology. Neuronal migration, subplate function, and axonal elimination are potential areas in which a defect leading to schizophrenia might operate in cortical development. Neuronal proliferation is unlikely to be affected, and there is as yet no evidence that synaptic pruning and stabilization are involved, although these processes could be present in the absence of major cytoarchitectural changes.

In the absence of severe defects of brain structure in schizophrenia, any developmental mechanisms that are disrupted as primary factors in the disease are likely to be those that govern the establishment, refinement, and maintenance of cortical connections. The disintegration of thought in schizophrenia may then be likened to a functional disconnection syndrome.

Functional connectivity in the cortex of individuals with schizophrenia is obviously disorganized, but defective anatomical connectivity has still not been demonstrated. Neurochemical changes, such as downregulation of GAD gene expression, and changes in dopamine receptors and in structural proteins that do not appear to result from neuroleptic treatment may, however, represent activity-dependent manifestations of defective circuitry. An associated defect in thalamic function, dependent on the loss of thalamic cells and/or of corticothalamic inputs, could lead to disintegration of thought processes by a failure in functional brain states dependent on collective oscillation of large ensembles of cortical and thalamic neurons.

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