DENDRITIC CORRELATES OF HUMAN CORTICAL FUNCTION

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INTRODUCTION

The dendrite systems of neurons have ben studied in detail since the time of Golgi (7) and Cajal (1), initially for the fascination which their diverse patterns stimulated, and then, increasingly, for the insights they provided concerning neuron function. At the simplest level the contrasts between the cortical pyramidal cell with its highly oriented apical shaft and its sunburst of basilar dendrites, on the one hand, and the small spherical cerebellar granule cell generating short, claw-capped dendrites immediately adjacent to the cell body, on the other, appear obvious. Somewhat more subtle are the variations among individual cortical pyramids at different depths within the laminar organization (10), or the structural and topographical alterations among multipolar reticular neurons, either at different reticular sites, or at varying epochs in the life history of the organism (13). Although our understanding of dendrite structuro-functional relations remains incomplete, it seems increasingly clear that dendrite morphology powerfully reflects the idiosyncratic roles of each parent neuron, expressed at both genetic and epigenetic levels.

The geographical extent of the dendrite arbor delimits a territory or zone of potential interaction. Dendrite zones of adjacent cells overlap and interdigitate but each domain represents a preferential territory or target for specified afferent systems. The geometry of the dendrite field clearly develops as an expression of the significant synaptic influx. One thinks immediately of the flattened. two dimensional grid erected by the cerebellar Purkinje cell, perpendicular to the path of the parallel fibers, or the tight spherical swirls of neuronal dendrite systems in the principal portion of the inferior olive as they relate to the conical terminal elaborations of olivary afferents (1, 16).

Equally important is the immediate environment of the dendrite. Dendrite bundling is now known to be a fairly widespread phenomenon and becomes more obvious with maturation in cerebral cortex, brain stem, and spinal cord (5, 13, 17, 18). From the functional point of view it remains unclear whether the structural pattern serves intuitively obvious functions such as synchronization of dendritic electrical activity or, as we have suggested elsewhere, provides privileged intrafasciculsr zones where membrane-bound molecular arrays, representative of repeated input-output sequences, might gradually be organized (18).

Another conceivably important factor in spatial arrangement may be represented

in dendrite position vis a vis the capillary bed. Studies with oxygen-sensitive microe-lectrodes have demonstrated large oxygen gradients in cerebral tissue ranging from 70-80 mm of mercury immediately adjacent to a capillary to 3-4 mm of mercury only 50 um away, at a point approximately equidistant between two adjacent vessels (20, 21). Values as low as these approach minimal oxygen levels necessary for cellular cytochrome oxidase activities and suggest the possibility of *more* and *less* environmentally favored zones for neuron-dendrite function.

One other putative consequence of dendrite distribution in relation to the vascu-lar tree is the possible variation in concentration of substrate materials such as glucose, amino acids, etc. to which the blood brain barrier is selctively and variably patent. Although a large proportion of energy-demanding synthesizing activities (e.g. peptides, structural proteins, etc.) are centered in the nerve cell body, dendrites are also the site of significant levels of synthetic activity (e.g. the substantia nigra [9]). Spatial arrangements of dendrite shafts in relation to the capillary bed may therefore significantly affect the functional role of the dendrite. A wide range of electrotonic effects must be considered and may provide the single most power-ful set of constraints on dendrite function. Length of the individual dendrite seg-ment, its diameter and taper or flare, the number and sequence of bifurcations, the angles generated by the daughter branchlets, the number of dendritic segment orders and the nature of dendrite terminals are all important. Equally significant is the presence or absence of dendrite spines, their density patterns (which vary markedly throughout the dendrite tree), and their individual morphology. Clearly, the electrotonic characteristics of the blunt, short-stemmed spine differs appreciably from that of the thin, long-stemmed 'lollypop' variety found most frequently on higher order, peripheral dendrite segments (12).

THE BACKGROUND AND NATURE OF THE STUDY.

Almost 35 years ago, during the course of a year's fellowship study at the Institute of Physiology in Pisa, we had the opportunity to make a short trip to the Vogts' Brain Research Institute in Neustadt. Here, Oscar and Cecile Vogt showed us, from their great collection of human brain material, several intriguing examples of apparent correlation between brain structure and specific cognitive gift or talent. In the case of a musician who had been born with the gift of perfect pitch, layer IV of the principle auditory cortex (Heschl's gyrus) was almost twice as thick as that of an ungifted control. Similarly layer IV of the primary visual cortex (area 17) was very much thicker in the brain of an artist who had maintained the capacity for eidetic imagery throughout his life, compared with visually ungifted controls. The Nissl type sections which the Vogts studied did not seem to suggest a larger number of neurons so much as a larger cortical area occupied by approximately the same number of neurons. Since the cell packing density was lower, we deduced that a more complex neuropil separated the neurons in this layer. Exciting as these data were with their implication of correlation

between functional complexity and degree of anatomical elaboration, it proved difficult to follow up on the observations of the Vogts. Brain tissue from gifted individuals was not easy to obtain.

THE CONTENT OF THE STUDIES.

In the following section, the results of several ongoing studies are summarized. They represent initial attempts by our laboratory to continue and expand this type of investigation. The first work uses speech as a representative high level cognitive operation and compares dendrite pattern and complexity in the speech dominant cortical zone (area opercularis and triangularis of the left hemisphere) of Broca with its propositionally ungifted homologous area on the right. These were matched with the motor areas in the inferior portion of area 4 just behind them where motor control of pharyngeal, laryngeal, mouth and tongue muscles seem centered. The Broca speech zones were considered "strategic" areas for motor speech while those just behind them in the motor strip were considered to be "tactical" in function.

The second study compared levels of dendrite complexity in four operationally identified zones of human cerebral cortex. Two sites were chosen in primary sensory cortex, the area of thoracic representation which was considered a less informationally complex area, and the finger representation area which we assumed to be a more informationally complex zone. These sites were compared, in turn, with two others; one far forward on the superior frontal gyrus (area 9) of prefrontal cortex and the other on the supramarginal gyrus (area 40) of the parietal lobe. Both of these were selected as examples of associative cortical zones where complex computational activities are commonly believed to be carried out (2, 6).

Several working hypotheses were generated at the beginning of these studies. 1) Positive correlations should exist between the degree of complexity of the neural computations subserved by an area and the total length and complexity of the dendrite systems of the neurons involved. 2) Operationally more complex cognitive tasks entail the necessity for larger amounts of dendritic surface providing a greater area for synaptic transactions. 3) Dendrite field complexity should be expressed by more highly branched dendrite systems and/or longer dendrite segment lengths and/or higher dendritic spine densities.

SOME PROBLEMS INHERENT IN THE USE OF HUMAN MATERIAL.

At the outset, it should be pointed out that both of these studies, based on analysis of Golgi stained sections from post mortem human brain material, suffer from several shortcomings. Since our source of material was a large Veterans Administration Hospital, we had no control over the type of material that was made available and none of the patients was known to us personally. The kinds

of correlative information which were most important to us in studies of this type were precisely those which were usually least frequently noted in the patients' histories and charts. Thus language facility and writing facility, possible multilingual gifts, details of occupation, hobbies, specific talents, outstanding personality attributes, and even handedness were seldom recorded. In some respects, working 'blind' served the needs of impartiality in collecting the quantitative data. However, hospital policy and compassionate concern for the families involved made retrospective inquiries about this type of information very difficult. As a result, the amount of correlative data available for both of these studies was minimal. It might reasonably be hoped that with increasing frequency of correlative studies of this sort, the development of brain banks, and the donation of brain material from deceased individuals with special skills or histories of unusual achievement may gradually ameliorate this problem.

Another aspect of the problems associated with the use of human tissue in this type of investigation, is the enormous range of circumstances under which the patient reaches the end of his life and the intervals before the tissue becomes available for fixation and impregnation. It has become increasingly clear that dendritic tissue continues to be plastic and remoldable until the end of life. Dendrites grow with challenge and retract and resorb with lack of use (4, 8, 22). In the studies reported here, only brain tissue from patients without clinically evident neurological problems and without obvious neuropathological findings were used. Nevertheless, the specific events of the pre-agonal phase might have impacted significantly on the final morphological state of the dendritic tissue. A long period of terminal illness or even of relative inactivity, physical or intellectual, is bound to leave its mark on even the most exuberant growth of cortical dendrites. Periods of preterminal hypoxia which might accompany cardio-pulmonary disease can also be expected to have effects on the extent of the dendrite arbors, especially the most reactive terminal segments. Additionally, the length of the period between death and tissue fixation is also important and in this study we limited ourselves to brain tissue obtainable within the first 12-18 hours after death. Finally the well-known vagaries of the Golgi impregnation itself add another dimension of uncertainty to the studies. It is also becoming clear that gender is important in cortical function and in cortical lateralization (4). In the Broca speech study, all of the patients were male, and it would be desirable to repeat this type of work with a female population. In the second study, one out of eight patients was female, and we cannot yet tell how this influenced our data. Despite such caveats, these studies represent, at the least, a first step in attempting to establish correlates between human brain structure and specific types of cognitive activities.

STUDIES ON THE SPEECH CORTEX.

Tissue specimens from eight male brains ranging in age from 58 to 77 (mean age 65.9) were used in this study. They included blocks from left and right opercu-

lar areas of Broca in the inferior frontal gyrus, and from the orofacial area of the motor strip just behind. Following impregnation by a modification of the rapid Golgi method and mounting under cover slips, slides were coded to avoid investigator bias. Eight neurons were chosen from each of the four regions of each brain. Criteria for selection included 1) cell body depth beneath the pial surface of 400-1300 um (thus including pyramidal cells of the deeper portions of layer II and layer III); 2) the presence of at least three well developed primary basilar dendrite systems with well developed peripheral branching systems; and 3) location of the pyramidal cell body approximately in the middle of the 120 um thick section.

Analysis of the dendrite enveloppes was performed in two ways. The first consisted of a modification of the Sholl technique in which a series of concentric, equidistant circles is superimposed on the cell body and the number of dendrite intersections per ring is counted (19). This provides a useful first order approximation of the complexity or 'profile' of the the dendrite ensemble. In the second, cells were drawn with a camera lucida at a total magnification of 312.5. Depth coordinates (the z axis) were read directly from the calibrated fine focus of the microscope for cell body, each dendritic branch point and each dendrite tip. The apparent status of each tip (i.e. broken, cut, or intact) was noted. Planar coordinates for each branch point and terminal (x and y values) were subsequently measured with a TRS-80 microcomputer controlling a digitizing pad and the data were than transfered to a main fram computer for analysis.

In line with our initial working hypotheses already noted, our expectations were that the left opercular (motor speech) area would exceed the right opercular area in total length and complexity of the dendrite systems, and that both opercular regions would exceed the primary motor areas just behind them.

Analyses by the concentric ring method of Sholl are epitomized in Figure 1. In brains 1, 3, and 4, the number of dendrite intersections for cells in Broca's area on the left (left opercular) was significantly greater than that on the right (right opercular) and in fact for any of the other areas. The differences achieved significance between rings 6 and 14 (ring interval = 28 um). This distance of about 160 um from the center of the soma represents the approximate transition zone between third and fourth order dendrites. The reversal in the case of brain 5 where dendrite intersection values in the right operculum exceeded those of the left became more reasonable when it was learned at the conclusion of the study that this patient was one of two non-right handers. This was of particular interest since it is generally conceded that the majority of non-right handed individuals are still essentially "left brained".

Computer analysis of the digitized data from each dendrite tree provided several surprises. We took the total dendritic length, TDL, of a cell as a measure of the amount of dendritic surface area potentially available for synaptic interaction. In the six right handed patients, TDL in the opercular region exceeded that in the precentral areas by about 10% (F = 2.89, df = 1,134, p = .091) but the difference was significant only in the left hemisphere (t = 2.37, df = 1,134, p < .05). We were
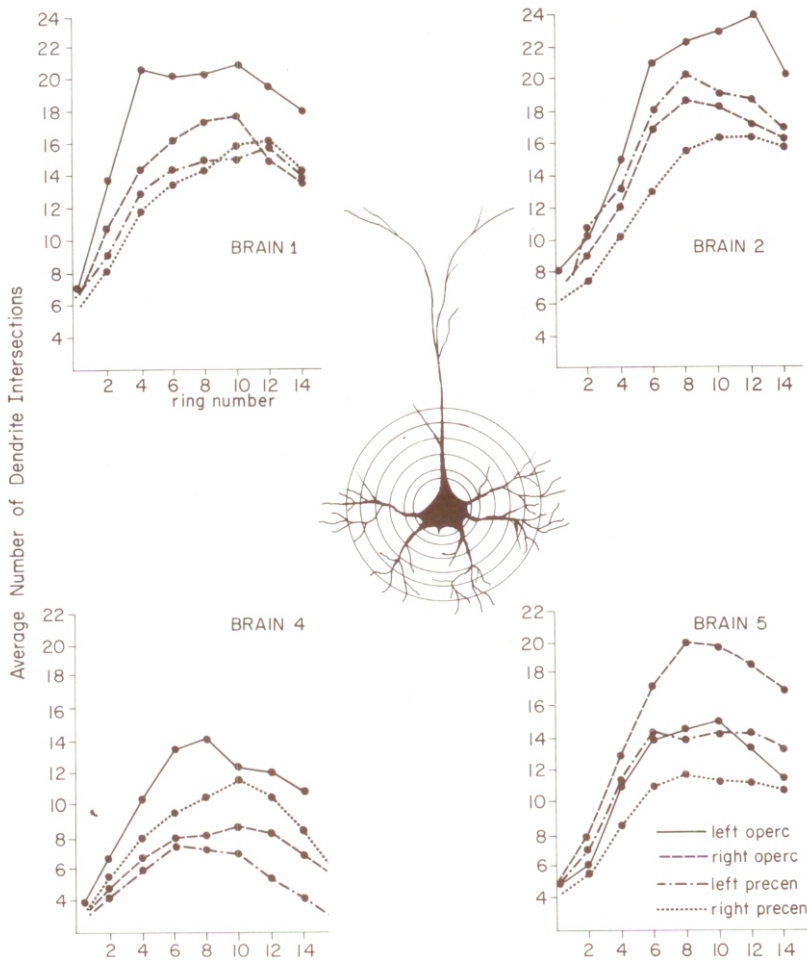
Fig. 1. — *Graphs summarizing the average number of dendrite intersections per ring in a Sholl type of analysis of four cortical areas in cases 1, 3, 4, and 5.*

Note that dendrite systems from cells in the left opercular region (Broca's area) consistently produce a greater number of intersections with the concentric target rings (center illustration) especially beyond ring 6 in all cases except that of brain 5. This patient with reversed ring-dendrite pattern (right opercular higher in number of intersections than left) was found to have been a non-right-hander. Abbreviations: left operc., left opercularis-triangularis region of Broca; right operc., right opercularis-triangularis region; left and right precen., left and right precentral regions, respectively.

surprised by the lack of significants in left-right differences in TDL. However, it then became apparent that when dendrite systems were analyzed by segment order, significant quantitative differences could be found. The fraction of TDL composed of higher order dendrites (fourth plus fifth plus sixth orders) was greater on the left than on the right (F = 7.43, df = 1,134, p = .007) and was also larger in the opercular than in precentral areas. Thus higher-order dendrite branches of left opercular neurons constituted a greater fraction of the total dendrite tree

than did similarly situated branches in the right operculum (Fig. 2). Complementary asymmetries were found in comparing dendrite systems of left and right precentral neurons where significantly larger proportions of right sided dendrite systems (p < .005) were devoted to lower (first plus second plus third) order branches (14, 15).
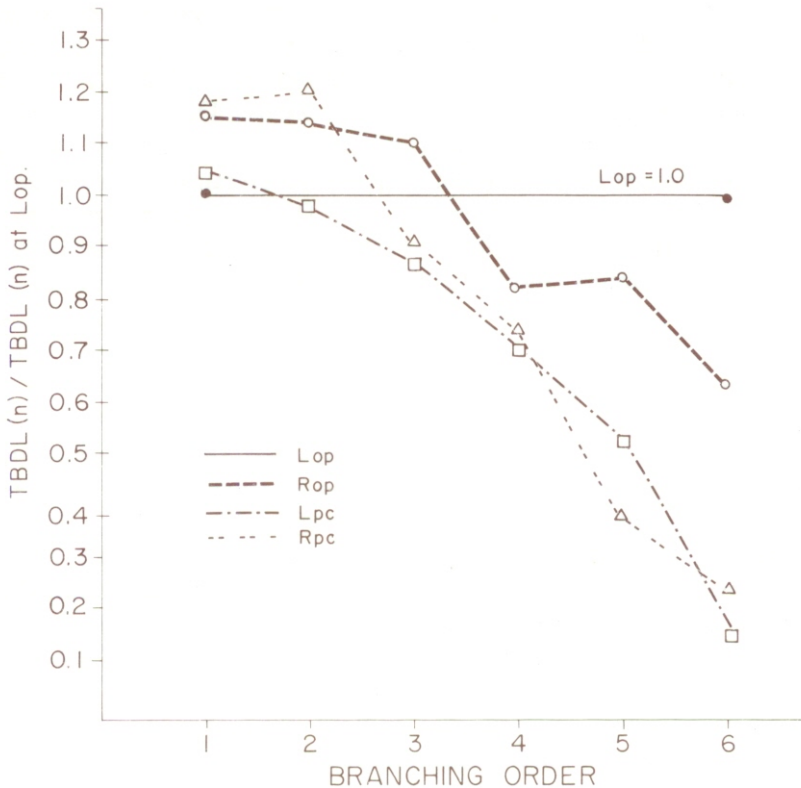

Fig. 2. — *Comparison of total basilar dendritic length at each branching order, TBDL (n), in relation to values in the left opercular region, Lop, in six right handed individuals.*

The value for Lop at each segment order is kept at 1.0. Note the larger number of higher order segments in dendrite systems of Broca's area compared to all other areas. Abbreviations: Lop, left opercularis-triangularis; Rop, right opercularis-triangularis; Lpc, lft precentral; Rpc, right precentral. Slightly modified from Scheibel *et al.* (15).

Dendrite system develop in centrifugal fashion (1, 3) with higher order branches being succesively added during the early years of postnatal life. It is also increasingly clear that these peripheral branches are the most plastic components of the dendrite ensemble and are subject to growth and remolding throughout the entire life span (4). If the adult dendrite arbor is conceived as a temporo-spatial record of dendritic development, these left-right differences in branching pattern can be interpreted as representing differential growth sequences peculiar to the two hemispheres and to the areas involved (14, 15) Greater length of lower order

dendrite branches suggests that portions of right hemispheric cortex may "lead" the left during the first year of life when the infant depends largely on sensory impressions of a highly concrete nature and is limited to relatively large-scale and undifferentiated motor acts (the sensory-motor period of Piaget [11]). To examine this hypothesis, we have recently analyzed the same left and right opercular and left and right precentral cortical areas in an age-graded series of infant brains from the immediately postnatal period through the age of 6 years. This epoch encompasses the period of primary language acquisition as well as that of the most important early sensory and motor skills. These data indicate that dendritic length of neurons in the right opercular and precentral regions does initially exceed that in matched areas on the left, an asymmetry that is not finally overcome until the fifth or sixth year of life. During this period, the greater growth of dendrite systems on the left is expressed primarily by the higher order dendrite branches. (Simonds and Scheibel, in preparation).

STUDIES ON SENSORY AND ASSOCIATION CORTEX

As already indicated, the second study investigated the possible relationships between dendrite complexity and the specific roles of several more-or-less functionally characterized cortical areas, including those responsible for thoracic and finger representation in the primary sensory strip area (areas 3, 1, and 2) and sites in superior prefrontal (area 9) and supramarginal (area 40) zones, all on the left. Specimens from a series of twelve patients were obtained although, because of technical difficulties, data from only nine could be used. In this case, 8 neurons were analyzed from each of the 4 areas selected in each brain and the Sholl method of concentric ring analysis was utilized for collecting data.

This material is presently under analysis (Scheibel et al., in preparation) but several findings are worthy of note. In apparent agreement with our initial working hypothesis, dendrite systems in the sensory area for trunk representation are consistently the least complex and most restricted in area. This seems intuitively appropriate since sensory input from the trunk is generally limited, especially when compared with that of the face, hands and feet. Beyond this, however, it has proven more difficult to develop a correlative hierarchy between the assumed computational complexity provided by a cortical area and the complexity of the dendritic tree. We had initially predicted that prefrontal and parietal association areas, by virtue of their "high order" cognitive tasks should also invariably possess the richest arbors. In the majority of cases, this was true but in three individuals, dendrite systems of the finger area exceeded all the rest in extent and intricacy. Subsequent information obtained from the families indicated that one of these individuals was a machinist and the other, an office worker-typist. Both of these tasks presumably require a high order of manual dexterity and finger skill. The third was reported to be a salesman without further information about the specific kind of work he did, nor about his hobbies.

No clear cut advantage has so far emerged in our study of dendrite patterns from the two associational areas, and we cannot obtain, in this series of cases, sufficient data about the personalities and life patterns of the individuals to make any possible correlations meaningful. However, comparison of dendrite intersection patterns when graphically displayed indicate that prefrontal dendrite systems characteristically have sharper peaks centering approximately upon the eighth concentric ring whereas parietal dendrite systems tend to rise, peak, and descend more gradually, thereby producing a more rounded 'dome' effect. We can only assume that the latter represents a somewhat enhanced branching pattern in the central portion of the dendrite enveloppe, probably among third and fourth order dendrite segments.

CONCLUSIONS

These introductory studies can only hint at the problems and the promise of attempts to correlate human cortical histology with cognitive function. Our data already suggest that within broad limits there are recognizable relationships between the type of neural operation and the pattern and complexity of dendritic structure. We have little but intuitive notions as to what constitutes a 'difficult' as opposed to a 'less difficult' computational task for neurons. Do higher order dendrite systems in the left opercular region of Broca elaborate preferentially under the increasing stimulus of speech formulation needes, or does their preprogrammed growth provide a milieu in which all of the computations necessary to expressive speech can find substrate. Clearly, restatements of the classic nature-nurture problem are non-productive and both must be assumed to operate interactively.

Of considerable interest is the difference in dendrite structure between dendrite ensembles of right and left opercular and motor zones. On the right side, a greater proportion of the dendrite tree is made up of lower order (earlier appearing) segment orders. On the left, more of the ensemble seems composed of higher order (later appearing) segments. Apart from the temporal factors (both ontogenetic and phylogenetic) subsumed within these observations, does this provide some suggestion as to where certain types of brain operations are centered within the dendrite enveloppe? Is it possible that complex lexical and syntactic operations depend most heavily on the outer, high order dendrite segments while more basic, affective and emotional (prosodic) elements of speech are more adequately supported by lower order branches? Again, there is an intuitively attractive element to this since the outer order segments are reported to be the most modifiable elements of the dendrite tree throughout life. Although basic vocabulary is undoubtedly an overlearned items for most speakers of any language, the continuously changing demands made upon vocabulary and syntax by man's social environment would seem to imply continuous challenge and, accordingly, change (4, 8).

Initial evaluation of our studies of sensory and association cortices also underline several factors. Interindividual variation is enormous and unless the number of subjects in large, the data are likely to be submerged in noise. The consistently

less extensive dendrite ensembles in the sensory receptive area for trunk would seem to argue for less input or for less computation, and more likely for both. We seldom explore the environment with the skin surfaces of our trunk and neither the sensitivity nor two point discrimination of this area are of high order. Fingers are exquisitely sensitive tactile monitors and the density of sensory information they report is very high. It is perfectly realistic to suppose that the larger dendrite arbors characteristic of finger receptive areas are a function of the increased afferent stream, whether or not this throws any light on the complexity of the processing operations which are assumed to follow. It must also be remembered, however, that our data have examined only one parameter of the cortical matrix exclusive of apical dendrite systems, spines, afferent and efferent axonal arbors, collaterals, the enormous arays of local circuit neurons, the neuroglia, etc.

Suggestive differences in profiles of dendrite ensembles such as those noted between area 9 and area 40 must await further analysis and more extensive information about the life history and personality characteristics of the individuals involved. However, the early observations of the Vogts, and the very tentative correlations suggested by these studies suggest that we may reasonably expect a correlative neuroanatomy — and neurochemistry — of human cognitive function fo develop with time.

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