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Three dimensional growth of the mouse isocortex

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INTRODUCTION

In previous papers (Smart & Smart, 1982; Smart & McSherry, 1982; Todd & Smart, 1982) the histogenesis of the isocortical segment of the lateral telencephalic wall in the mouse was examined at a single coronal level of the rostral telencephalon. The purpose of the present study is to describe the sequence of events as seen in coronal sections spanning the entire rostrocaudal extent of the isocortical segment of the hemisphere. The procedure adopted was to prepare reconstructions of the lateral surface of the telencephalon at successive stages during the neuron production period and to project certain features of intermediate layer histology onto the reconstructed surface. The features selected for display were the depth of the layer modified by the degree of nuclear crowding within it. Taken together these parameters provided a measure of the local productivity of the periventricular layers. The results of this procedure indicate that isocortical neuron release commences about 11 days post-conception (E11) and spreads from a rostral focus across the lateral telencephalic wall. A second period of neuron release leading to the establishment of the cortical plate originates at the same site about late E13 and is similarly propagated across the periventricular germinal layers. These results amplify a model of mouse isocortical histogenesis described in an earlier work (Smart, 1973).

MATERIALS AND METHODS

General histological material

Mouse embryos were taken at daily intervals of prenatal life from E10 to E19. Prior to E13, the brains were fixed by immersion in Bouin's fluid and, thereafter, by intracardiac perfusion with Bouin's fluid. The complete heads (or at later stages the excised brains) were embedded in paraffin wax, sectioned at a thickness of 6 μm and stained with haematoxylin and eosin. At each age several brains were sectioned in the coronal, sagittal and horizontal planes.

A series of brains at similar embryonic and postnatal stages was treated by the rapid Golgi method of Stensaas (1968) and serially sectioned at various thicknesses from 40 to 80 μm. The radial processes of ventricular cells stained by this procedure were used to relate neuron populations of the intermediate layer to their putative sites of origin in the germinal layers.

Preparation of photographic atlases

The orthogonal reconstructions on which intermediate layer changes were to be plotted were based on photographic atlases prepared as follows. From the library of serial sections stained with haematoxylin and eosin, sets were selected that were

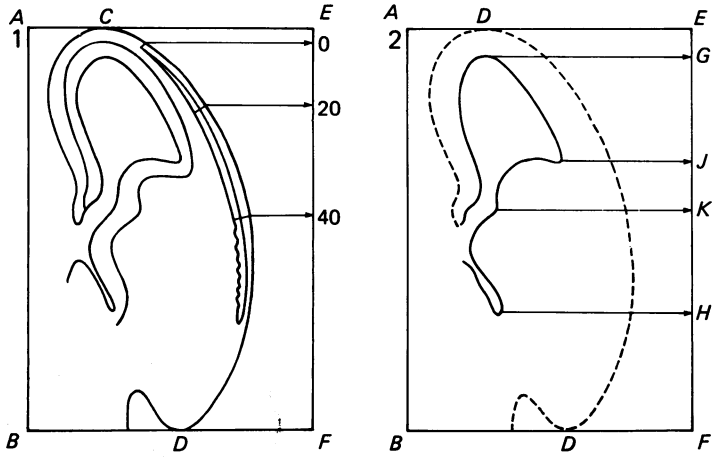


Fig. 1. Method of orthogonal projection described in text. The diagram used as an example is an outline of a section from the photographic atlas of an E14 telencephalon cut in the coronal plane at the level of the interventricular foramen. The figures 0, 20 and 40 refer to the depth of the cortical plate in micra at the locations indicated. Operationally, these 'spot depths' are first projected radially onto the surface of the telencephalon and then orthogonally onto line EF which is drawn parallel to the median plane, AB. The orthogonal projection is then assembled from the points marked on EF from each plate of the atlas using a master-profile as longitudinal control.

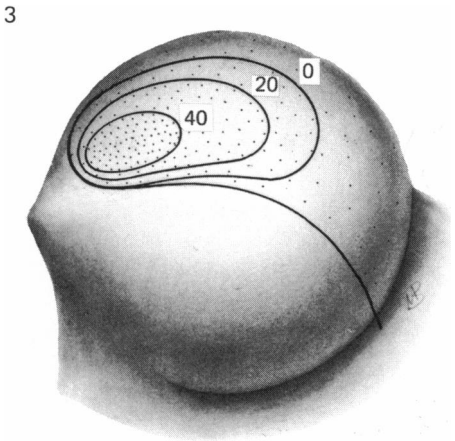
Fig. 2. Similar procedure for preparing orthogonal projection of ventricular surface. *G*, dorsal boundary of ventricle or 'roof flexure'; *H*, ventral boundary of ventricle; *J*, caudatopallial angle; *K*, sulcus between ventricular elevations.

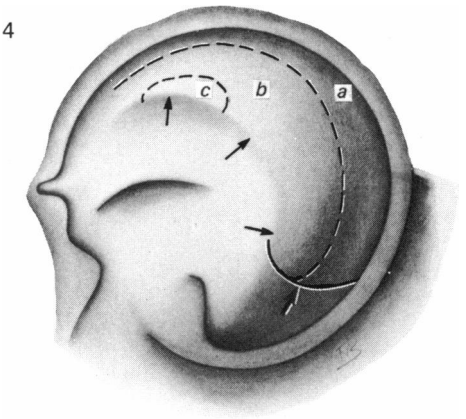
judged to be representative of each day of development. The selected sections were symmetrically cut in a plane as closely parallel to the 'ideal' coronal plane as possible. The 'ideal' coronal plane was defined as that which on passing through the brain just grazed the rostral margin of the interventricular foramen and the caudal margin of the anterior commissure. This corresponded to the orientation of the coronal plane in the plates of Sidman, Angevine & Pierce's (1971) atlas of the adult mouse brain. Prior to E15 when the anterior commissure had not yet decussated, a best estimate was made of the corresponding orientation.

At each age, every twentieth section containing the telencephalon was photographed and printed at a final magnification of $\times 100$. Thus, for each day of post-conceptional age between E10 and E19, a set of photographs of sections taken at intervals of 120 μm through the telencephalon was available at a scale sufficiently large to show considerable histological detail.

Preparation of orthogonal reconstruction

Each plate was treated as follows. A line AB was drawn parallel to the median plane (Fig. 1). Two lines were then drawn at right angles to AB to graze the dorsal and ventral curvatures of the telencephalon at C and D respectively (Fig. 1). These were extended beyond the telencephalon to equal distances from the mid-line (Fig. 1: AE and BF) and their ends joined. An orthogonal reconstruction of the lateral surface of the telencephalon was prepared by transferring the points E and F in each photograph seriatum on to graph paper as y coordinates, each line of points being separated by 120×100 μm (the distance between sections at $\times 100$ magnification). Longitudinal control was achieved by estimating the best fit to an





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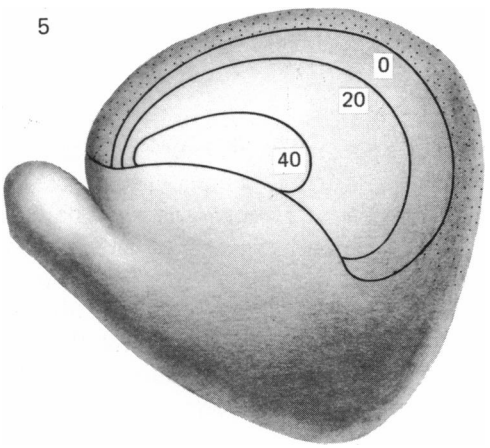

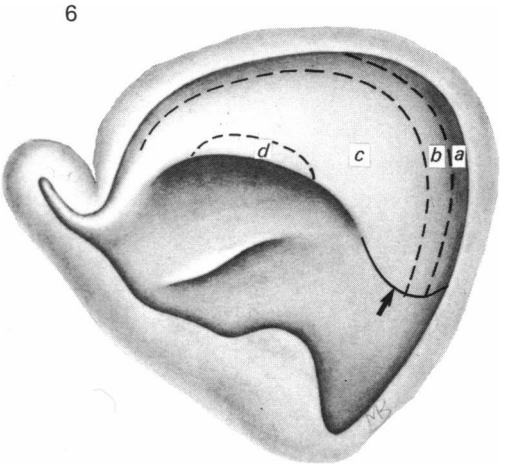

Fig. 3. Reconstructed lateral view of telencephalon of E13 mouse embryo. Stippling indicates extent of area receiving released neurons. Contour lines indicate total depth of intermediate layer in micra.

Fig. 4. Reconstructed lateral view of ventricle of E13 mouse. Fine arrows indicate the caudatopallial angle; the dorsal profile of the ventricle coincides with the 'roof flexure' (see Fig. 2). The part of the ventricular layer concerned with isocortical neuron production lies between the caudatopallial angle and roof flexure; the caudoventral boundary of this area is indicated by the unbroken line marked by the heavy arrows. The pecked lines divide the isocortical surface into areas related to the stages of development illustrated in Fig. 11 and indicated by the same lower case letters.

Fig. 5. Reconstructed lateral view of telencephalon of E14 mouse. Contour lines indicate depth of cortical plate in micra. Stippled area outside contours indicates area in which cortical plate has not yet appeared.

Fig. 6. Reconstructed lateral view of lateral ventricle of E14 mouse. Conventions as in Fig. 4.

optimised sagittal profile derived from brains cut in the sagittal plane and from photographs of the profile of fresh and hemisected brains. Shading was added to simulate the varying regional curvatures of the surface. Next, on each plate of the atlases of the E12 and E13 brains, the radial depth of the intermediate layer was measured in steps of 20 μm and the locations of these increments projected onto the pial surface as 'spot depths' (Fig. 1; 0, 20, 40). After the appearance of the cortical plate only the local depth of the plate was marked, also in 20 μm steps, on the pial surface. The positions of these spot depths were then projected orthogonally onto the reconstructions of the telencephalic surface. Equal spot depths were joined up to give a system of contour lines, portraying the variation in depth of the intermediate layer (or at later stages, the cortical plate) at 20 μm intervals.

A similar projection procedure was used to reconstruct the lateral aspect of the ventricular surface. In this case lines were drawn at right angles to AB to graze the dorsal and ventral boundaries of the ventricle to cut EF at G and H respectively as in Figure 2. Similarly, the caudatopallial angle and the bottom of the fissure between the two ventricular elevations were projected onto EF at J and K respectively. The sections were then fitted to the optimised profile. After shading, the final reconstructions were depicted within a ghost outline of the surrounding telencephalon. These drawings were used for mapping the location of periventricular cells giving rise to isocortical neurons.

Reasons for adopting intermediate layer depth as a useful parameter

The early intermediate layer is formed by released neurons accumulating among the radially orientated basal processes of ventricular cells. As nuclear size and distribution density did not vary greatly during the initial stages of neuron production, the radial depth of the intermediate layer was regarded as providing an index of local neuron release. For similar reasons, when the cortical plate appeared, its depth was taken as a usable index of the number of neurons formed during the later stages of neuron production. The necessary assumption for using the intermediate layer as what is, in effect, its own histogram is that released neurons accumulate opposite their site of origin and do not migrate tangentially to any great extent. This is an assumption which has been made or implied by most investigators since the early studies of cortical embryology. It has been reaffirmed in recent years by workers investigating the possible mechanisms involved in guiding the translocation of neurons from their site of production in the periventricular germinal layers to their peripheral destinations (Berry & Rogers, 1965; Morest, 1970; Rakic, 1972, 1978; Levitt & Rakic, 1981).

The number of neurons adjacent to a segment of ventricular layer was also taken to be a function of the duration rather than the rate of neuron release in that locality. Consequently, the depth contours linked points in the isocortex of equal age and, thus, at equivalent stages of development. Intermediate layer depth, therefore, carried qualitative as well as quantitative information and the contour lines traced fronts of histological change as well as revealing local depth.

RESULTS

Development of the intermediate layer and cortical plate

At E10, the incipient cerebral vesicle consisted of a hemispherical outpocketing of the neural epithelium truncated against the wall of the neural tube. Apart from

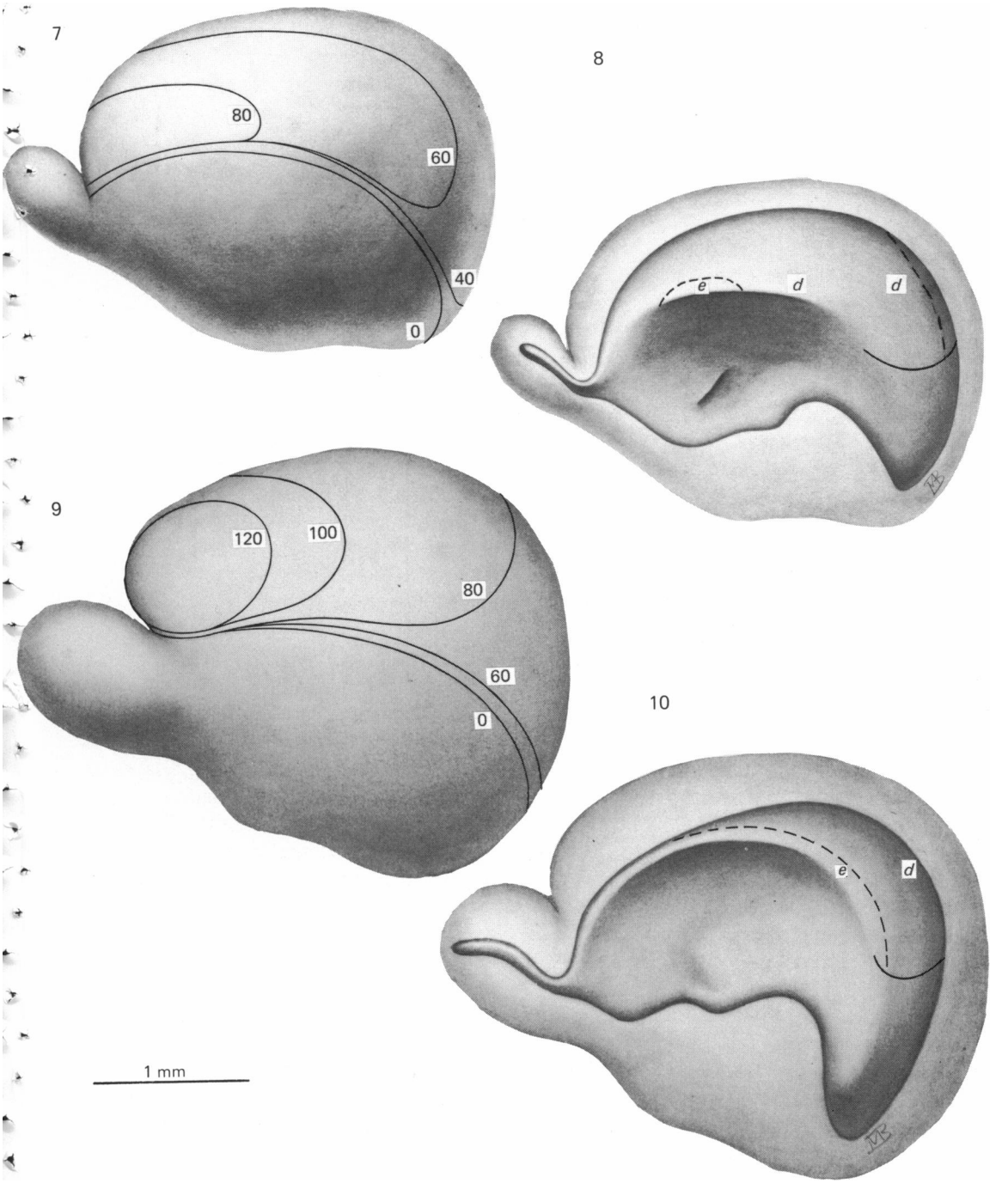

Fig. 7. Reconstructed lateral view of telencephalon of E15 mouse. Conventions as in Fig. 5.
Fig. 8. Reconstructed view of lateral ventricle of E15 mouse. Conventions as in Fig. 4.
Fig. 9. Reconstructed lateral view of telencephalon of E16 mouse. Conventions as in Fig. 5.
Fig. 10. Reconstructed view of lateral ventricle of E16 mouse. Conventions as in Fig. 4.

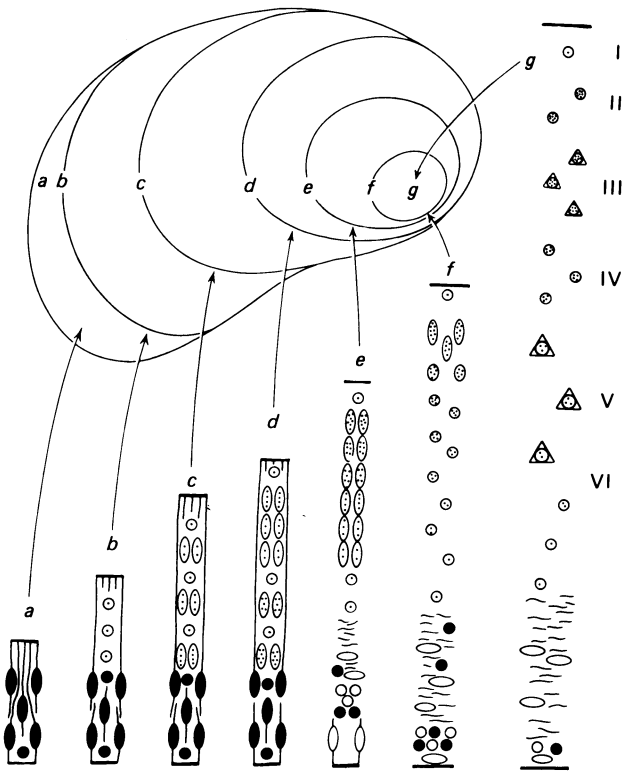

Fig. 11. The diagrams depict the gross changes occurring in an average radial strip of the mouse isocortex. Solid ovals or circles represent neuron precursors capable of mitosis, and open circles post-mitotic cells. The number of dots within a neuron nucleus in (*a*)–(*g*) is proportional to the age of the neuron. (*a*) stage of primary division; (*b*) release of preplate neurons; (*c*) increased neuron release leading to (*d*) establishment of cortical plate and continuing production of cortical plate neurons: (*e*) termination of neuron production, appearance of fibre tracts and subventricular layer concerned with neuroglia production; (*f*) commencement of maturation and dispersal of cortical plate neurons; (*g*) maturation completed, neuronal compartment has increased in breadth and three or more times in depth since stage depicted in (*e*). The diagram inset at the top left is a schematic representation of the lateral pallial wall and depicts the asymmetric propagation across the wall of the stages of neuron release and maturation summarized in (*a–g*).

a very few rounded nuclei located deep to the pial surface, there was no evidence of neuron release.

By E11 the vesicle had increased in area. An intermediate layer had developed rostrally in the ventral telencephalon spreading a short distance dorsally into the lateral wall. This was considered to represent the incipient piriform cortex and was thus excluded from the present study. Elsewhere in the lateral wall neuron release was minimal, being restricted to a few scattered cells lying immediately deep to the pial membrane.

During the E12 period, the portion of telencephalic wall relevant to this study increased in area. In its rostral part adjacent to the piriform area, a localised area of neuron release appeared representing the first isocortical cells, and by E13 the area had spread further across the lateral wall (Fig. 3). Ventrally, the isocortical population was distinguished from the immature piriform cortex by the greater packing density of its nuclei. In other directions, the isocortical intermediate layer diminished

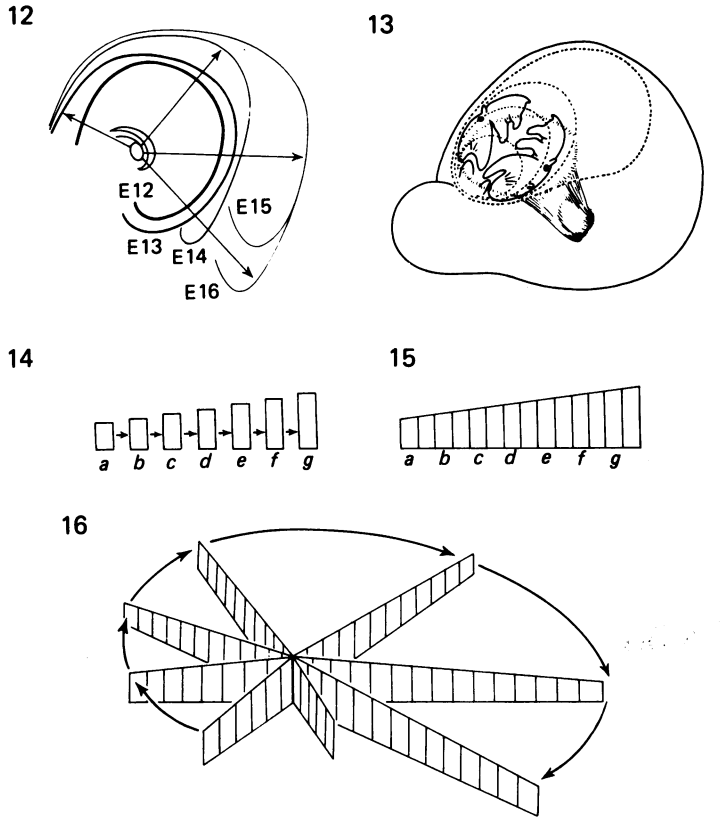

Fig. 12. Profiles of lateral ventricle, taken from Figs. 4, 6, 8 and 10, superimposed so that dorsal boundaries of interventricular foramen coincide.

Fig. 13. View of E16 telencephalon from in front and above. The animalculus of sensorimotor representation of the body surface in the adult mouse (as depicted by Woolsey, 1960) has been 'shrunk on' to the isocortical surface. The pharynx-tongue-lip area appears to lie at or near the site of production of the first isocortical neurons. The animalculus also appears to coincide with the first cortical area to receive thalamic radiations.

Fig. 14. The columns represent the same radial strip of tissue progressing through its history of neuron release, migration and maturation. Lower case letters refer to stages in Fig. 11 (*a–g*).

Fig. 15. A linear gradient is represented by adding radial strips as in Fig. 14 along an axis so that the history of each unit begins progressively later.

Fig. 16. A three dimensional gradient is represented by a series of linear gradients as in Fig. 15 radiating from a focus. The form of the perimeter of the system is determined by the order in which the addition of radial units is terminated.

in depth, virtually disappearing as the angle of greatest curvature of the roof, or 'roof flexure', was approached.

In the late E13 or early E14 period, the cortical plate appeared in the outer intermediate layer as an area of crowded nuclei, deepest rostrally, at the original site of isocortical neuron release and diminishing in depth when followed caudally and dorsally (Fig. 5).

By E15, the nuclear crowding characteristic of the cortical plate had reached the roof flexure along its entire rostrocaudal extent. The depth of the plate had also increased while maintaining its original taper as indicated by the contour lines in Figure 7.

By E16, the cortical plate had increased further in depth and the contour lines continued to register a decrease in depth when traced rostrocaudally (Fig. 9).

After E16, the picture became complicated by progressive organisation of cortical plate neurons into the definitive cortical layers, so that the depth of a now heterogeneously packed cortical plate no longer bore any simple relation to the number of arriving neurons.

Changes in ventricular morphology

Lateral views of the ventricular surface are portrayed in Figures 4, 6, 8 and 10. The area related to ventricular cells with processes radiating through the isocortical intermediate layer lay between the caudatopallial angle and the line of maximum curvature of the ventricular roof, or roof flexure, which is taken to mark the dorsal boundary of the isocortex (Smart & McSherry, 1982). During growth both these lines moved in relation to each other and to other landmarks. By superimposing the profiles of the ventricles at each age so that the dorsal boundaries of the interventricular foramen lay in register, it was apparent that the line of the caudatopallial angle lengthened and moved centrifugally with respect to the interventricular foramen. A similar course was followed by the line of the roof flexure (Fig. 12). During these movements, the distance between the roof flexure and the caudatopallial angle decreased rostrally after E14 (Figs. 6, 8). This approximation of the two boundaries continued and was carried further caudally by E16 (Figs. 8, 10). Reference to models of ventricular casts confirmed that this approximation of the two lines represented a true decrease in area of the isocortical generative surface and was not the result of foreshortening of a curved surface inherent in an orthogonal projection.

DISCUSSION

The results of plotting the chosen intermediate layer parameters indicate that, after a period of ventricular cell proliferation leading to increase in area of the pallium, release of isocortical neurons commences at a rostral focus coextensive with the region of the caudatopallial angle and spreads from there across the lateral pallial wall (Figs. 3, 4). Similarly, the increased neuron formation from the periventricular layers which leads to the cell crowding characteristic of the cortical plate originates at the same rostral site and its front of propagation follows that of the initial wave of neuron release (Figs. 5, 7, 9). Termination of neuron release, with a corresponding decline in the ventricular layer, also seems to originate at the caudatopallial angle and to follow the preceding fronts of growth and differentiation.

Increments to the pallial wall originate mainly along the roof flexure where mitotic activity is high and neuron release minimal (Smart, 1973). Consequently, cell division in this zone is creating more ventricular cells and thereby adding to the area of the ventricular layer; more ventrally, on the other hand, the ventricular layer is producing neurons which leave the layer and hence do not increase its area. This growth zone at the isocortical perimeter is obliterated in a rostrocaudal direction as the spread of isocortical neuron release meets a corresponding spread from a similar rostral site on the medial wall, concerned with generating mesocortical neurons. In Figure 12 the profiles of the roof flexure at successive ages are superimposed; this reveals how cessation of ventricular layer growth, extending caudally along the roof flexure, sculptures the form of the ventricular cavity and with it the outline of the overlying tissue (Figs. 3–10). Spread of isocortical neuron production in a ventral direction

from the focus of origin is minimal; hence this boundary is correspondingly concave (Figs. 3, 5, 7, 9), mirroring the curvature of the caudatopallial angle (Figs. 4, 6, 8, 10), and bestowing an interesting 'mussel shell' outline to the isocortical area and its inscribed contours, which is reminiscent of the gnomonic growth pattern discussed by Thompson (1963).

The contours themselves correspond to stages of intermediate layer development and indicate a continuum of histological change across the pallial wall. Stages from the histological sequence are represented diagrammatically in Figure 11 (*a–g*), while in the inset diagram to this Figure the sequence is shown radiating from a rostral focus. In such a system, the number of stages present at any one time would depend on the duration and rate of propagation of individual stages. For example, there would obviously be more stages present if their duration were short and they were slowly propagated; conversely, a stage of long duration rapidly propagated would occupy the whole isocortical surface. This affects the possibility of differential sensitivity of the isocortex to damage during development. For example, at E14 (Fig. 5) four of the stages depicted in Figure 11 are present and each stage might respond differently to transient injury at this time.

The preplate population and its early synaptic connections are held by Marin-Padilla (1971, 1978) and Rickmann, Chronwall & Wolff (1977) to be the relict of premammal isocortical organisation, and the cortical plate to represent a new histogenetic feature peculiar to mammals. This seems to be a reasonable hypothesis. The basic histogenic changes required (the production of more neurons and their rapid migration to the outer intermediate layer) could have evolved gradually during the considerable number of generations that elapsed between the origin of protomammals and the establishment of mammalian status. The trend during this time was evidently to create more cortical territory by lengthening the gradient of neuron release and to form a deeper cortical plate by increasing neuron birth from the periventricular germinal layers.

A clue to the functional origin of the isocortical system is suggested by the location of the initial focus of origin of the gradient of neuron release (Fig. 13). This appears to coincide with the most ventral part of the mammalian somatotopic animalculus, generally depicted as the location of the sensorimotor organisation controlling the throat, tongue and lips. In a recent treaties on the origin of mammals, Kemp (1982) cites evidence that in Cynodonts the unreptilian characteristic of soft, muscular lips had developed. This group, considered on other grounds to be suitably protomammalian, may therefore exhibit an early stage in the functional transformation of the reptilian oropharyngeal apparatus and the primitive isocortex may have developed as one of its telencephalic correlates. Such a link between the beginning of the pallial cell production gradient and a peripheral sensorimotor field undergoing adaptive change may have been extended to incorporate isocortical representation of the remainder of the body axis in a sequence recorded by the anatomical progression of the somatotopic animalculus. In the human isocortex also, Sidman & Rakic (1982) have noticed a concentric differentiation gradient with its origin near the ventral end of what will become the central fissure. This area is well known to be the site of oropharyngeal representation in man (Penfield & Rasmussen, 1950). Sidman and Rakic, however, place the origin of the human gradient in the adjacent insular cortex. In the mouse, on the other hand, the origin lies clearly within isocortical territory, and the insular cortex originates in relation to the tapered ventral edge of the cortical plate (Smart & McSherry, 1982: Fig. 10). This tapered segment appears to represent

a ventral propagation of isocortical plate into adjacent piriform territory, making the insula developmentally a mixed cortex similar to the mesocortical area of the medial wall. In man, there is a corresponding ventral fringe of the cortical plate which is less well developed and is also described as giving rise to the insular cortex. This fringe is classified by Rose (1928) as 'bicortex' and by Filimonoff (1974) as 'cortex intermedius' on the grounds that it is only partly derived from cortical plate neurons. Thus, in man, as in the mouse, the origin of the isocortical gradient of neuron release would appear to lie dorsal to the insular fringe.

In any event, the oropharyngeal region in man is more centrally placed within the isocortex than in the mouse. This indicates that the differentiation gradient has been propagated more symmetrically about its origin to generate the proportionately larger frontal lobe characteristic of the human brain. The location of the cortical oropharyngeal area relative to the perimeter of the isocortex may therefore be useful as an index of differential growth. Its site is known in a few species from direct neurophysiological studies. In others, a near estimate may be obtained by locating the barrel fields which mark the vibrissal area of the upper lip. An extensive comparative study of this feature has been made by Woolsey, Welker & Schwarz (1975). In some species, for example the mouse and rat, the barrel fields occupy much the same relative position within the cortical boundary, indicating that the larger rat isocortex corresponds to a scaled up mouse cortex. In other species, for example the porcupine and rabbit, the relative positions of the barrel fields differ, suggesting that there are different patterns of differential growth in these animals. Differential growth is, therefore, an index of the way the cell production gradient has been varied to create different proportions of collateral association cortex.

In addition there are also species variations in the depth of the cortical plate and in the mode of its transformation into mature cortex. Therefore, in order to assess the histogenetic status of the cortex in a particular species, it would be necessary to prepare (i) a series of drawings illustrating the progression of events in an average sample of isocortical tissue, (ii) corresponding sets of contour maps showing the progression of these events across the pallial wall. Conversely, the repetitiveness of the events in isocortical histogenesis encourages an attempt at modelling its growth pattern. For example, the radial migration of neurons within a unit of isocortical tissue (Figs. 11*a–g*, 14) provides one dimensional positional data. A developmental gradient can be represented in two dimensions by the serial entry of such samples along an axis (Fig. 15; Smart, 1973: Fig. 22; Smart & Smart, 1982; Smart & McSherry, 1982; Todd & Smart, 1982). Growth in three dimensions may be represented by a system of such linear gradients radiating from a focus (Fig. 16; Smart, 1973: Fig. 21 in this paper). The shape of the perimeter of the system can be modelled by varying the number of increments received at the ends of the gradients; for example, in the rodent, increments would cease in a rostrocaudal sequence (Figs. 11 inset, 16). This procedure is currently enabling us to translate the stages of cortical development into a form suitable for computer-simulation of different patterns of cortical growth. The exercise involves an interesting paradox as it links one of the oldest of neurohistological techniques, namely the recording of the developmental history of an area by drawing radial samples of each stage to the ability of modern computers to summate one dimensional data derived from such strips into three dimensional patterns.

SUMMARY

The three dimensional growth of the mouse isocortex was examined by plotting the variations in intermediate layer depth on orthogonal projections of the telencephalic surface at successive periods of development; a histological status was assigned to each depth. Thus portrayed, the development of the isocortex was seen as a propagated sequence of histological change, commencing at a rostral focus coextensive with the caudatopallial angle and thence spreading across the telencephalic wall. Growth was asymmetric about the focus of origin and terminated in a rostrocaudal direction as the spread of neuron production reached and extinguished a growth zone along the sagittal perimeter of the hemisphere.

The possibility of mouse isocortical histogenesis representing a variation of a general mammalian pattern was noted, as was the evolutionary and methodological significance of the apparent coincidence of the origin of the gradient of isocortical neuron release with the region of cortex representing oropharyngeal structures. An alternative form of representation of the isocortical gradient, as the summation of a number of radial strips of tissue each with a similar history of neuron release and migration, was used to lay a foundation for a three dimensional model.

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