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Neurodevelopmental abnormalities in schizophrenia: Insights from neuropathology

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Abstract
Growing epidemiological, genetic, and clinical neurobiological evidence indicates that abnormalities in brain development play determining roles in the pathobiology of schizophrenia. Neuropathological research has made significant progress in delineating cellular and molecular abnormalities in schizophrenia that have relevance to neurodevelopment. This paper reviews the neurodevelopmental processes of neurogenesis, neuronal migration, differentiation, synaptogenesis, neuron and synaptic pruning, and myelination and the reported neuropathological findings in schizophrenia that may be a consequence of disturbances in these processes. While many neuropathological findings in schizophrenia are controversial or await confirmation, reported abnormalities in neuron density, number and morphology, cytoarchitecture, dendritic arbors and spines, synapse-related proteins, and the well-established absence of gliosis or any other evidence of neurodegeneration or neural injury all provide support for the neurodevelopmental model of schizophrenia.

Growing evidence indicates that abnormalities in brain development play determining roles in the pathophysiology of schizophrenia. Genetic factors are strong, and some researchers estimate that as much as 85% of the variance in risk for the disorder is accounted for by genes (Cannon, Kaprio, Lonnqvist, Huttunen, & Koskenvuo, 1998a; McGuffin, Anderson, Owen, & Farmer, 1994). A history of gestational and perinatal complications has also been found to be common in individuals who later manifest schizophrenia. These include maternal starvation during the 1st trimester of pregnancy (Susser, Neugebauer, Hoek, Brown, Lin, Labovitz, & Gorman, 1996), influenza infection during the 2nd trimester (Mednick, Machon, Huttunen, & Bonnett, 1988), rhesus and ABO blood-type incompatibility (Hollister, Laing, & Mednick, 1996), and perinatal anoxic birth injuries (Cannon, Mednick–Hollister, Bearden, & Hadley, 1999).

The developmental model of schizophrenia is further supported by findings of minor physical anomalies (e.g., reduced head circumference, which reflects decreased brain; low set ears; abnormal palate height) that are often seen in association with abnormal CNS development (McNeil, Cantor–Graae, Nordstrom, & Rosenlund, 1993; O'Callaghan, Larkin, Kinsella, & Waddington, 1991). Other evidence comes from retrospective analyses of early childhood development using such items as school records and home movies. These find that motor, language, and social development are often delayed among schizophrenics compared to normal and sibling controls (Jones, Rodgers, Murray, & Marmot, 1994; Walker, 1994).

There is also emerging evidence from structural neuroimaging studies showing that abnormalities in regional gray matter and cerebrospinal fluid volumes are common in individuals with schizophrenia and some of their unaffected siblings (Cannon, 1996; Can-

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non, vanErp, Huttunen, Lonnqvist, Salonen, Valanne, Poutanen, & Standertskjold–Nordenstam, 1998; Pfefferbaum & Marsh, 1995). These findings likely reflect genetic (or shared environmental) developmental effects. Finally, one of the most consistent neurobiological findings in schizophrenia has been ventriculomegaly seen in CT and MRI studies (Liddle, 1995). The degree of ventricular enlargement correlates with poor premorbid adjustment and has been found at the first onset of symptoms. Altogether, these diverse clinical findings provide strong circumstantial evidence for the role of abnormal neurodevelopment in schizophrenia.

One of the major goals of schizophrenia research is to delineate abnormal neurobiological processes at the cellular and molecular level that could culminate in the disease. For the neuropathologist interested in development, this represents a considerable challenge. Neurons in the nonhuman primate and human brain are born, migrate, and assume their mature phenotype in a complex and highly orchestrated process during fetal development and the immediate postnatal period (Arnold & Trojanowski, 1996a, 1996b; Nowakowski & Rakic, 1981). By the time the clinical expression of schizophrenia is apparent, neurogenesis and development is essentially complete. Recent work has found that neuronal progenitor cells in the dentate gyrus are capable of generating new neurons in the adult human (Eriksson, Perfilieva, Bjork–Eriksson, Alborn, Nordborg, Peterson, & Gage, 1998), though their number is very small and it is likely that there are no, or extremely limited, functional implications of such adult neurogenesis. While cerebral neurons are capable of some connectional plasticity even into late life, they are to a large degree morphologically static and molecularly homeostatic. Thus it would appear that the opportunity to examine neural development in schizophrenia is unavailable.

Neuropathological researchers have approached this challenge in several ways. Some have focused on cytoarchitecture and patterns of innervation as "smoking guns" of remote problems in neuronal migration or developmental connectivity. Others have looked for postmaturational neurodegeneration or neural injury in the brains of patients with schizophrenia and, finding none, have suggested that aberrant neurodevelopment must be responsible by default. A further opportunity is to examine the adult expression of developmentally relevant molecules in neural systems such as the hippocampus or olfactory system in which there is a higher degree of plasticity throughout life.

Biology of Normal Neurodevelopment

As a framework upon which studies of neurodevelopmental pathology can be based, it is important to understand the processes and stages of normal cerebral development. Studies in nonhuman mammalian species have demonstrated several principles by which cortical development occurs (Angevine, 1965; Austin & Cepko, 1990; Bayer, Altman, Russo, Dai, & Simmons, 1991; Nowakowski & Rakic, 1981; Rakic, 1972; Schatz, Chun, & Luskin, 1988). Primitive neurons, or neuroblasts, are born in a germinal matrix lining the ventricles. The mechanisms that determine the proliferation of these neuroblasts and their ultimate fate as unique neurons involves the interaction of both intrinsic cellular signals (e.g., transcription factors) and extrinsic signals (e.g., growth factors). Nascent neurons migrate both radially along radial glial fibrils and tangentially, assume their position in the cortical plate in an “inside-out” fashion, and establish dendritic arborization and synaptic contact once they have stopped migrating. Programmed cell death (also known as apoptosis) and synaptic pruning ensues for cells that fail to establish adequate synaptic connectivity or access to growth (trophic) factors.

It should be noted that maturation of the cortex is not uniform. For instance, in the rodent there is variability between brain regions with frontal cortices developing prior to occipital cortices, ventrolateral cortices adjacent to the rhinal sulcus developing prior to dorsomedial cortices, and higher order association cortices developing prior to primary sensory and motor cortices (Bayer et al., 1991). Among cortices, neurons destined for the hippocampal region are perhaps the earliest to be

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born (Angevine, 1965; Nowakowski & Rakic, 1981; Rakic & Nowakowski, 1981), but in terms of neuroblast migration and cytoarchitectural maturation, the hippocampal region is late relative to much of the neocortex (Humphrey, 1964; Nowakowski & Rakic, 1981).

The migration of neurons to their final destinations within cortical or subcortical structures is a fundamental cellular process that is necessary for the ensuing development of an orderly neural organization in the brain. Migration is contingent upon the complex orchestration of expression of cell–cell recognition receptors, cell adhesion molecules that allow a migrating cell to interact with other cells and the extracellular matrix, and activation of specific ion channels that induce second messenger-mediated signals for the cellular changes involved in the motility of nascent neurons. These second messengers then regulate polymerization of stiff and contractile cytoskeletal proteins which ultimately controls the rate of neuronal movement during migration, the neuronal morphology and polarity, and their final resting position. These events determine neuronal identity prior to the formation of synaptic connections (Rakic, Cameron, & Komuro, 1994).

Numerous genes are involved in neuronal migration, and mice with spontaneous genetic mutations or experimentally induced (knockout) mutations have been very instructive in delineating mechanisms of neuronal migration. For instance, the reeler mouse is a spontaneous mutant mouse strain in which there is an abnormal pattern of layering of neurons in the cerebral cortex and cerebellum (Lambert-de-Rouvroit & Goffinet, 1998). Neurons migrate to the cortex in an "outside-in" fashion, rather than the normal "inside-out." Reeler mice lack a functional gene product, the protein reelin which is a developmentally regulated protein produced in abundance during the period of neuronal migration (Curran & D'Arcangelo, 1998). This protein is also present in humans (Meyer & Goffinet, 1998). Reelin is secreted by the marginal zone cortical neurons (Cajal–Retzius cells) into the extracellular space near the cortical surface and is thought to help guide the newly arriving migrating neurons to the proper destination. Without this protein, the laminar patterning of the cortex and cerebellum of the reeler mouse is severely disorganized. As a consequence, normal synaptic connections and patterns cannot form, leading to neurologic dysfunction.

Neurons differentiate at the end of migration. They enlarge as they sprout dendritic and axonal processes, extend the length of their axons and dendritic arbors, and establish synaptic connections. Axons and dendrites are tipped by motile growth cones as they grow. Functional neuronal circuits are established when growth cone activity ceases and pre-and postsynaptic sites differentiate. During development, imbalances in growth factors or neurotransmitters may lead to faulty synaptic connections and regressive events including programmed cell death.

The behavior of growth cones and neuronal differentiation in general is influenced by a host of extracellular neurotransmitters and growth factors, including excitatory amino acids, monoamines, acetylcholine, and members of the neurotrophin family of growth factors as well as other growth factors (e.g., fibroblast growth factor, epidermal growth factor; Mattson, 1989). Neurotrophic factors are endogenous, soluble proteins regulating survival, growth, morphological plasticity, or synthesis of proteins for differential functions of neurons. Examples of neurotrophic factors are nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and ciliary neurotrophic factor (CNTF). These growth factors stimulate a multitude of cellular effects at the structural and functional level that result in the promotion of survival and differentiation of responsive neurons. Actions include stimulation of structural protein synthesis, general metabolic processes, and mechanisms necessary for neurotransmitter synthesis and release.

As in migration, intracellular signaling systems are also critical in mediating neuroarchitectural responses to neurotransmitters and growth factors by altering the status of the cytoskeleton and vesicular substrates. These include ion channels and second messenger kinase systems involving calcium, cyclic nucleotides, and diacylglycerol.

It is noteworthy that beyond their role in

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neurodevelopment, many of these same extracellular and intracellular molecular signaling mechanisms play a role in neural plasticity in the mature nervous system. Neuroarchitecture may change adaptively throughout life as new synapses form, old ones disintegrate, and new neurite outgrowth occurs. Characterizing the determinants of ongoing neural plasticity in schizophrenia may represent an opportunity for researchers to identify abnormalities pertinent to both current neural status as well as events during the formation of the brain.

Myelination is another process of maturation where oligodendroglial cells ensheathe axons in a lipoproteinaceous insulating material. This insulation increases the speed and efficiency of axonal depolarization, and thus electrical signal transduction is greatly enhanced. Myelination is a relatively late developmental process that is at least partially dependent on the amount of activity within given pathways. For instance, pathways connecting visual areas show a decreased degree of myelination, as well as atrophy of cortical ocular columns in the occipital lobe in blind persons (Scholtz, Swettenham, Brown, & Mann, 1981) and in animals that have had their eyesight experimentally destroyed (Horton & Hocking, 1997). The timing of myelination varies greatly from region to region in the human nervous system. Myelination has been observed as early as 10 weeks gestational age in the spinal cord (Tohyama, Lee, Rourke, & Trojanowski, 1991), 23 weeks in the brain stem, 25 weeks in the basal ganglia (Hasegawa, Houdou, Mito, Takashiuma, Asanuma, & Ohno, 1992), but almost at term in the hippocampus (Arnold & Trojanowski, 1996a; Benes, 1989). Myelination in the hippocampus continues through childhood with a striking increase in adolescence in some subfields. Similarly, myelination in the prefrontal cortices is most active during adolescence and even into adulthood (Yakovlev & Lecours, 1967).

Neuropathological Studies of Schizophrenia With Relevance to Neurodevelopment

Despite a century of investigations into the neuropathology of schizophrenia, we still have not identified the defining lesions for the disorder and the many abnormalities that have been described are almost all either controversial or as yet unconfirmed. In addition, while some of the findings are more suggestive of aberrant development than others, none can be attributed with certainty to development as opposed to postmaturational injury. The following will briefly summarize the major neuropathological studies of schizophrenia with comment on their relevance to neurodevelopment (see Table 1).

Gross neuroanatomy

Quantitative gross anatomic studies have tried to verify volumetric abnormalities in schizophrenia that have been described using in vivo neuroimaging. Findings from these studies are generally consistent with the predominant in vivo findings of ventricular enlargement (Brown, Colter, Corsellis, Crow, Frith, Jagoe, Johnstone, & Marsh, 1986; Bruton, Crow, Frith, Johnstone, Owens, & Roberts, 1990; Crow, Ball, Bloom, Brown, Bruton, Colter, Frith, Johnstone, Owens, & Roberts, 1989; Pakkenberg, 1987), decreased hippocampal–parahippocampal size (Bogerts, Falkai, Haupts, Greve, Ernst, Tapernon–Franz, & Heinzmann, 1990; Bogerts, Meertz, & Schonfeldt–Bausch, 1985; Falkai, Bogerts, & Rozumek, 1988; Jeste & Lohr, 1989), and decreased parahippocampal cortical thickness (Altshuler, Casanova, Goldberg, & Kleinman, 1990; Brown et al., 1986; Colter, Battal, Crow, Johnstone, Brown, & Bruton, 1987). All of the studies that examined ventricular size have confirmed the finding of enlargement, but several studies have not been able to replicate the findings of abnormal hippocampal and parahippocampal volume or size (Altshuler et al., 1990; Benes, Sorensen, & Bird, 1991b; Brown et al., 1986; Bruton et al., 1990; Colter et al., 1987; Heckers, Heinsen, Geiger, & Beckmann, 1991; Heckers, Heinsen, Heinsen, & Beckmann, 1990). Findings in other regions, including decreased volumes of the dorsomedial nucleus of the thalamus (Bogerts et al., 1985; Lesch & Bogerts, 1984; Pakkenberg, 1990; Pakkenberg, 1992), cerebellar vermis (Weinberger, Kleinman,

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Table 1. *Neurodevelopmental events and possible related neuropathological abnormalities that have been described in schizophrenia* (*see text for details*)

Neurodevelopmental Process	Approximate Timing[a]	Possible Related Neuropathological Abnormalities
Neurogenesis	E4 weeks–E32 weeks	Atrophy Neuron number
Neuronal migration	E4 weeks–P4 months	Cytoarchitecture Neuron orientation Number and distribution of white-matter neurons Guidance molecules (e.g., N-CAM, reelin)
Programmed cell death	E6 weeks–P6 months	Neuron number Cytoarchitecture Number and distribution of white-matter neurons Trophic factors
Synaptogenesis	E20 weeks–childhood	Synaptic density Synapse-related protein and mRNA expression Trophic factors
Dendritic and axonal arborization	E22 weeks–adulthood	Neuron density Neuron size Cytoskeletal protein expression (e.g., MAP2) Dendritic length and branching Dendritic spine number and clustering patterns Growth cone protein expression Trophic factors
Myelination	E23 weeks–adulthood	No studies to date
Synaptic elimination	P4 months–adulthood	Synaptic density Synapse-related protein and mRNA expression

[a]E, embryonic age; P, postnatal age.

Luchins, Bigelow, & Wyatt, 1980), and brain stem (Bogerts, Hantsch, & Herzer, 1983; Lohr & Jeste, 1988), still await replication, while results of basal ganglia volumetric studies have at best been unconfirmed (Arendt, Bigl, Arendt, & Tennstedt, 1983; Bogerts et al., 1990; Bogerts et al., 1985; Brown et al., 1986; Heckers et al., 1990; Heckers, Heinsen, Heinsen, & Beckmann, 1991; Pakkenberg, 1990), or even contradictory for the internal globus pallidus (Bogerts et al., 1990; Heckers, Heinsen, Heinsen, & Beckmann, 1991). It should be noted that gross anatomic studies do not address the issue of development versus postmaturational neural injury–degeneration. Ventriculomegaly or regional volume abnormalities may result from developmentally based dystrophy or degeneration-related atrophy.

Cytoarchitecture

Investigations of abnormal cytoarchitecture in limbic cortices have been among the more compelling with relevance to neurodevelopment. " Cytoarchitecture" refers to the three-dimensional spatial arrangement of neurons within a given region of cortex or subcortical nucleus. Modern investigations of cytoarchitecture have reported various abnormal arrangements and laminar distributions of neurons within the ventromedial temporal lobe. These have been interpreted as reflecting unsuccessful migration of neurons.

The earliest study by Kovelman and Scheibel (1984) and later Conrad, Abebe, Austin, Forsythe, and Scheibel (1991) reported that pyramidal neurons within the ammonic subfields of the hippocampus showed significant variability in their axes of orientation which was most severe at the interfaces between subfields. This disorganization in the normally uniform alignment of neurons was interpreted as a developmentally based migration disturbance. However, there have been several attempts to replicate these findings with similar and different methods and none have been successful (Altshuler, Conrad, Ko-

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velman, & Scheibel, 1987; Arnold, Franz, Gur, Gur, Shapiro, Moberg, & Trojanowski, 1995; Benes, Sorensen, & Bird, 1991; Christison, Casanova, Weinberger, Rawlings, & Kleinman, 1989; Zaidel, Esiri, & Harrison, 1997).

Abnormal neuronal migration during brain development has also been suggested in qualitative cytoarchitectural studies of the entorhinal cortex, a limbic periallocortex intimately related to the hippocampus. Jakob and Beckmann (1986, 1989, 1994) reported disturbed laminar differentiation in up to two-thirds of their series of 66 cases. One of the key features of this disturbance was that neurons characteristically found in layer II (or layer pre-α in the nomenclature of Braak, 1980) seemed to be heterotopically positioned into deeper layers. Arnold, Hyman, van Hoesen, and Damasio (1991) evaluated entorhinal cytoarchitecture in six carefully screened schizophrenia cases from the Yakovlev archives and observed various abnormalities among all six. These included bizarre invaginations of the normally smooth entorhinal cortex surface, a paucity of cells in superficial layers, attenuation of the deeper layers, poor laminar differentiation, poorly developed clusters of neurons in layer II, and apparent heterotopic displacement of layer II–type neurons (see Figure 1). In contrast, others have reported no obvious cytoarchitectural abnormalities in the entorhinal cortex (Akil & Lewis, 1997; Krimer, Herman, Saunders, Boyd, Hyde, Carter, Kleinman, & Weinberger, 1997).

One of the chief criticisms that can be made of the above studies of the entorhinal cortex is that they are qualitative descriptions and thus subject to differences in interobserver experience and bias. This is especially important in the entorhinal cortex where it is normal to have some variability in cytoarchitecture occurring both between cases and within cases at different levels along its rostral caudal axis (Beall & Lewis, 1992). This might lead to either missed findings or interpretation of findings as abnormal when they really represent normal variability.

There have been three studies that have provided quantitative data about entorhinal cytoarchitecture. Falkai et al. (1988) found

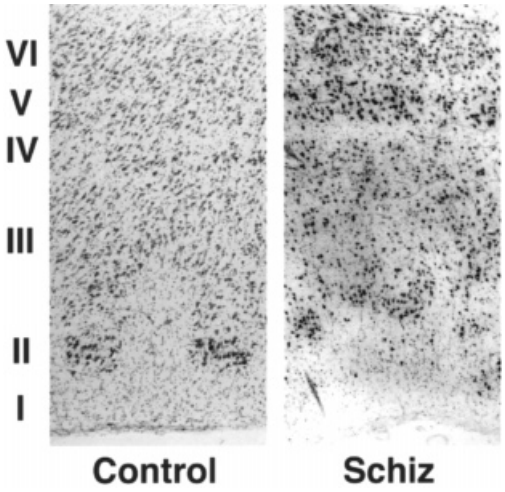


Figure 1. Cytoarchitecture of the entorhinal cortex. Compared to the nonpsychiatric control case, the entorhinal cortex of this 37-year-old male with schizophrenia exhibits a disorganized cellular arrangement in superficial layers with poorly formed clusters of neurons in layer II, a patchy distribution of neurons in layer III, and smaller neuron size in layers II and III.

that total neuron number was reduced 37% and that there were trends toward a greater reduction in neurons in deep layers and layer II clusters compared to layer III. Krimer et al. (1997) reported no laminar disorganization in the entorhinal cortex although certain subfields exhibited a decrease in neuron density.

Arnold, Han, and Ruscheinsky (1997) recently examined the distribution of neurons within individual layers of a rigorously defined subarea of the rostral entorhinal cortex using spatial point pattern analysis. This method applies various statistical analyses to interneuronal distances measured in the *x*, *y* plane. They found an abnormally clustered dispersion of neurons and reduced effective radius surrounding neurons ("dead space") in layer III, increased effective radius in layer II, and no abnormalities in layer V. They reported that these data provided further evidence for subtle aberrant cytoarchitecture in the entorhinal cortex that were generally concordant with their earlier qualitative study.

Cytoarchitectural abnormalities also have been observed in the anterior cingulate cortex in schizophrenia. Employing tracings of neu-

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ronal aggregates and measures of interneuronal distances, Benes and Bird (1987) found that aggregates of neurons were smaller and more widely spaced in layer II in schizophrenics compared to controls and that there was a subtle but significant increase in the frequency of larger nearest neighbor distances in layer III. Subsequent work by Benes and colleagues found a decreased density of local circuit neurons, an increased number of vertical axons (contributing to altered neuropil space), and an altered distribution of catecholaminergic innervation (Benes, Majocha, Bird, & Marrotta, 1987; Benes, McSparren, Bird, SanGiovanni, & Vincent, 1991; Benes, Sorensen, Vincent, Bird, & Sathi, 1992; Benes, Todtenkopf, & Taylor, 1995; Benes, Vincent, Alsterberg, Bird, & SanGiovanni, 1992). Altogether, these findings have been interpreted as reflecting a "miswiring" of the anterior cingulate cortex.

Several other studies have focused on the nature and position of interstitial white-matter neurons lying deep to temporal and frontal cortices in schizophrenia. These neurons are considered to be remnants of the cortical subplate and thus provide some indication of brain development. Akbarian et al. (Akbarian, Bunney, Potkin, Wigal, Hagman, Sandman, & Jones, 1993; Akbarian, Vinuela, Kim, Potkin, Bunney, & Jones, 1993) found abnormal numbers and positioning of NADPH–diaphorase neurons deep in subcortical white matter in frontal and temporal lobes. Another useful marker of interstitial white-matter neurons is the microtubule-associated protein MAP2, and two groups have reported abnormalities in density or distribution of these neurons in schizophrenics. One found an increase in the density of neurons in superficial portions of the white matter (close to the cortical border) compared to controls, while the densities were similar in deeper portions (Anderson, Volk, & Lewis, 1996). In contrast, another group reported a decrease in the density of MAP2 white-matter neurons in superficial portions of the midfrontal gyrus white matter, while the density was increased in deeper portions. Similar results were noted using other markers of interstitial neurons (Akbarian, Kim, Potkin, Hetrick, Bunney, & Jones, 1996). Because the subplate is important in directing the establishment of normal connectivity, disturbance of the subplate could lead to altered connection formation. If confirmed, these findings would thus serve to link theories of abnormal neuronal migration and the miswiring of connections.

Although aberrant neuronal migration has been the interpretation most commonly invoked for cytoarchitectural abnormalities, there are other possible explanations. The ultimate cytoarchitecture of a given region is determined by complex developmental and regressive neurobiological processes. Many changes occur after migration. As noted previously, a host of intrinsic signaling mechanisms responding to extrinsic growth factors and neurotransmitters influences neuron survival, morphology, neurite outgrowth, and patterns of synapse formation. Those young neurons that fail to establish adequate synaptic connectivity and access to trophic factors do not survive. Furthermore, the spatial organization of neurons depends not only on the number of neurons that migrate to a particular position and survive, but also on the neuropil space in which those neurons reside. Finally, environmental factors during growth and development (e.g., infection, ischemic injury, trauma), as well as neurodegenerative changes that are part of normal aging, may further alter the cytoarchitecture that is observed at postmortem examination.

From a functional standpoint, the distribution of cells within a given brain region may have important implications in that the ability of local neuron ensembles to work in a coordinated fashion depends on the integrity of their synaptic connectivity. Physical proximity or arrangement likely reflects the circuits' integrity.

From a molecular standpoint, successful neuronal migration during brain development is contingent upon the orchestrated expression of a series of trophic factors and guidance molecules. As mentioned above, one protein that is important for neuronal migration is reelin. This protein is secreted by the early arriving pioneer marginal zone neurons (Cajal–Retzius cells), remnants of which can be found in superficial cortical laminae in the

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adult. Impagnatiello, Pisu, Pesold, Uzunov, Dwivedi, Pandey, Caruncho, Costa, and Guidotti, (1998) recently reported decreases in reelin mRNA and protein in various regions of the brain from patients with schizophrenia.

Another family of proteins are the neural cell adhesion molecules (N-CAMs), which are important for neuronal migration and may be involved in ongoing synaptic plasticity. Barbeau, Liang, Robitaille, Quirion, and Srivastava (1995) reported a decrease in the number of hippocampal hilar neurons immunoreactive for the embryonic polysialylated N-CAM isoform in subjects with schizophrenia, and interpreted this as consistent with altered plasticity in the disorder and, further, supportive of neurodevelopmental hypotheses in schizophrenia. Vawter, Cannon–Spoor, Hemperly, Hyde, VanderPutten, Kleinman, and Freed (1998) have also examined N-CAMs in schizophrenia and reported an increase in the several N-CAM isoforms in hippocampus and prefrontal cortex. They suggested that these findings could be due to structural brain abnormalities, abnormal glial processing of N-CAM, or abnormal regulation of N-CAM expression.

Neuron number

Determining whether the whole brain or particular brain regions have the normal complement of neurons has been the subject of many postmortem studies in schizophrenia. Are there fewer neurons that would reflect abnormalities in the birth or survival of neurons during development? Unfortunately, most studies have had methodological limitations that prevent answering this question. While conceptually simple, making an accurate estimate of total neuron number within a structure, particularly a given region of the cerebral cortex, is technically arduous, and has been the subject of a number of recent commentaries (Guillery & Herrup, 1997; Saper, 1996). It requires systematic sampling, three-dimensional, nonbiased counting methods, and determination of a region's total volume. Total neuron number would be calculated as the product of the neuron density and region volume. Almost all investigations have determined neuron density but not region volume, and so total neuron number cannot be determined. Neuron density alone may or not be an adequate proxy for neuron number.

The majority of studies of neuron counts have focused on the ventromedial temporal and frontal lobes. Findings have been controversial. Many studies reported decreased neuronal density in various regions including the hippocampus (Falkai & Bogerts, 1986; Jeste & Lohr, 1989), entorhinal cortex (Falkai et al., 1988; Krimer et al., 1997), superior temporal gyrus (Holinger, Rosen, & Galaburda, 1995), dorsolateral prefrontal cortex (Benes, Davidson, & Bird, 1986), anterior cingulate cortex (Benes et al., 1986; Benes, McSparren, et al., 1991), as well as cerebellar Purkinje cells (Reyes & Gordon, 1981) and substantia nigra (Bogerts et al., 1983). Recent and more rigorous investigations often have failed to confirm these findings. For instance, no abnormalities in total neuron density have been observed in ammonic subfields of the hippocampus or entorhinal cortex using more advanced counting methods (Arnold et al., 1995a; Benes et al., 1991b; Heckers et al., 1991a), although one recent report found a decrease in a subpopulation of nonpyramidal neurons in CA2 (Benes, Kwok, Vincent, & Todtenkopf, 1998). One stereological study of subcortical cerebral nuclei has found a decrease in the total neuron number of the mediodorsal nucleus of the thalamus and nucleus accumbens (Pakkenberg, 1990), while another reported a selective decrease in parvalbumin-immunoreactive thalamocortical projection neurons in the anteroventral nucleus of the thalamus (Danos, Baumann, Bernstein, Franz, Stauch, Northoff, Krell, Falkai, & Bogerts, 1998).

Recent studies of the dorsolateral prefrontal cortex reported an *increased* density of smaller neurons in association with a decrease in the interneuronal compartment (neuropil) of portions of the dorsolateral prefrontal cortex (Rajkowska, Selemon, & Goldman–Rakic, 1998; Selemon, Rajkowska, & Goldman–Rakic, 1998). This is of particular interest because the neuropil is largely composed of neuronal processes (axons, dendrites) as well as astrocytes and their processes. A decrease

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in the neuropil might indicate a decrease in dendritic arborization or axonal input.

Neuronal somatodendritic morphology

One of the more consistent neuropathological findings in schizophrenia has been a multiregional decrease in neuron size. While reports are still relatively few in number, smaller neurons have been reported in the hippocampus (Arnold, Franz, et al., 1995; Benes, Sorensen, & Bird, 1991), entorhinal cortex (Arnold, Franz, et al., 1995), dorsolateral prefrontal cortex (Rajkowska et al., 1998), anterior cingulate cortex (Benes et al., 1986), substantia nigra (Bogerts et al., 1983), locus coeruleus (Karson, Garcia–Rill, Biedermann, Mrak, Husain, & Skinner, 1991; Lohr & Jeste, 1988), and cerebellar Purkinje cell layer (Tran, Smutzer, Doty, & Arnold, 1998). In contrast, primary motor cortex and primary visual cortex neuron sizes have been found to be normal (Arnold, Franz, et al., 1995). The reasons for this smaller neuron size are unclear at present. On a purely anatomic basis, the size of neuronal somata generally correlates with the length and size of axons that need to be metabolically supported as well as the extent of dendritic arborization. If dendritic arbors were attenuated in schizophrenia, it could help account for both smaller neuron size and the decreased neuropil–increased neuron density described above. Using Golgi staining, several studies have reported abnormalities in dendrites in schizophrenia, including decreases in dendritic spines and shorter dendrites with fewer distal processes (Garey, Ong, Patel, Kanani, Davis, Hornstein, & Bauer, 1995; Glantz & Lewis, 1995, 1996; Rosoklija & Dwork, 1998), although in two, dendritic lengths and branch patterns appeared normal (Glantz & Lewis, 1995, 1996). These studies were either small or preliminary, and thus the findings must be considered inconclusive at this point.

Investigations of the neuronal cytoskeleton

Neurons have complex three-dimensional shapes that are stereotyped (neuron body, axon, dendritic arbor), but also different according to particular neuronal cell types. The characteristic shape of each part of the neuron is engendered by the composition and framework of its neuronal cytoskeleton (Burgoyne, 1991). Microtubules and neurofilaments are the main cytoskeletal elements determining neuronal morphology. In axons, neurofilaments form dense arrays, while microtubules are arranged in small clusters among the neurofilaments. In contrast, microtubules are much more prominent in dendrites, with a more uniform distribution and neurofilaments are present solitarily or in small fascicles. Beyond the function of providing scaffolding for the neuron and its processes, the neuronal cytoskeleton also plays dynamic roles in cell division and neurite outgrowth in the developing nervous system, in the transport of materials along axons and dendrites in both directions, and in mediating plastic changes in neuronal morphology that may underlie the long-term modifications required for learning and memory. These events occur in response to both intracellular and extracellular signals.

Arnold, Lee, Gur, and Trojanowski (1991) qualitatively surveyed the hippocampal formation with a panel of antibodies directed at a variety of developmentally regulated neuron-specific cytoskeletal proteins in six prospectively accrued schizophrenic cases. They reported that two microtubule-associated proteins (MAP2 and MAP5) appeared selectively diminished in expression in the subiculum and entorhinal cortex compared to controls, while other cytoskeletal proteins appeared to be normally expressed (tubulins, tau, neurofilament proteins). Decreased MAP2 expression in subiculum was also observed by Rosoklija et al. (1995, p. 626) in 40% of their schizophrenia sample, although they questioned the disease specificity in that some patients with other neuropsychiatric conditions also showed decreased subicular MAP2.

These initial explorations of the neuronal cytoskeleton in schizophrenia offer some promise for understanding the molecular bases of neuronal morphologic abnormalities. But they were both conducted in elderly samples of schizophrenics and so it is difficult to say to what extent this abnormal expression of developmentally regulated proteins reflects

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an abnormality that played a role in the abnormal development of the nervous system, early course of the disease, or aging. Further investigations in young populations will help address this.

Synaptic pathology

It has been theorized that the bizarre thought processes and cognitive dysfunction of schizophrenia may result from aberrant patterns of connectivity, or "miswiring" of the brain (Benes, 1993; Frith & Done, 1988; Gray, Feldon, Rawlins, Helmsley, & Smith, 1991; Stevens, 1992). Quantitative studies of synapses and synapse-related proteins and mRNAs have begun to explore this hypothesis. Results to date have been somewhat inconsistent, although the number of studies are still relatively few. As noted above, Golgi studies indicate a decrease in the number of dendritic spines (Garey et al., 1995; Glantz & Lewis, 1996). Electron microscopy studies have also found abnormalities with aberrant clustering or densities of dendritic spines (Aganova & Uranova, 1992; Ong & Garey, 1993; Roberts, Gaither, Peretti, Conley, & Lapidus, 1995; Soustek, 1989).

Synaptic density has been assessed immunohistochemically with monoclonal antibodies directed at various synaptic vesicle related proteins. Results have been controversial, although the regions assessed and the methods used have varied. Synaptophysin density in prefrontal cortices has been found to be decreased by some (Glantz & Lewis, 1997), while synaptophysin and other presynaptic proteins were reported to be increased by others (Gabriel, Haroutunian, Powchik, Honer, Davidson, Davies, & Davis, 1997). In another immunochemical study, synaptophysin was unchanged in the hippocampus, but synapsin was decreased (Browning, Dudek, Rapier, Leonard, & Freedman, 1993). One study found no change in synaptophysin density in the ventromedial temporal lobe by optical densitometry of immunohistochemical reaction product, but there was a decrease in synaptophysin mRNA levels by in situ hybridization histochemistry (Eastwood, Burnet, & Harrison, 1995). Obviously, we await further studies to clarify this area.

In normal development, neurons initially produce widely distributed axonal projections, many of which are removed during development to form more mature and restricted terminal fields (Lohoff, Delhaye–Bouchaud, & Mariani, 1996). Furthermore, supernumerary synapses are eliminated after their overproduction earlier in development. Changes in synaptic density in schizophrenia may be due to any of a number of processes, including impaired synapse formation, abnormal synaptic pruning (increased or decreased), increased sprouting of new synapses in response to neural injury, or synapse loss due to degenerative processes. In normal frontal cortex, synaptic density peaks during childhood and then declines by 30–40% during adolescence before stabilizing during adulthood (Huttenlocher, 1979). It has been hypothesized that schizophrenia may result from pathological alterations in developmentally regulated synaptic pruning (Feinberg, 1982; Hoffman & McGlashan, 1997). This hypothesis has even prompted interesting computer simulations of the effects of connectional pruning in a speech-perception neural-network model. In this model, pruning enhanced perceptual ability but when excessive, perception declined and spontaneous simulated word hallucination occurred (Hoffman & McGlashan, 1997).

Investigations of connectivity and synaptic integrity in schizophrenia are still at an early stage. One difficulty inherent in the immunohistochemical studies of synapse-related proteins is that they measure average levels of synaptic proteins and do not delineate inappropriate synaptic connectivity as opposed to total connectivity of a particular region of interest. Thus, for synapse-related proteins that are common to all synapses (such as synaptophysin), unless there is a specific deficit in the molecular orchestration of synaptic transmission, only a dramatic loss (or increase) in synapse density will be detected, while "miswiring" will be unnoticed. To evaluate aberrant connectivity, investigations that combine and relate diverse techniques will be necessary. These might include immunohistochemical identification of specific cell types, synaptic

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density, and neurotransmitter-specific innervation, perhaps combined with Golgi, confocal, or electron microscopic delineation of dendritic and axonal anatomy.

Growth factors and other molecules related to development and plasticity

Despite the well-recognized importance of growth factors in neurodevelopment and the dynamic regulation and plasticity of the mature nervous system, there has been virtually no investigation of this area in schizophrenia. Only one preliminary study has been reported, in which BDNF mRNA was reported to be decreased in schizophrenia (Brouha, Weickert, Hyde, Herman, Murray, Bigelow, Weinberger, & Kleinman, 1996). Obviously, much more work in this area is warranted.

Another molecule that has been studied in schizophrenia and which is important in axon growth, targeting, and synaptogenesis is growth-associated protein 43 (GAP-43). GAP-43 synthesis remains at high levels throughout axogenesis and then declines with the establishment of stable synaptic relationships, but remains high in areas of high plasticity (Benowitz, Apostolides, Perrone–Bizzozero, Finkelstein, & Zwiers, 1988). GAP-43 studies in the brain in schizophrenia have been controversial. One study of visual and frontal association cortices found elevated levels (Perrone–Bizzozero, Sower, Bird, Benowitz, Ivins, & Neve, 1996), while another, preliminary study found decreased expression in other regions (Shannon–Weickert, Hyde, Webster, Herman, Weinberger, & Kleinman, 1997).

Neurodegeneration and postmaturational neural injury

Data from postmortem studies of neurodegeneration, neural injury, and astrocytosis have figured prominently in discussions of developmental versus postmaturational pathophysiologies of schizophrenia. In the postnatal brain, reactive astrocytosis occurs as an acute nonspecific inflammatory response to injury due to a variety of causes (e.g., infectious, ischemic, toxic, autoimmune). It is characterized by proliferation and somatic enlargement of astrocytes, and the extension of astrocytic processes (Norton, Aquino, Hozumi, Chiu, & Brosnan, 1992). After the acute phase, astrocytic bodies shrink while finer fibrillary processes remain as a chronic marker of the past injury. Neural injury that occurs in the course of brain development or as a result of programmed cell death does not result in this type reactive gliosis and leaves no trace of glial reaction. Some postmortem studies of schizophrenia using traditional histological stains (e.g., Holzer) have reported excess fibrillary gliosis in several subcortical areas, most notably periventricular and periaqueductal regions (Bruton et al., 1990; Stevens, Altshuler, Bogerts, & Falkai, 1988; Stevens, 1982). In contrast, studies using immunohistochemistry with antibodies directed against glia fibrillary acidic protein (GFAP) have so far failed to find any excess gliosis, with special attention paid to the presence or absence of gliosis in the ventromedial temporal lobe to explain the nature of the above-noted cytoarchitectural and morphometric abnormalities in the hippocampal region (Arnold, Trojanowski, Gur, Han, & Choi, 1998; Crow et al., 1989; Roberts, Colter, Lofthouse, Bogerts, Zech, & Crow, 1986; Roberts, Colter, Lofthouse, Johnstone, & Crow, 1987; Stevens et al., 1988). The failure to find evidence of excess gliosis in this region has been interpreted as supportive of an abnormal development mechanism in the pathogenesis of schizophrenia.

As described previously, an increased recognition of cognitive and functional impairment among elderly patients with schizophrenia has stimulated further search for evidence of Kraepelinian neurodegeneration in schizophrenia. Postmortem studies have attempted to determine the neuropathological basis for this dementia. Arnold, Gur, Shapiro, Fisher, Moberg, Gibney, Gur, Blackwell, and Trojanowski (1995) and Purohit, Perl, Haroutunian, Powchik, Davidson, and Davis (1998) conducted autopsy examinations in patients derived from their clinically well-characterized populations and found no recognized neuropathologic abnormalities to explain the severe dementia. Of particular interest was the minimal degree of neurofibrillary tangle and

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senile plaque formation. Further studies failed to identify excess AD-related protein abnormalities (Powchik, Davidson, Nemeroff, Haroutunian, Purohit, Losonczy, Bissette, Perl, Ghanbari, Miller, & Davis, 1993), decreased cholinergic activity (Haroutunian, Davidson, Kanof, Perl, Powchik, Losonezy, McCrystal, Purohit, Bierer, & Davis, 1994), or abnormal apolipoprotein E genotype distribution (Arnold, Joo, Martinoli, Roy, Trojanowski, Gur, Cannon, & Price, 1997; Powchik, Friedman, Haroutunian, Greenberg, Altsteil, Purohit, Perl, & Davidson, 1997) that might be associated with dementia. These findings were concordant with two other studies which also used carefully diagnosed patients (Bruton et al., 1990; el-Mallakh, Kirch, Shelton, Fan, Pezeshkpour, Kanhouwa, Wyatt, & Kleinman, 1991). Typically, neuropathological diagnoses to account for a progressive dementia in the elderly can be identified in up to 95% of cases, and AD accounts for 50–60% of late life dementias. The lack of neuropathological findings to explain the cognitive deterioration in these studies of elderly patients with schizophrenia was unexpected and raises very interesting questions vis a vis the pathophysiology of poor outcome schizophrenics.

In a comprehensive evaluation of neurodegeneration and neural injury in an elderly sample of chronically institutionalized schizophrenics (two-thirds of whom exhibited clear dementia), Arnold et al. quantified six different neurodegeneration markers in ventromedial temporal lobe, prefrontal cortices, and primary visual cortex (Arnold, Trojanowski, et al., 1998). Immunohistochemistry with sensitive and specific antibodies were used to label neurofibrillary tangles, amyloid plaques, Lewy bodies, ubiquitinated dystrophic neurites, astrocytes, and microglia. The densities of these markers were determined using nonbiased, computer-assisted methods. There were no differences between normal elderly matched controls and patients with schizophrenia, while both groups had far fewer of these lesions than a control group with Alzheimer's disease. They concluded that if evidence of neurodegeneration or neural injury could not be found in this sample of poor-outcome elderly schizophrenics, then it was most certainly not to be found in any younger or less ill community based sample. They further speculated that the deterioration observed in the majority of their sample could be due to an interaction between a developmentally abnormal brain and normal aging processes.

Efforts toward an integration of molecular genetics and molecular neuropathology

New technologies offer great opportunities for investigation and integration of findings in molecular genetics and molecular neuropathology. In the recent past, a number of studies have investigated alterations in the expression of individual candidate genes in schizophrenia using in situ hybridization and Northern blotting, and these have yielded some insights into the role of these particular genes. Some of these are reviewed above. However, the neurobiological complexity and inheritance patterns of schizophrenia attest to its multigenic nature. Schizophrenia likely arises from the coordinate dysregulation of several or possibly many genes.

New microarray methodologies have been developed recently that permit investigation of coordinate gene expression (Duggan, Bittner, Chen, Meltzer, & Trent, 1999). Microarrays have candidate cDNA probe sequences immobilized on a solid support and allow for the simultaneous assessment of thousands of genes. Compared to the candidate gene approach, which typically assesses the expression of one or a small number of selected genes, microarrays provide a more complete representation of the orchestrated expression of thousands of genes and also can simultaneously measure the levels of expression of these genes in different tissue samples. In this way, the pattern of coordinate gene expression may serve as a neuromolecular fingerprint for schizophrenia that can be compared with the fingerprints of normals and patients with other diseases.

Differential expression profiles for regional brain tissue and even single cells within the entorhinal cortex in schizophrenia have been reported in preliminary studies using microarrays (Eberwine, Ginsburg, Arnold, Trojanowski, & Hemby, 1998). Future studies offer much promise. For instance, within a

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microarray one can choose to examine the coordinated expression of multiple genes important in signal transduction or neurosecretory pathways. Another potential use that more closely complements molecular genetic linkage studies is to examine the orchestrated expression of various mRNAs and expressed sequence tags whose genes map to putative chromosomal linkage sites for schizophrenia.

Conclusions

Epidemiological and clinical neurobiological evidence increasingly supports a neurodevelopmental formulation of schizophrenia. In concert, we witness a greater focus on development-related topics in cellular and molecular neuropathological investigations. The challenges for neuropathological studies of schizophrenia are many, given the lack of any suitable animal models for the disease, the time frame at which the disease can be diagnosed, and the time until death at which postmortem studies occur. Nonetheless, as our knowledge of normal neurodevelopmental processes evolves, new opportunities present themselves. For instance, neuronal precursor cells capable of dividing have recently been successfully cultured after being obtained from temporal lobe periventricular subependymal zone in human adults undergoing temporal lobectomy for epilepsy (Pincus, Keyoung, Harrison–Restelli, Goodman, Fraser, Edgar, Sakakibara, Okano, Nergaard, & Goldman, 1998). Characterizing the molecular phenotype of this population of neurons in postmortem studies may reveal clues about early neuronal molecular development in schizophrenia or other neurodevelopmental disorders.

In a similar vein, there should be a continued focus on regions of the central nervous system in which there is a ongoing neural plasticity. The hippocampus is one such area due to the dynamic molecular and ultrastructural changes associated with learning and memory (Wang, Ko, & Kelly, 1997). The olfactory neuroepithelium and olfactory bulb may be another excellent candidate region. There is constant regeneration of neurons in the olfactory neuroepithelium throughout life. These sprout new axons which are guided to the olfactory bulbs where they form new synapses (Arnold, Smutzer, Trojanowski, & Moberg, 1998). Furthermore, severe impairments in olfaction have been noted in schizophrenia (Moberg, Agrin, Gur, Gur, Turetsky, & Doty, 1999).

Finally, we can use our expanding knowledge of neuron proliferation, migration, survival, differentiation, synapse formation, synapse pruning, myelination, and molecular genetics to identify additional molecules for study in schizophrenia. As described above, studies on some have already commenced, including N-CAMs, reelin, microtubule-associated proteins, and GAP-43. However, other entire classes of molecules are virtually untouched, such as the neurotrophin family and other growth factors, apoptosis-related molecules, signal transduction molecules that regulate gene expression, and myelin promoting factors. Studying these and other molecules relevant to neurodevelopment using both candidate gene approaches and microarray technologies offer much promise.

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