Myelination of Cortical-Hippocampal Relays During Late Adolescence

by Francine M. Benes

Abstract

The normal developmental series of brains in the Yakovlev Collection has been examined to explore the possibility that various brain regions implicated in schizophrenia may show changes in myelination during late adolescence, a period coinciding with the appearance of early symptoms of this disorder. The prefrontal, cingulate, and parahippocampal (entorhinal) cortex, as well as the perforant pathway, cingulum bundle, and hippocampus, were closely examined because these regions have recently been found to show various neuropathological differences in schizophrenia. Observation of these specimens has confirmed earlier reports by Yakovlev and Lecours (1967) that primary motor and sensory cortices show robust myelination early in the first decade of life. In contrast, associative cortical areas show increased amounts of myelin staining only by the second decade, although some cortical areas, like the cingulate and basofrontal cortex, remain poorly myelinated throughout life. The most striking finding, however, was the appearance of increased myelination of the subicular and presubicular regions during the late adolescent period. Increased myelination in the subiculum was localized to a discrete region at the surface where fibers of the perforant pathway are known to aggregate as they course toward the area dentata. The comparable region in the adjacent presubicular area that also showed increased myelin staining probably contains distal portions of the cingulum bundle. Support for this latter possibility was obtained from a single case in which a stereotaxically placed lesion causing interruption of the cingulum bundle showed less myelin in the presubicular area of the effectively lesioned side. These previously unreported findings are discussed in relation to normal brain circuitry mediating motivational, attentional, and affective behavior. It is suggested that myelination of key linkages in this circuitry may be "permissive" for the expression of a previously latent defect in schizophrenic brain.

Recent anatomical investigations suggest that schizophrenic brain may contain structural abnormalities in several different areas that include dorsolateral prefrontal cortex (Benes et al. 1986), anterior cingulate cortex (Benes and Bird 1987), the entorhinal cortex (Jacob and Beckmann 1986), the parahippocampal gyrus (Bogerts et al. 1985; Brown et al. 1986), and the hippocampus (Kovelman and Scheibel 1984; Bogerts et al. 1985). While the etiological significance of these various anatomical defects is unknown, their presence nevertheless suggests the possibility that schizophrenia may involve a defect in the central corticolimbic circuitry of the brain (Benes and Bird 1987; Benes et al. 1987). The brain areas that make up this loop were believed by Papez (1937) to subsume a major role in the emotional component of cognitive behavior, and more recently Mesulam (1983) suggested that some of these areas might mediate volitionally driven attentional responses. Since motivation, attention, and affect are centrally disturbed in schizophrenia, neuroanatomical findings

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in these brain regions may reflect altered integration among the elements of this circuit.

One strategy for deciphering the pathophysiology of schizophrenia is to relate various neuroanatomical findings to clinical phenomena associated with the disorder. A question that is frequently asked is why schizophrenic symptomatology tends to become manifest between 16 and 20 years of age (Kraepelin 1919). One interpretation of this observation is that some normal developmental event in the brain may serve to trigger the disorder. It has long been known that development of the human brain continues well beyond childhood. For example, increases in the myelination of the prefrontal cortex are believed to occur up to the fourth decade and possibly beyond (Yakovlev and Lecours 1967). Since abnormalities in this cortical area have also been observed in schizophrenic brain (Benes et al. 1986), these late developmental changes may play some role in the pathophysiology of schizophrenia. Since recent investigations in schizophrenic brain also suggest that these patients may have abnormalities in the loop of Papez (Benes and Bird 1987; Benes et al. 1987), it seems reasonable to consider whether elements of this circuit may show changes in myelination during late adolescence. This question is relevant because this corticolimbic circuit, in conjunction with the dorsolateral prefrontal cortex, appears to mediate several functions that are centrally disturbed in schizophrenia (Benes and Bird 1987; Benes et al. 1987).

Methods

The specimens in the Yakovlev Collection at the Armed Forces Institute of Pathology, Washington, DC, are under the curatorship of Mohamed Haleem. Normal specimens in the collection cover a wide range from the earliest stages of the embryonic period through the 10th decade of life. The specimens used for this study were from the perinatal period, and 3.5, 4, 6.5, 11, 19, 20, 32, 36, 40, 54, and 64 years of age. An additional specimen from a healthy 17-year-old that had been prepared in a manner identical to those of the Yakovlev Collection has also been included. All specimens had been imbedded in celloidin and cut serially at a thickness of 50 μm in the coronal, sagittal, or horizontal plane. For this report, only coronal sections were used for the photomicrography. In some cases, however, specimens cut in other orientations were also examined to give different perspectives of fiber orientation in a given brain region. Appropriate levels of cut that included dorsolateral prefrontal, basofrontal, anterior cingulate, primary motor, primary sensory, primary visual, superior temporal, parahippocampal, and hippocampal cortices were photographed at the same magnification. In most cases, associative areas of cortex adjacent to the primary areas were also examined. To control for variability of the intensity of myelin staining, specimens were photographed at a magnification of approximately 5x. This permitted comparisons of the degree of staining of various structures in relation to each other. When the staining for a given specimen was more or less intense than for other specimens, it occurred proportionately throughout. Assessments of the degree of myelination for a particular region were made in relation to other structures within the same section, as well as similar structures in other specimens. An additional control for interspecimen variability involved printing of the photomicrographs at different exposures so that similar densities could be obtained across the various specimens.

Results

In general, many of the observations that have been made here were consistent with concepts described earlier by Yakovlev and Lecours (1967). For example, in the first decade of life, primary motor and sensory areas show a robust development of myelination that is generally complete by approximately 6 years of age. Associative cortical regions, on the other hand, show very poor myelination until the second decade, while some remain poorly myelinated throughout life. The following areas were examined in more detail:

Prefrontal Cortex. The prefrontal cortex could be divided into basofrontal cortex and dorsolateral cortex. Basofrontal or orbital cortex showed poor myelination throughout all specimens regardless of age. The dorsolateral prefrontal area, however, showed sparse myelination confined to the subcortical zone beneath layer 4 during the first decade (figure 1A), but by 11 years of age, (figure 1B) there was possibly a slight increase in the degree of myelination of fibers radiating through layers 4 and 6 and forming the so-called faciculi radiati. If present, this increase did not constitute a striking difference. At 20 and 32 years of age (figures 1C and 1D), little difference in the amount of myelin could be discerned.

Cingulate Cortex. The anterior and posterior cingulate cortices showed a
Figure 1. Photomicrographs of Weigert-stained specimens of dorsolateral prefrontal cortex

A. A 65-year-old. B. An 11-year-old. C. A 20-year-old. D. A 32-year-old. Bar in A = 0.5 mm and applies to other micrographs shown. Cortical laminae 1-6 are indicated as numbers in C.

light degree of myelination that appeared in the second decade and remained relatively constant throughout subsequent decades (not shown).

Parahippocampal Gyrus. The parahippocampal gyrus (figure 2) showed a relatively heavy degree of myelination in the subcortical zone beneath layer VI that was similar throughout all the specimens (figure 3). Lighter staining of myelin in the cortical mantle itself was also seen in the second decade and beyond.

Subiculum and Presubiculum. At 3.5 (figure 3A), 4 (not shown), 6.5 (figure 3B), and 11 years of age (figure 3C), the subiculum and presubiculum (figure 2) showed light staining of myelinated fibers immediately beneath the surface. At 17 (not shown), 19 (figure 3D), and 20 years of age (figure 3E), there was an increase in the amount of myelin-stained material in this same region, and this did not appear to change appreciably at 32, 40, or 54 years of age (figures 3F, G, and H). The differences between the 11-year-old (figure 4A) and the 17-year-old (figure 4B) are seen more strikingly at higher magnification.

One of the cases in the Yakovlev Collection had been subjected to a cingulotomy procedure for the control of chronic pain. Examination of this specimen revealed that only the lesion on the left side affected this structure (figure 5A). The presubicul ar region on the left side (figure 5B) of this specimen showed less myelinated material at the surface than the right side (figure 5C).

Hippocampal Formation. The alveus and fornix showed heavy myelination even at birth (not shown), and
Figure 2. Photomicrograph of medial portion of the temporal lobe

The location of the hippocampus (hipp), area dentata (ad), alveus (open arrowheads), fornix (fx), subiculum (sub), presubiculum (ps), and parahippocampal gyrus (phg) are shown. The section shown is at the level of the lateral geniculate nucleus (Ign), which lies above the subiculum. Bar = 4 mm and applies to all other micrographs shown.

Discussion

The data reported in this study must be considered quite preliminary due to the small numbers of specimens, the variability of myelin staining, and the inability to perform quantitative analyses. Given these qualifications, however, if the current findings prove to be accurate, they may suggest that normal brain ontogeny could involve late adolescent increases in the myelination of certain portions of the central corticolimbic circuitry of the brain. The interval during which this occurs is notable for its overlap with the time of onset of schizophrenia (Kraepelin 1919). Earlier work by Yakovlev and Lecours (1967) had suggested that prefrontal cortex undergoes continued myelination through possibly the fourth decade. The current study, however, has failed to corroborate this finding. The reason for this discrepancy is unclear, but it is possible that quantitative methods might reveal differences that are otherwise too subtle to appreciate by visual inspection. It is conceivable that the earlier study employed higher magnifications and may have thereby emphasized more subtle differences than those reported here.

The changes noted in the subiculum and presubiculum during development were far more striking than those seen in other areas during the adolescent period. It is noteworthy, however, that they seemed to occur most extensively during the late adolescent period. The subiculum and presubiculum are notable for their strategic location within the corticolimbic circuitry of the brain. Although little is known about the function of the subiculum and presubiculum, anatomical investigations have demonstrated that these two brain areas show different patterns of afferents and efferents. The subiculum receives its principal input from the CA1 sector of the hippocampus (Hjorth-Simonsen 1973). It sends efferent fibers, via the postcommissural portion of the fornix, to the hypothalamus (Raisman et al. 1966) and, via the precommissural fornix, to lateral portions of the medial septal nuclei and the nucleus accumbens (Chronister and White 1973). The subiculum also projects to the frontal pole, particularly medial prefrontal cortex (Irle and Markowitsch 1982). The presubiculum, on the other hand, receives its primary inputs from widespread areas of the cortex including the dorsolateral prefrontal (Irle and Markowitsch 1982) and inferior parietal (Seltzer and Van Hoesen 1979) areas. The presubiculum sends efferents to many sites, including the dorsal and medial entorhinal area (Shipley 1974), and dorsolateral prefrontal (Irle and Markowitsch 1982) cortex. The perforant pathway carries fibers from all...
Figure 3. Set of photomicrographs of the hippocampal formation, subiculum, and presubiculum

A. A 35-year-old. B. A 65-year-old. C. An 11-year-old. D. A 19-year-old. E. A 20-year-old. F. A 32-year-old. G. A 44-year-old. H. A 54-year-old. Arrow heads indicate the location of myelin-stained material that is sparsely represented until 19–20 years of age. The amount of myelin-stained material appears to increase up to 32 years of age, but not beyond. Bar in A = 2 mm and applies to other micrographs shown.

regions of the entorhinal area (Hjorth-Simonsen and Jeune 1972; Van Hoesen and Pandya 1975) that pass through the subicular region en route to the stratum moleculare of the area dentata where they terminate on granule cell dendrites (Lorente de Nó 1934; Ramon Y Cajal 1911, 1955; Blackstad 1956; Nafstad 1967; Fifkova 1975). This so-called perforant pathway represents one of the most extensive inputs to the hippocampal formation. Interestingly, fibers of this pathway aggregate at the surface of the subiculum where the significant increases in myelination were noted during late adolescence, although they are not actually considered to be part of the region. The cingulum bundle, a vital link of the cingulate cortex and to some extent the dorsolateral prefrontal area (Goldman-Rakic et al. 1984), with the hippocampal formation, terminates in a similar location within the presubiculum (Ramon Y Cajal 1911, 1955; Domesick 1969; Pandya et al. 1981; Vogt and Miller 1983; Goldman-Rakic et al. 1984). The fact that differences in the structure of the entorhinal cortex, cingulate cortex, and hippocampus have been recently reported in schizophrenic brain suggests the possibility that changes in myelination of the perforant pathway and the cingulum bundle could somehow be related to the appearance of certain early symptoms of schizophrenia.

Core features of the schizophrenic syndrome include disturbances in motivation, attention, and affective experience (Bleuler 1911/1950). Mesulam (1983) has theorized that attentional mechanisms mediated through the cingulate cortex are linked to motivational drives, motor and sensory representations, and
ocular responses. Attentional behavior can be conceptualized as involving activity that not only arises in the cingulate cortex, but also motivational responses mediated through the dorsolateral prefrontal cortex, affective responses mediated through the hippocampus, and finally, ocular saccades initiated through frontal eye field 8 (figure 6). The reciprocal linkages among dorsolateral prefrontal, anterior cingulate, frontal eye field 8, and hippocampal cortices could represent a level of integration that is critical to normal motivational, attentional, and affective behaviors. When these behaviors are disturbed, as in schizophrenia, there might be altered activity in these brain areas due to independent defects occurring in each, or alternatively, to a primary defect in one causing a cascade effect in the others.

The question that the current study raises is whether myelination of one or perhaps two linkages of this circuitry could in some way permit a preexisting latent defect to become manifest. Some retrospective analyses have suggested that many schizophrenic patients have sustained hypoxic insults at birth (Parnas et al. 1982). Studies in monkey have shown that early lesions of the prefrontal area do not produce any immediate impairment of the delayed response task, a performance skill specifically mediated through this area, until puberty (Goldman 1974). These data have suggested that developmental changes during pubescence, such as hormonal ones, may produce alterations that allow the latent defect to appear (Goldman 1974; Nonneman et al. 1984). Similar mechanisms in schizophrenia that involve normal developmental events during adolescence have been postulated by others (Murray and Lewis 1987; Weinberger 1987). Such changes could involve increased myelination of certain pathways that mediate performance of the delayed response task. In the case of schizophrenia, a preexisting defect, whether arising from a genetic predisposition, an acquired perinatal insult, or perhaps some combination of the two, could remain dormant until some new developmental epoch begins. The changes in myelination of inputs to the hippocampus during the late adolescent period could provide a "permissive" environment for the expression of faulty corticolimbic integration that may occur in relation to schizophrenia.

At present, too little is known about the neuroanatomical substrates of schizophrenia to speculate any further on how this might occur. It does seem evident, however, that a consideration of integration among widespread aspects of corticolimbic circuitry will be necessary to understand the complex and diverse symptoms that arise in this disorder.
Figure 5. Set of photomicrographs of Weigert-stained sections from a patient with chronic pain subjected to a cingulotomy procedure

A. A stereotaxically placed lesion is in evidence in a position inferior to the cingulate gyrus on the left side. The right side shows faint evidence of an electrolytic lesion, but it spares the cingulum bundle. B. The hippocampus and parahippocampal gyrus on the left side of the brain. C. Same as in B, but on the right side of the brain. There is myelin-stained material located at the surface of the subiculum on both sides of the brain. In the presubicular area (arrowheads), the myelin-stained material is reduced on the left side of the brain. Bar in A = 4 mm and also applies to the other micrographs.
Figure 6. Schematic diagram representing reciprocal connections among several brain regions involved with motivationally driven attentional behavior

Frontal Eye Field (Saccadic Eye Movement)

Prefrontal Cortex (Motivation)

Cingulate Cortex (Attention)

Hippocampus (Affective Drive)

The prefrontal and cingulate cortices, as well as frontal eye field 8 and the hippocampus, are the principal components of this circuit.

Future studies will seek to replicate and extend these preliminary findings by obtaining a larger cohort with both male and female subjects and employing quantitative techniques to consider more systematically how individual variations and/or gender differences may influence the data reported from this exploratory project.

References


Hjorth-Simonsen, A., and Jeune, B.


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