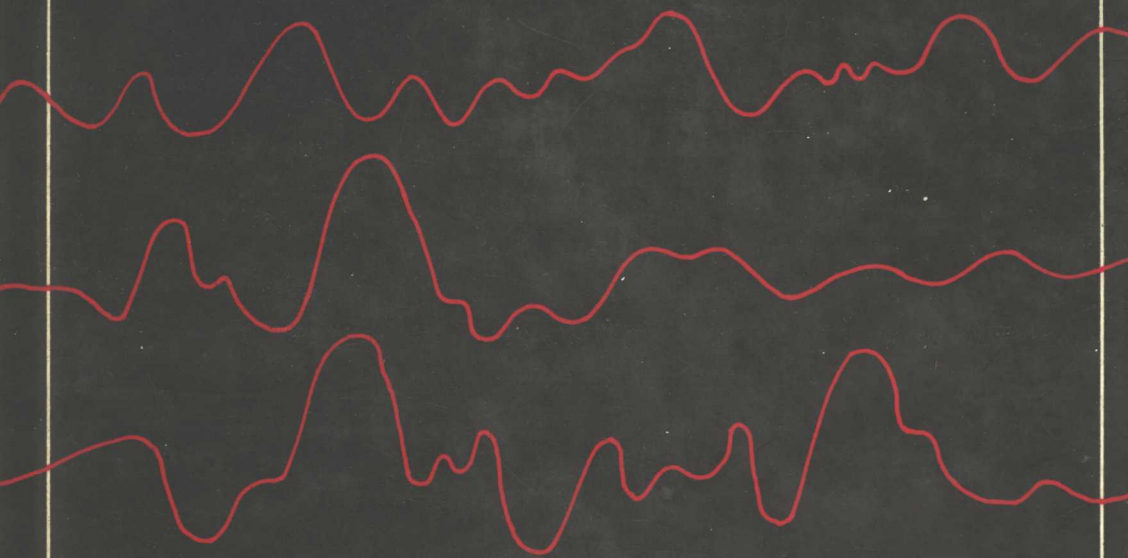
# BRAIN AND BEHAVIOURAL DEVELOPMENT



Edited by
John W. T. Dickerson
& Harry McGurk

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# BRAIN AND BEHAVIOURAL DEVELOPMENT

*Interdisciplinary perspectives on structure and function*

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# INTRODUCTION

The study of structural and functional relationships between brain growth and behavioural development in the human subject is an area of enquiry which cuts across traditional disciplinary boundaries. Biologists, nutritionists, paediatricians, physiologists, psychologists—all have overlapping interests and perspectives on the topic. Yet here, as in so many other areas of research enquiry, the predominant tendency is for investigators to work within the constraints imposed by the concepts and methodologies drawn from a single discipline. Similarly, published material on the topic tends to be written from the viewpoint of a particular disciplinary approach and the field is impoverished thereby.

This volume has been prepared in recognition of the essentially interdisciplinary nature of brain and behavioural development studies. It is the outcome of collaboration between anatomists, biologists, developmental psychologists, nutritionists and psychophysiologists. Each contributor has made important and original contributions to the research area with which the book is concerned. Moreover, an interdisciplinary perspective has informed these authors' approaches to their own research and is reflected in the contributions presented here.

The volume is not intended as a comprehensive text on the cross-disciplinary study of brain and behavioural development processes. Rather, our aim has been to identify a number of active research areas in this general domain within which attempts are being made to integrate our understanding of changes in anatomical and biochemical structure and functions on the one hand with our knowledge of developmental changes in the structure and function of behaviour on the other. Further, each contributor was invited to elaborate his own documented perspective on a topic area rather than to passively review the literature. It has been our intention also that contributors should reflect not only the academic and theoretical significance of particular research problems but also their significance for the development of remediation strategies to counteract the effects of disease, injury and adverse environmental circumstances on the development of brain and behaviour.

The readership to which the book is addressed includes advanced undergraduate and graduate students in biology, clinical and developmental psychology, nutrition and physiology; it will be of interest also to practising paediatricians and nutritionists and to other professionals involved in the child health services. The first four chapters are primarily concerned with aspects of brain structure—anatomical and biochemical—and with the impact of nutritional deficiency, hormone imbalance and toxic agents upon these developing structures; Chapters 5–8 explore relationships between behavioural functions and the structure of the developing brain.

Historically, descriptive anatomy preceded elucidation of physiological processes, and the first chapter sets the scene with a discussion of the development of the human nervous system from an anatomical viewpoint. Distinct but overlapping phases of growth occur, culminating in neuronal and glial differentiation. Development is completed by the growth of the complex dendritic tree, the linking of the dendrites through the development of synapses and the elaboration of the myelin sheath which results in the insulation of nerves and makes possible the efficient passage of nervous impulses. These processes are described in various regions of the central nervous system, including the cerebral and cerebellar cortices, the basal ganglia, the brain stem and the spinal cord. Development is a dynamic process and, as with other aspects of the subject, limitations in the availability of material and in the applicability of certain methods make it necessary to draw upon animal studies in order to make reasonable inferences about the processes in the human brain.

Inferences and extrapolation of this kind are necessary when we try to understand the possible effects of adverse environmental factors on the growth of the human brain. Animal experimentation, then, has necessarily made a considerable contribution to our knowledge. There are, however, considerable differences between experimental animals and man. Not least of these is the timescale over which developmental changes occur. Moreover, the stage of development of the brain in the newborn differs from one species to another. This is clearly of considerable importance in relation to the timing of the brain growth spurt which we now know is a once-and-for-all process. It is therefore of fundamental importance to consider the comparative aspects of brain growth and development. This theme is developed from a biochemical viewpoint in the second chapter, which includes some discussion of the important concept of 'critical periods'. These are strictly age-related and species-specific. Moreover, there is not one critical period but many, related to the growth of the different structural entities in the brain which may be expressed in anatomical and biochemical terms, and to these are related, in ways that we do not understand, critical periods of behavioural and psychological development.

The brain grows and develops rapidly early in life and this is when the various processes are most vulnerable to the nutritional environment. Protein-energy

malnutrition (PEM) is the most prevalent single factor which might adversely affect brain growth and development and permanently interfere with the achievement of genetic potential. It has been estimated that some 100 million of the world's children are affected to varying degrees and these are mostly in the developing countries. An understanding of the ways in which malnutrition interacts with other factors in the environment is a necessary basis for the prevention of the permanent stigmata of the condition in the children themselves and also to the future eradication of the condition as a result of better education and opportunities. To provide schools and extensive training programmes without first making sure that children have the capacity to benefit from the facilities makes bad political sense. The importance of an understanding of the effects of malnutrition on brain development is such that an entire chapter has been devoted to its consideration.

Malnutrition of the kind discussed in Chapter 3 is very unlikely to occur in Western societies. However, normal growth and development depends also upon the endogenous regulation of synthetic and metabolic processes in which hormones play a central role. In the neonate, a deficiency of thyroxine in particular results in a distortion of brain growth and development and results in cretinism. Similarly, an excess of corticosteroids during the period of the brain growth spurt produces a distortion of development which is in some ways similar to that produced by protein-energy malnutrition. Growth and development is also affected by the activity of enzymes and these activities are regulated not only by the amounts of enzyme proteins but also by their cofactors, vitamins and trace elements. These biological factors along with a number of pollutants and toxic materials are discussed in Chapter 4.

Technological advances during the past thirty years have greatly facilitated the recording of the brain's electrical activity, via surface electrodes, from the scalp of human subjects. Recording methods are now relatively simple and safe, and electroencephalographic (EEG) data have greatly informed our understanding of the relationship between bioelectrical events within the cortex on the one hand and change in behavioural state on the other. Similarly, investigations of cortical-evoked potentials consequent upon sensory stimulation have increased our understanding of brain function during perceptual, attentional and other cognitive activities. All this is with respect, primarily, to the mature organism. Chapter 5 is devoted to consideration of the contribution which electrophysiological recording techniques can make to our understanding of brain activity and behaviour in the developing organism. The author relates structural changes in the cortex of the pre-term, full-term and developing infant to changes in electrophysiological activity and in behaviour. The value of EEG developmental milestones for diagnostic and prognostic purposes during early infancy is advocated, though their use as indices of cognitive development during later stages of growth is seriously questioned.

The fact that the brain comes in two more or less symmetrical halves, that these halves are contralaterally organized with respect to their control over body activity, and that humans are predominantly right-handed have led to speculations and controversy over the relative dominance of the right and left hemispheres in the control of specific psychological functions. Traditionally, the left hemisphere has been recognized as dominant in the mediation of speech and language, and the right hemisphere as dominant in visual-spatial tasks. Too often, however, this relative dominance has been interpreted as if man had two brains, one adapted for verbal, the other for perceptual functioning. Such oversimplification of roles distorts what is known about the extent to which duplication and symmetry of function exists and the extent to which the two hemispheres work together as an integrated system. Overelaboration of the functional asymmetry of the two halves of the adult brain has also tended, on one hand, to misinform the kind of question which has been asked about the ontogeny of hemispheric specialization and, on the other to a confounding of questions about equipotentiality with questions about the capacity of the cortex for reorganization following injury. These and related issues are addressed in the sixth chapter of this volume where the author argues that both symmetric and asymmetric organization of hemispheric functions are characteristic of the human brain, at least from the beginning of postnatal life. On this basis, it is argued that the basic developmental problem should be reformulated in terms of how, during their acquisition process, skills that are being newly learned are integrated with functions that are already symmetrically or asymmetrically organized.

Two facts about the developing brain have long been acknowledged. Firstly, as previously indicated, the immature brain is more vulnerable to environmental insult than is the mature brain. Secondly, if injury or damage does occur, its effects on the developing brain are more diffuse and less specific than on the adult brain. The latter, together with the child's greater potentiality for at least partial recovery of functions disrupted through injury, attests to the functional plasticity of the developing compared with the mature brain. How the diffuse effects of injury are mediated in terms of brain structure and function, and how the potential for recovery is to be interpreted, are issues of considerable controversy. Resolution of the issues involved is of theoretical and practical importance. Discussion and evaluation of the relevant evidence forms the subject matter of Chapter 7; implications for effective remediation regimens are considered.

As in so many other domains, analysis of the relative contributions of nature and nurture to the development of sex differences in behaviour has been the occasion of much polemical discussion. Chapter 8 is devoted to discussion of structural processes and mechanisms which might underlie sex differences, in particular behavioural and cognitive functions. Hormonal influence on brain

activity and sex differences in brain differentiation feature large in the discussion. It should be recognized, however, that investigation of potential relationships between sex differences in behaviour implies no commitment to biological determination. Rather, such evaluation is necessary to inform our understanding of the raw material upon which education and culture may operate to influence behavioural expression in a diversity of fashions. As the author argues, brain differences between male and female may well underlie the predilections for the two sexes to act in particular ways, but they cannot be construed as constituting a biological *imperative* for the development of psychological sex differences.

We should like to thank our contributors for their patient cooperation throughout the various stages of preparation of the volume. Our thanks are due also to Edna Springham, Roslyn Gilbert and Mary Lewis for their assistance in preparation of the typescript.

John W. T. Dickerson
Harry McGurk

CHAPTER ONE

# THE DEVELOPMENT OF THE HUMAN NERVOUS SYSTEM

MARTIN BERRY

## Introduction

A massive escalation in the volume of research effort in developmental neuroscience has occurred over the past ten years. Unfortunately, during this period investigation of the ontogeny of the human nervous system has attracted very little attention and it is difficult to understand the cause. Constraints like a lack of either material or technique no longer apply, since changes in the abortion laws in many countries have made fresh human embryos available to most laboratories in which modern neurobiological staining and tracing techniques are practised. Perhaps the brake applied to a new surge of research is the belief that developmental neuroscience has not matured to the point where it can tackle the apparent complexities of human brain development. Paradoxically, as Sidman and Rakic (1973) have pointed out, the long time-course of the period of human brain development allows temporal resolution of events that in other mammals are compressed often to the extent that sequential stages are indiscernible. Moreover, the large size of the human brain relative to that of most other mammals facilitates the morphological study of individual centres along with their chemical and behavioural correlates. In any event, we need to know more about how our brains develop, not merely for purely academic reasons but also to understand the aetiology and sequelae of congenital brain disease—particularly since this is at present a rapidly expanding area of medicine aided by advances in foetal diagnosis.

Within the brain, a series of distinct but overlapping phases of development characterize regional growth. These may be listed chronologically as neurogenesis, neuroblast migration and neuronal differentiation. Gliogenesis, glioblast migration and glial differentiation probably take place *pari passu* with the former but they are less precisely documented. The phases of neurogenesis and neuroblast migration extend into the latter part of the first year of life, and perhaps beyond in certain areas. In most cases neuronal differentiation begins during migration with the elaboration of an axon. Dendritic growth usually commences when migration has ceased. Synaptogenesis occurs as dendrites grow and, indeed, it has been suggested that adhesive interaction between growing axons and dendrites determines all the physical characteristics of the dendritic field (Berry *et al.*, 1980*a*). Glial neuronal interaction is apparent from the beginning, since it is glial processes that provide the substrate for migration. Myelination is under way in the second trimester, and the blood brain barrier matures in the last trimester (Pappas and Purpura, 1964). Gliogenesis continues into adult life. The stem cell source is from dormant glioblasts dispersed within the neuropil and the subependymal layer.

Of course, each brain region develops differently, and much regional ontogeny is already documented in existing text books of human embryology. This review concentrates on those areas of the human brain which have received the most attention over the past ten years or so. These regions include the cerebral and cerebellar cortices, the basal ganglia, the brain stem and the spinal cord.

## Neurogenesis

All neurones originate from germinal cells located within a layer which cuffs the neural tube and ventricles of the primitive nervous system. Some of the dividing cells become relocated elsewhere within the developing neuropil to form secondary germinal centres, but the major part of the nervous system is formed from matrix cells in the ventricular and subventricular zones (Fig. 1.1). Within this population three species of cell are probably produced—radial glia, neuroblasts and germinal cells. The cell lineage of each type is poorly understood. There is some measure of agreement that activity in the germinal epithelium can be divided into two phases—a proliferative and a migratory phase (Berry, 1974)—and that definitive neuroblasts are formed only throughout the latter. During the proliferative phase the structure of the epithelium is that of a typical pseudostratified columnar type with the basal processes attached to the subpial basement membrane and the apical processes anchored to each other by terminal bars at the lumen. Proliferation within the epithelium is associated with a peculiar interkinetic movement of the germinal cell nucleus (Seymour and Berry, 1975, 1979). Division occurs at the luminal edge, haploid daughter nuclei migrate to the subpial margin where they synthesize DNA, and

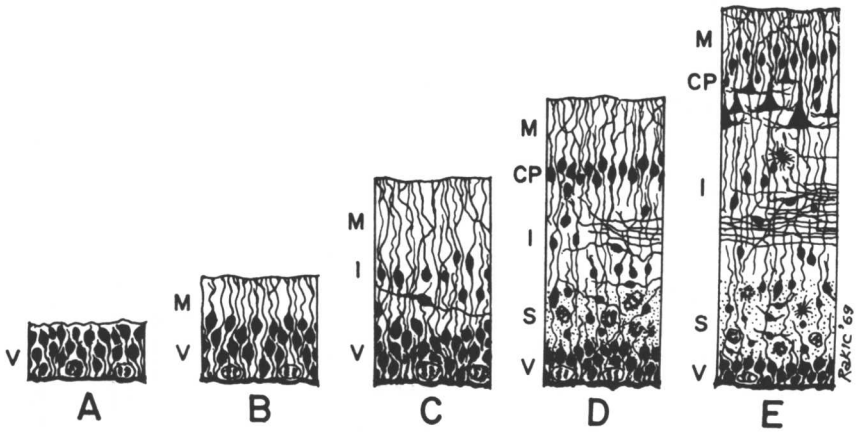


**Figure 1.1** Semidiagrammatic drawing of the development of the basic embryonic zones of the cortical plate. Terminology from Boulder Committee (1970): CP, cortical plate; I, intermediate zone; M, marginal zone; S, subventricular zone; V, ventricular zone. Stages A, B and C are common to the primary germinal epithelium in all parts of the CNS. D and E are specific to the cerebral neocortex but the migration of cells to form the cortical plate is a phenomenon not fundamentally different from the establishment of many other neural centres.

diploid nuclei then return to the luminal border to complete mitosis. Many of the changes in cell shape associated with interkinetic nuclear migration can be seen in a typical scanning electron micrograph of the neuroepithelium (Fig. 1.2). Although these changes were first described in the neuroepithelium of the cerebral vesicle of the rat (Seymour and Berry, 1975, 1979) and mouse (Meller and Tetzlaff, 1975) parallel studies on the human subventricular zone (Fujita, 1973*a*, 1975; Fujita *et al.*, 1975; Hattori and Fujita, 1974, 1976*a*,*b*) suggest that the process may be similar in man—see Fig. 1.15. During the proliferative phase, glia and neural germinal cells may be produced but their morphological differentiation is not apparent until the marginal layer appears.

As proliferation continues in the subventricular zone, a fundamental change occurs in the organization of the neural epithelium which culminates in the appearance of the marginal zone. One can only speculate about the possible changes in structure of the germinal epithelium which could represent the first signs of differentiation of the constituent cells into radial glia and neuronal matrix cells. Thus, radial glia may maintain their attachment at the inner and outer limiting membranes as mural thickness increases. Presumptive neural matrix cells, however, may detach their basal processes which come to lie within the subventricular zone (Fig. 1.1). Thus, the marginal zone may be occupied only by radial glia process at this early stage. Thereafter, interkinetic nuclear migration is confined to the ventricular and subventricular zones and continued

growth separates the outer margin of the subventricular zone from the pial surface widening the marginal zone. The stage is now set for neuroblast production and migration.

During the migratory phase of neurogenesis, germinal cells produce definitive neuroblasts and probably more radial glia. The daughter cells which differentiate into neuroblasts leave the subventricular zone and migrate to other regions in the CNS, whilst daughter cells retaining germinal cell status continue interkinetic nuclear migration within the ventricular/subventricular complex. Throughout the migratory phase of neurogenesis the germinal epithelium undergoes intense mitotic activity. Most neuroblasts leaving the subventricular zone never divide again and differentiate into neurones. Some, however, do establish secondary germinal centres elsewhere in the CNS, such as in the ganglionic eminence in the forebrain (Rakic and Sidman, 1969), in the dentate gyrus (Angevine, 1965; Schlessinger *et al.*, 1978; Stanfield and Cowan, 1979; Kaplan and Hinds, 1977); and the external granular layer of the cerebellum

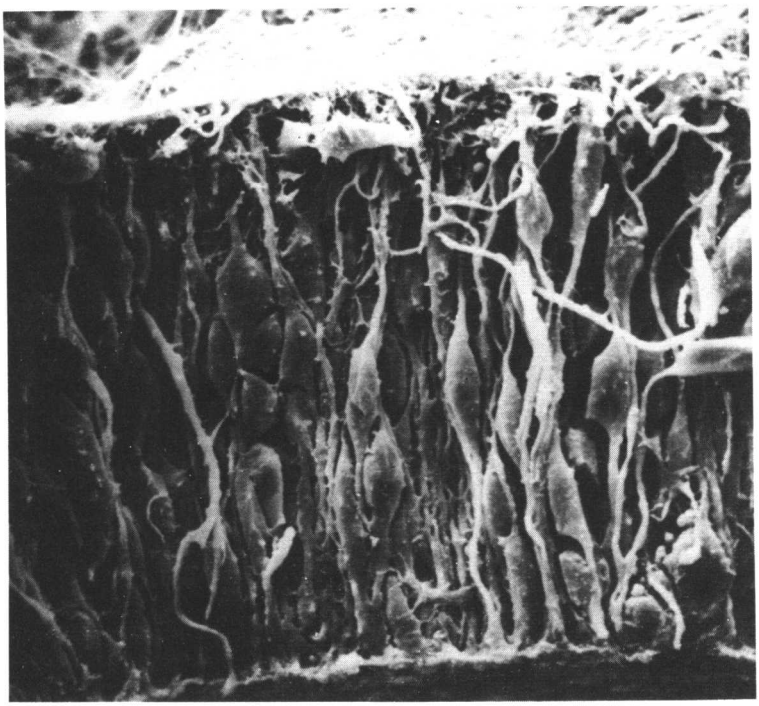

**Figure 1.2** Scanning electron micrograph of the wall of the telencephalic vesicle of a foetal rat aged 14 days post-conception. Note the pseudostratified nature of the epithelium (pial surface is uppermost) — × 1050.

(Rakic and Sidman, 1970; Zecevic and Rakic, 1976) and the olfactory lobe (Kaplan and Hinds, 1977). In general both primary and secondary neurogenesis cease at the end of the migratory period except in the dentate gyrus and olfactory

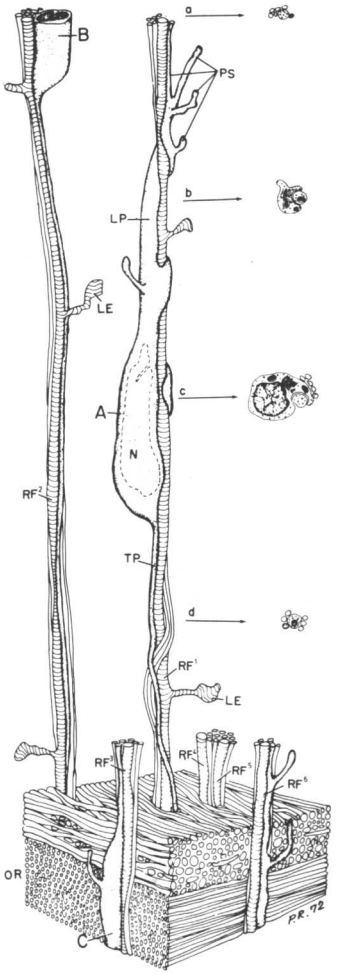


**Figure 1.3** Three-dimensional reconstruction of migrating neurones, based on electron micrographs of semi-serial sections. This reconstruction was made at the level of the intermediate zone indicated by the rectangle and asterisk in Fig. 1.14. The lower portion of the diagram contains uniform, parallel fibres of the optic radiation (OR) and the remainder is occupied by more variable and irregularly disposed fibre systems. The relationships of radial glial fibres (RF, 1-6) with migrating cells (A, B and C) and with other vertical processes is seen. The soma of migrating cell A, with its nucleus (N) and voluminous leading process (LP) are also shown. Cross-sections of cell A in relation to several vertical fibres are drawn at levels a–d. LE, lamellate expansion; PS, pseudopodia (from Rakic, 1972, with permission).