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STONE AGE INSTITUTE PUBLICATION SERIES
*NUMBER 4*

*Series Editors Kathy Schick and Nicholas Toth*

# THE HUMAN BRAIN EVOLVING:

## Paleoneurological Studies in Honor of Ralph L. Holloway

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*FRONT COVER CAPTIONS*

*Center: Portrait of Ralph L. Holloway.*
*Upper left: A modern human brain.*
*Upper right: Ralph measuring landmarks on an endocast ca. 1976.*
*Lower right: Homo habilis cranium KNM-ER-1813 from Koobi Fora, Kenya (photo by Holloway).*
*Lower left: Ralph with an endocast of the Flores "hobbit" cranium.*

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# CHAPTER 12

# The Role of Vertical Organization in the Encephalization and Reorganization of the Primate Cortex

Daniel P. Buxhoeveden

## Introduction

While cortical enlargement dominated the thinking of hominid evolution and paleoneurology, it was not until the last few decades that the mechanisms responsible for this were made known. The answer was provided by the radial unit hypothesis as revealed by the seminal work of Pasko Rakic (1972, 1978). The significance of this work to the field of paleoneurology cannot be overstated and it is now gaining the attention it deserves. The model provides insights into the relationship between cortical size and re-organization, and it sheds light on the proliferation of cortical regions and the relationship between surface area and cortical depth. I have chosen to address two main topic areas based on the radial unit hypothesis. The first considers the relationship between cortical enlargement, reorganization, and minicolumn size. The second section briefly considers what is known about the size of minicolumns in the primate order and suggests possible implications.

## Defining the Micro-Vertical Organization of the Cortex

The minicolumn is a particular feature of cortical organization; one based on vertical components of cortical function at a spatially small scale. It does not disregard horizontal organization and recognizes that the complexity of the brain allows for multiple ways of processing information. The use of the vertical organization of the cortex is an attempt to find unifying principles in cortical organization which integrate horizontal lamina and intrinsic circuits into a testable model. There is arguably substantial evidence of functionality at this level of organization, and as a computer model minicolumns demonstrate self-organizing and other functional properties that are sometimes surprising (Amirikan and Georgopoulos, 2003; Favorov and Kelly, 1996; Hasselmo, 2005; Johannsson and Lansner, 2007; Kohn et al, 1997; Lucke, 2004; Lucke and Malburg, 2004; Mountcastle, 1997, 2003; Rao et al, 1999; Sugimoto et al., 1997). However, it is also important to recognize there is considerable debate and conflicting evidence regarding the ubiquity and functionality of the adult anatomical elements, where various approaches sometimes yield different conclusions (Catania, 2002; Jones, 2000; Kreiger et al, 2007; Rockland, 2004; Swindale, 1990), and species specific differences complicate the picture, though if anything, the primate cortex may display a heightened columnar organization.

Variation in neuronal types and connectivity at the microcircuit level may rule out a rigid over aching definition of the minicolumn (and the larger cortical column). The minicolumn appears to be a common template rather than a stereotypical component in all brains and regions (Buxhoeveden and Casanova, 2002; Mountcastle, 2003; Silberberg et al., 2002). Nonetheless there are local and species-specific examples of repeating configurations of minicolumns and Mountcastle (2003) noted that "The important point is that columnar organization depends upon a certain set of properties common to all neurons in the elementary unit, but that other properties may vary between different neurons in the same minicolumn." Mountcastle provides a conceptual basis to variability upon the basic template by stating that "differences in afferent input are convolved with different intrinsic operations in different cortical areas to produce what we call different functions." Silberberg et al. (2002) also

concludes that despite the great range in microcircuitry, stereotypical features exist nonetheless at multiple levels indicating a deterministic basis for them and suggests that all neocortical microcircuits may be subtle variations of a common template (see also Jin et al., 2001; Kisvarday et al., 2002; Kosloski, et al., 2001). Thus, a broader conception of the minicolumn is to see it as a 'template' for a shared set of properties of a given set of neurons across several or more lamina. It seems to be a general principle that cortical neurons with similar stimulus selection properties are found in close proximity to each other (Reich et al., 2001) and the minicolumn is the vertical component of that association. Further, in addition to being a dynamic component (both anatomically and physiologically), it is important to think of the minicolumn as part of larger organizing units in the cortex and not an end in itself.

The minicolumn in the adult traces its foundations to the development of the cortex itself, a cortex which contains highly visible ontogenetic cell arrays and from which the adult cortex will emerge. There is evidence that the ontogenetic units become the adult components of vertical organization (below). The anatomical components are often conspicuous features of cortex across taxa, and metabolic and physiological evidence have helped to provide evidence of functionality at this level (Mountcastle, 1997). Because horizontal lamina within the vertical organization maintain functional specialization, it is not surprising that the activity of columns may be seen at levels that encompass several layers only, and not the entire depth. This speaks to the flexibility of the system and not against the concept of narrow vertical organization. Some of the major questions surrounding minicolumns are the extent to which they are present throughout the cortex, the different forms they may acquire in diverse cortical regions or species, and whether functionality is always present at the narrowest level of vertical organization. The last question addresses the possibility that the minicolumn (and cortical column) may represent one type of functional unit among others; a system that may be activated for selected purposes but is not a general processor of information. I suspect that to the extent this is the case, it is the rare and probably not descriptive of the primate cortex, but the jury is still not in.

The anatomical minicolumn has at least three basic characteristics that when combined, set it apart from other elements in the cortex. These are *vertical organization, periodicity*, and *interconnected multiple components*. *Vertical organization* describes the interconnections of neurons within the vertical plane that crosses several lamina. This may not always refer to all six layers. In fact, as Rockland and Ichinohe (2004) have noted, there is no single anatomical element that we know of which actually encompasses all six layers. The closest to this are the long apical dendrite bundles that extend from Layer V to layer I, but even here, layer VI is excluded. However, the interrelated sharing between the different components does result in a vertical physiology that can cross all of the layers. Intrinsic optical studies for example, display a narrow vertical interconnectivity across the depth of the cortex (Kohn et al, 1997)

*Periodicity* refers to anatomical components that are located next to each other in a repeating fashion within a region or on a larger scale up to the entire cortex. This does not infer clone-like identical units, nor does it mean the spatial distances or physiological properties or anatomical elements are exactly the same. This repetition occurs within a very narrow size range, with the majority of spacing distances falling within 30-60 microns. These two characteristics comprise the most fundamental aspects of cortical vertical units. The reality of these features in neocortex is generally not controversial; especially if there is recognition of variability (Mountcastle, 2003).

The third characteristic is a combination of the first two; repeating *multiple vertical components* that share an anatomical relationship. One of the problems associated with the minicolumn is that it is composed of many parts that are not readily visible at the same time. The six-layer minicolumn is the product of interconnected sub-systems. The specificity of lamina and intracolumnar inhibition, means that the entire unit would rarely, if ever, be active at precisely the same moment, though delayed metabolic activation of these units across layers may be observed by intrinsic optical signaling as noted above (Kohn et al., 2002, 1997; Tommerdahl et al., 1993). The individual cells within a column are integrated by the interaction of multiple overlapping subsystems, and it is this which makes them a unit, and not a single anatomical entity.

The anatomical elements that typically comprise vertical organization include three fiber systems and two anatomical cell types. They are the (long) apical dendrites, myelinated axons, double bouquet cell axons, pyramidal cells in layers III, V, VI, and double bouquet cells. The double bouquet cell axon bundles may be a component of function for minicolumn inhibition, but do not appear to be as ubiquitous as the others. The apical dendrite bundles contain at least two main 'systems' that can vary within cortex and species (Rockland and Ichinohe, 2004). The 'long' system begins in layer V and terminates in Layer I, containing apical dendrites from pyramidal cells of layers V, III, and II, and is visible throughout the cortex. A shorter one extends from layer VI pyramidal cells and terminates in Layer IV. There is evidence of regional specificity regarding the beginning and termination of these bundles (Rockland and Ichinohe, 2004), and there are interesting specializations within the bundles themselves (Vercelli et al., 2004). However, apical dendrites of pyramidal cells seem to always bundle together and are present in a repetitive fashion. Myelinated axons bundle together as well, becoming prominent in the infragranula layers. In these instances, vertically oriented periodicity is the constant feature whereas the specifics are not. This pattern can

also be said about other basic features of the cortex, such as pyramidal cells, which vary in size, distribution, neurotransmitters, and connectivity. The brain utilizes the 'template' of the pyramidal cell in numerous ways and therefore it is a building block of cortex. The fact that narrow vertical units consists of somewhere around one hundred cells make it a more powerful functional entity than the single cell, in the same way that the larger cortical column has more measurable physiological effects than the subunits within it.

Based on the discussion above, I prefer to use the term 'reiterative micro-vertical organization' because it is a descriptive term restricted to defining observed phenomena. Those are the characteristics of periodicity, vertical orientation, and at the micro-anatomical scale, which distinguish it from the larger metabolic or cortical columns. The term is applicable to cell arrays, various forms of apical dendrite bundles and their pyramidal cells, myelinated axon bundles, double bouquet cells and their axons, and output minicolumns (Vercelli et al, 2003). Vercelli et al (2004) coined the term 'output minicolumn' based on a detailed examination of apical dendrite bundles in rat V1. These bundles are present early in development and the cells from which they derive are probably clonally related (Rakic, 1988). The 'output minicolumns' describes segregated bundles within the minicolumn based on their projections. Certain projections bundle together as a subset within the main bundle. The only separate bundles based on output are those going to the dorsal lateral geniculate nucleus and are found in layer VI, a system that was already described by Escobar et al, (1986). This fascinating discovery demonstrates the basic vertical template on the one hand, with intra-columnar specificity on the other, and is an example of a term that describes a specific organization and anatomical relationship.

While we have been traditionally focusing on vertical organization as a processor of information, LaBerge (2001, 2006, 2007) argues that two types of mental activity take place within the cortical column; information processing and subjective experience. He posits that sustained attention is expressed in a cortical column by repeated surges of current that are found in the long layer V apical dendrite bundles (i.e., the micro-vertical unit or minicolumns). Information processing requires input and initiates a response in the form of output. On the other hand, with subjective experience, the activation of the long apical dendrites is the goal itself, and not a particular output. The input impulses are said to be converted into waves, which act as repeated surges of current within the apical dendrite shafts which forms the wave activity measured at the scalp as EEG oscillations. If true, this reveals another dimension of function at the level of the apical dendrite bundle, how single bundles contribute to the overall capacity of the larger cortical column. It also means that the conventional analysis of connectivity does not necessarily describe the functionality of the vertical system in total. A striking aspect of the morphology of layer V apical dendrites is that they bundle together and have a very long length versus diameter ratio. The apical dendrites are so long compared to their typical diameter that it is the equivalent of a 100 meter-long tube that is 16.66cm in diameter which yields a length-diameter ratio of 600:1. The result is that most inputs (except for those close to the soma) would decay before arriving to the soma. Those that do arrive lose their temporal and rate information. Supragranula apical dendrites, while not as long as those in layer V, still have a lengthy ratio. By comparison, basal dendrites typically have about a 5:1 ratio and are considered ideal for the processing of input information. Basal dendrites are in a much better position to relay direct information, or to do information processing. Furthermore, basal dendrites have many side branches while apical dendrites, whose orientation is vertical, have only a few. Other potential changes that may be occurring in these bundles have not been tested. These include a narrowing of the spacing between them, changing the diameter-length ratio of individual dendrites and bundles, and changes in the number of dendrites per bundle.

The relationship between the apical dendrite anatomy and the mental states alluded to above, can only be speculated. However, it provides a theoretical basis as to how alterations in the morphology of the apical dendrites can have effects on attention and other mental states. Properties of the wave form would potentially have a relationship with the number of long apical dendrite bundles per unit area as well as the intensity of their individual activity, which is based on length and number of cells within the circuit and the distance between them.

## CorticoNeurogenesis

The genesis of the cortex occurs in the ventricles by a series of symmetrical and asymmetrical divisions (Rakic and Korack, 2001). In the first phase, cells located in the ventricular zone produce two additional progenitor cells with each mitotic cell division (Rakic, 1988). This symmetrical division is responsible for the number of founder cells which controls the total number of ontogenetic columns that will be produced in the cortex. According to the radial unit hypothesis, it is the number of these ontogenetic columns that determines the cortical surface area (Rakic and Kornac, 2001). At some point, progenitor cells begin to divide asymmetrically, producing one daughter cell that becomes a neuron and will move out into the cortical plate, and which will not undergo further division. The second phase is responsible for the number of cells within a column and the thickness of the cortex. Several clones of neurons that share a common site of origin in the ventricular zone use a common migratory pathway along the fascicles of the radial glial cells to settle within the same column in the cortical plate (Rakic, 2003). Radial glial cells create long fascicles that extend from the ventricular zone to the top of the cortical plate so that they span the entire width of the cerebral

wall during corticoneurogenesis. New born nerve cells use these to traverse the cortical plate. Though there are small differences between radial glial cells among mammals, overall they are very similar in morphology and chemistry.

On the other hand, some cortical interneurons do not originate from the ventricular zone and migrate in a radial fashion. In rodents, this is most notable as the majority of cortical interneurons originate from the ganglionic eminence of the ventral telecephalon and migrate tangentially to the cortical plate (Marin and Rubenstein, 2001). In mice, up to 25% of all cortical neurons migrate non-radially, whereas in humans this percentage is less than 10% of the total (Letinic et al., 2002). Thus there are taxonomic specializations associated with this process.

The total amount of radial units that will be present in the cortex are controlled during embryogenesis by a few regulatory genes, while the final pattern and size of cytoarchitectonic regions is thought to be the work of a different set of genes (Rakic and Kornac, 2001).The final configuration of columns within a cytoarchitectonic area, is therefore the result of the genetic influences described above and epigenetic factors such as interactions of cells, inhibitory neurons, and afferent systems. It is clear to see that alterations in these genes or their influences can have profound effects on the cortex. The increase in founder cell number is exponential and not linear, so that a small prolongation of cell division or changes in length of the cell cycle would result in significant increases in the number of ontogenetic units produced.

The importance of adult vertical organization is based on its connection to the ontogenetic cell column. This relationship may either be a direct one, that is, the ontogenetic units and adult minicolumn are the same (see below), or the ontogenetic unit is the template upon which the adult cortex might possibly overlay new circuits according to regional and species requirements. Direct confirmation that a given ontogenetic column becomes an adult one in the same animal, is not possible using post-mortem studies since that requires different sets of animals for each age group. However, studies examining the size of fetal columns and fiber bundles in post-mortem tissue and early interconnectivity between pyramidal cells support the hypothesis that they are, at the very least, the basic pyramidal cell core described above, remains intact in the adult cortex (Buxhoeveden et al., 1996; Curtetti et al., 2002; Krmpotic-Nemanic et al., 1984; Lohmann and Koppen, 1995; LoTurco and Kriegstein, 1991; Ong and Carey, 1990; Peinado et al., 1993; Vercelli et al., 2004). In the early cortex, prospective pyramidal neurons are clustered into vertical columns which are also coupled by gap junctions (LoTurco and Kriegstein, 1991; Peinado et al.,1993).

## Summary

Despite recent advances, fundamental questions about the cortex such as the number of cell types in the cortex, or the convergence of inputs to cells in the cortex, remain elusive (DeFelipe et al., 2002a). Perhaps the most cautious approach to micro-vertical organization is one that avoids oversimplification. Evidence supports the physiological basis for sub-cortical column organization in areas as diverse as motor, barrel cortex, and prefrontal cortex (Amirikian and Georgpoulos, 2004; Bruno et al., 2003; Georgpoulos et al., 2007; Ohki et al., 2005; Vercelli et al., 2004; Rao et al., 1999). Precisely defining how the minicolumn is anatomically and physiologically organized for different regions of the cortex remains a complex question (Ohki et al., 2005). Vertical organization appears capable of functioning at many different levels and the suggestion of 'structures at multiple spatial scales' is certainly plausible (Rockland and Ichinohe, 2004). The proposition that narrow vertical organization performs two distinct generalized functions (LaBerge, 2001, 2006) opens up new perspectives on the role of the narrow vertical unit that have yet to be explored. The ontogenetic column unit, as a template on which the adult cortex is built, may undergo more transformation in some regions of cortex than others, but the unifying feature seems to be in the outline and not the details (DeFelipe et al., 2002b). The fundamental structure would be defined as consisting of anatomical (and physiological) elements that are spatially narrow in size, demonstrate a vertical component to organization, and that can be found repeatedly within a cortical area. To the extent that this can be found in a given brain, the term 'reiterative micro-vertical organization' is one way of describing this template.

## Models for Evolutionary Change in the Cortex

Mutational events occurring on regulatory genes that control the number of founder cells could easily result in a substantial increase in the number of ontogenetic columns above the amount normally produced for a given region. These in turn would create more initial ontogenetic units and potentially more adult minicolumns. Provided that there has not been an increase in total afferents to the region, the presence of additional ontogenetic columns means there will be more units to compete for the same input, thus altering the ratio of column units to afferent. It is reasonable under this condition to envision a decrease in the amount of neuropil space per column which would result in the phenomena of smaller than normal minicolumns (See Figure 1).

If the ratio between new ontogenetic columns far exceeds that of existing afferents, it might be expected that pronounced cell death would result, causing severe disruption of ontogenetic units. From this perspective it would be very difficult to add new ontogenetic units to the cortex during evolution because it would seem to require a match between additional columns and the afferent input. However, it appears that this is not required. The majority of synaptic input to cells in the cortex derives from intracortical circuits and the thalamic affer-

ents contributes only a small portion of the mean number of synapses. A vertical unit of cells comprised of all the layers would thus have very only a small percentage of its synapses from the thalamus. The predominance of ispi and contralateral synaptic inputs found in the cortex can only help sustain new column units. However, this does not mean that thalamic input does not exert a strong influence on the response properties of cells and columns, which it does.

This means that rather than causing a strain on existing synaptic terminals, additional ontogenetic units immediately contribute to local and long distant circuits. The highest density of synaptic connections for a given neuron may be found within a relatively short distance of a parent neuron (Budd and Kisvardy, 2001; Elston 2000; Elston and Rosa, 2000), so that additional ontogenetic columns reciprocally connect to each other and become a major source for synaptogenesis. It is the subcortical and long distance afferent input that would have to be redistributed among the additional ontogenetic units and it is here that a drop in overall synapses per column might occur. In instances where there has been a significant increase in new ontogenetic units, without an increase in either subcortical or long distance input, the number of contacts per column would have to decrease as the ontogenetic units compete for these limited contacts during development. The afferent inputs would be distributed to a more units than before, resulting in form of signal divergence. On the other hand, the total number of synapses from local connections might be expected to undergo less of a drop, if any. The result would be a change in the ratio of intrinsic local synapses versus those from subcortical and other regions of cortex.

If there is a narrowing of cell columns that result from the assimilation of newer ontogenetic units, this would offset to some degree the expected increase in cortical surface area. Viewed in this manner, additional columns immediately become part of the cortical system, contributing synapses and receiving input in return. If there is significant cell death due to the sudden addition of too many new columns, this could lead to a rearrangement of connections between the affected region and its targets. This is one way that corticoneurogenesis could result in a re-reorganization that does not require an increase in brain size. An interesting result of adding significant numbers of columns units in one area would be on the efferent side, where the additional column units would give rise to an increase in axonal connections to their target regions. In these target areas this would result in more inputs. Hence, a change in one region would effect other areas even if they did not undergo alterations in the number of ontogenetic columns

## Scenarios for Re-Organization and Encephalization Based on Ontogenetic Columns

It is important to note that the following scenarios are highly simplistic models of corticoneurogenesis and do not take account of numerous other factors. The emphasis is solely on the impact of new ontogenetic columns on circuits and connections. I will examine four possible relationships (figures 1-4). In the first there is a substantial increase in the number of additional ontogenetic columns—without an increase in afferent input. In the second, the number of columns is stable but there is an increase in afferent input. In the third one there are more column units created but there is a corresponding increase in afferent input. In the last example there is an increase in the number of columns produced and an even larger increase in afferent input coming into that region.

*Additional Ontogenetic Columns without an Increase in Afferent Input (Figure 1).*

This is a situation in which more columns are produced in one part of the cortex only. Thus, the amount of afferent input from subcortical and cortical areas is presumed to be unchanged. This means the additional columns must compete for the same number of afferents as the 'normal' contingent of columns units did before. In order for the columns to survive as whole units, there would have to be a reduction in the total number of connections per column unit (but not necessarily in the intrinsic connections). The resultant fewer synapses per column would lead to a reduction in the neuropil space. Depending on the actual relationships that develop, it is possible in this instance for there to be no change in overall surface area in this particular region of the cortex because though there has been an increase in column units. The decrease in neuropil space compensates for this and the result is stasis in regards to cortex size. This is one way in which additional units can be added to cortex without there necessarily being a concomitant change in surface area. Variations in column size have been found across primate species, regions, hemispheres, and disease states.

*No Change in Number of Ontogenetic Units with an Increase in Afferent Input (Figure 2).*

In this example, there is no change in the number of column units produced but there is an increase in afferent input. This would presumably result in rich synaptic areas that would increase the neuropil space and thus the distance between columns. This is an example of where a region may increase in size without an increase in ontogenetic units. Both of these examples demonstrate the need to measure column size as well as cortical region. The larger columns would become more generalized processors of information (Gufstassen 1997, 2004) than they were before, signaling a change in function.

*More Column Units and a Matching Increase in Afferent Input (Figure 3).*

In this model there is an increase in the number

of ontogenetic units and incoming afferents. This represents an instance where others regions of cortex may have supernumerary columns that are sending out more axons and/or increases could be coming from subcortical regions as well, or a combination thereof. This model is one where the added columns and inputs balance out so the size of the columns in that region remain the same as before, but now the size of the cortical region has undergone an increase because of the additional ontogenetic units. Whether this is the more typical scenario in evolution remains to be seen. The reported differences in column size, like cortical depth, are small compared to surface area but significant nonetheless.

In this instance the increase from incoming fibers is disproportionately greater than the increase in columns. This could be due to a significant increase in cell columns in other regions (scenario #1) resulting in especially large amounts of ipsi and contralateral connectivity, or events in subcortical regions that give rise to new cells and more connections, or both. It would lead to both an increase in column size and surface area. This may reflect the human condition (except for V1) where humans display larger columns and larger cortical regions. The behavioral success and selection pressures created by tool making could feed regions pertinent to those activities (i.e., somatosensory, motor, higher order) whereas other selection pressures derived from socialization, deception, theory of mind, etc., could have been fueling this kind of thing in higher order association cortex. The small columns found in visual cortex may reflect a relative homeostasis as regards initial visual processing, where differences between human and nonhuman primates is emphasized farther down the processing chain.

In all of these it must be considered that a change in the number of cells produced during the second phase will affect cortical depth and hence the size of the columns along the y axis. Columns can add more cells to each unit when there has been an increase in the depth of the cortex. This allows for changes in intrinsic complexity without increasing the diameter. This also creates the potential for more cells per column without increasing density. Because changes in cortical depth have been small compared to surface area, this aspect tends to be overlooked. However, a mere 10% increase in depth, spread throughout the cortex, can signify considerable increases in processing capacity per column and total number of new cells.

## Summary

The addition of significant numbers of ontogenetic units in one region of the cortex with no increase in cortical or subcortical projections, would place all the units (in the affected region) at higher risk of increased cell death. Neurons must compete to attain enough synaptic connections to survive. If each new column contains about 80-100 neurons, then a 10% increase in ontogenetic units in a region containing 5000 minicolumns, means 500 new columns or about 4000-5000 new neurons would be added that have to find a home. The added ontogenetic columns have to compete with the 'existing' inputs for the limited amount of connections. The size of adult minicolumns would have to be based in some part on the interaction between the number of ontogenetic units created during neurogenesis, the amount of input to a region, and consequential intrinsic circuitry.

Based on the descriptions given above, it may be possible to make the following predictions regarding changes in the surface area. The first scenario would result in little or no change in surface area. The second would result in a modest enlargement of surface area. The third might also show a modest enlargement of surface area, and the last would result in the greatest increase in surface area. Further, all scenarios would probably tend towards some degree of change in circuitry and function. When coupled with other neurological changes (cell types, membrane properties, inhibition-excitation, up and down regulation, neurotransmitter quantities and subtypes, cell numbers, etc.), corticogenesis and the developmental period that follows can be envisioned as a time that is favorable to modification. However, most of it can be expected to account for individual variability rather than evolutionary events.

## Did Minicolumns Get Smaller in Primate Evolution and What is the Functional Significance?

Traditionally, the number of column units produced has received the most attention because of the vast differences in surface area of the cortex. In the scientific literature, the size of minicolumns typically refers to their horizontal width or diameter. This is because the scale of variation for column size among species pales in comparison to that of the surface area. Nonetheless, the three-dimensional size of minicolumns does vary across species and area and may play a role in organization.

In primates, columns in visual cortex (V1) are notably small, both in absolute and relative terms when compared with data for other small mammals (Table 1). Even humans have smaller minicolumns than reported for animals like the cat or rat. The functional significance may be related to the species-specific complexity of primate vision and suggests that smaller columns may represent enhanced processing complexity (Peters and Sethares, 1996, 1997). Differences in the size of columns can represent functional differences and circuits, and Seldon's (1981) study of lateralization of minicolumns in human auditory cortex demonstrated some of the ways in which this might occur. Basically, functional connectivity is the result of the relationship between the size of the columns vis-à-vis the amount of extrinsic and intrinsic fiber terminals. If there is no change in an afferent terminal system but columns are much smaller in one brain compared to another, the distribution of the inputs will be different so that the incoming signal will be broken down into more units than in the former brain. This would theoretically

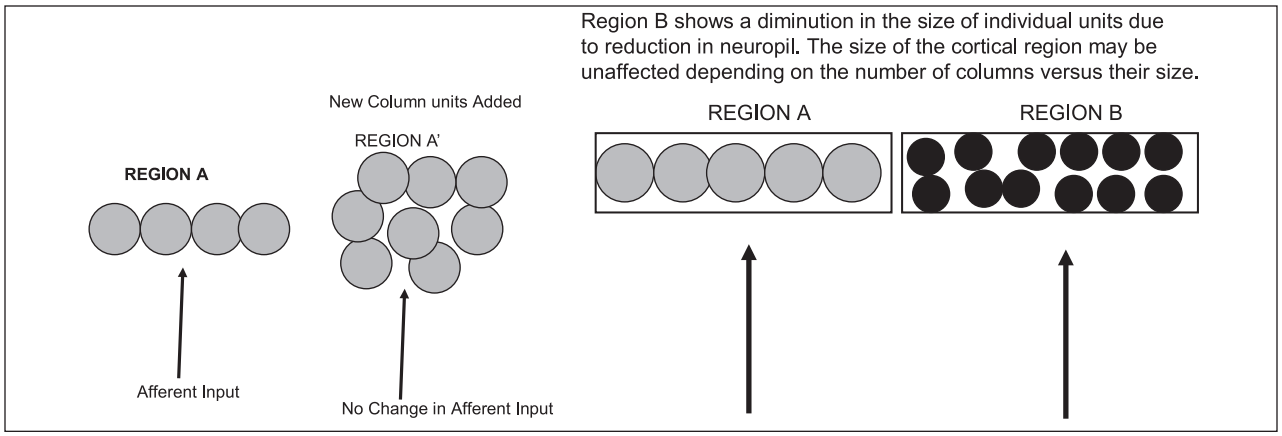


*Figure 1. An increase number of ontogenetic units in a region that has no increase in afferent input. Region A (far left) represents the region in its normal configuration of ontogenetic columns and A within a box represents the normal region with developing minicolumns. Region A' is the same region with additional units added as a result of a prolongation of symmetrical cell division. The columns that survive in part by local connections (see text) would have fewer long distance connections and there would be a decrease in neuropil space. This would result in an increase in column number but no substantive change in surface areas.*

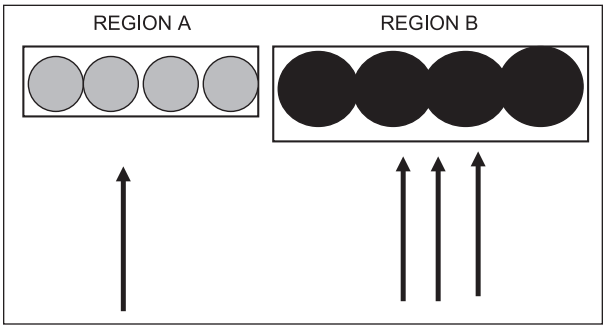


*Figure 2. Same Contingent of Ontogenetic Units with an Increase in Afferent. This is the reverse of A. Region B has the the same number of units but is now exposed to more incoming fibers. This should increase the neuropil space resulting in an increase in column size. In this scenario, the surface would increase without an increase in column numbers. Conversely, in Figure 1 there would be an increase in column number without an increase in cortical surface area. Changes in cortical depth have not been figured into these scenarios but could play an role as well by allowing for more cells per unit without requiring a change in their diameter.*

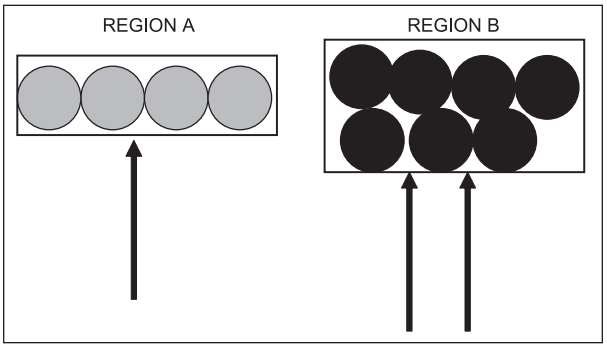


*Figure 3. More Column Units and a Matching Increase in Afferent Input. This should result in an increase in surface area by virtue of additional ontogenetic units, but not in the size of the individual columns. Changes of this nature favor stability in regards to the amount of neuropil space per column.*

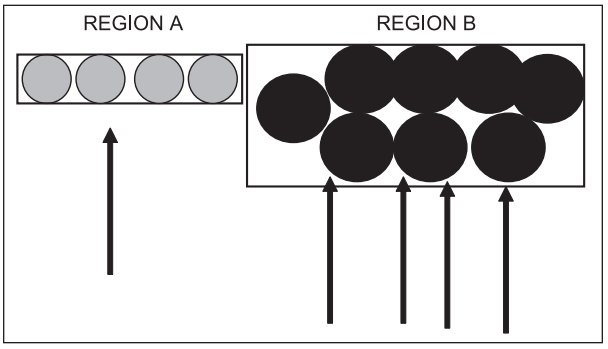


*Figure 4. Additional Columns with Disproportionate Increase in Afferent Input. This figure demonstrates a condition where there is an increase in the number of columns and a proportionately greater increase in afferent input. The expected results would be to see an increase in neuropil space per column and thus an increase in their size. The combination of more columns and larger ones would cause the most significant increases in surface area of any of these proposed scenarios.*

result in greater resolution or specificity of information processing (Gufstassen, 1997).

The 'size' of a minicolumn or ontogenetic cell column is usually defined according to the horizontal spacing distance between them, which can be measured on the basis of their pyramidal cells or fiber bundles. The major determinant of minicolumn size is the neuropil space that separates them in the horizontal plane (Seldon, 1981a). In the fetal cortex cells are packed tightly together and during development, the 'non-cell' space between them increases both in the vertical and horizontal axis. Thus, once the ontogenetic cell columns are in place, the emphasis on the expansion of this space causes the cells and their interconnected fiber systems to grow farther apart. A study of cell column development in humans showed that the neuropil space increases disproportionately to the column size during development (Buxhoeveden et al, 1996; unpublished data). Therefore, it is the increase in neuropil space that accounts for the majority of the enlargement of the individual columns. While other factors such as cell size, thickness of individual axonal or dendritic fibers, and bundle thickness contribute as well, this is more of a factor across species and brains of vastly different size.

Even though the horizontal spacing of minicolumns is a rather simplistic measure, differences found at this level represent profound changes in cortical development and organization. Changing the size of minicolumns affects the relationship between afferents, the intrinsic anatomy, and the physiology (Gufstasson, 2004; Seldon, 1981a). While the individual size of any given minicolumn varies according to extrinsic and intrinsic factors, the total number of cell columns is determined during corticoneurogenesis, so the *overall* number, and therefore the *mean* size of the columns, cannot change, provided their integrity remains intact (below).

A caveat must precede any discussion of data compiled for minicolumns size across species. The lack of uniformity in method and tissue preparation makes it difficult to make accurate comparisons across studies since this requires a stringent control of method, shrinkage, and preparation. Nonetheless, there is a degree of consistency in the results provided by the scientific literature that permits the making of certain generalizations. First, it can be seen that the size of minicolumns is not uniform but differs between species, within species, and within regions of the same brain (Buxhoeveden and Casanova, 2002, 2005). Secondly, there is no linear correlation between columns size and brain size for animals with diverse evolutionary history (Buxhoeveden and Casanova, 2002). However, it is possible that there may be some degree of correlation between column size and brain size within closely related taxonomic groups (Table 1).

Table 1, though limited in scope, represents data obtained by the use of very similar or identical methods and material preparation, which makes it more reliable than using results from disparate tissue, methods, and morphological elements. Even though the selection of species is small, a great number of primates are represented including all the greater and lesser apes. It is already apparent from this table that there is no correspondence between brain size and column size across diverse taxonomic categories. With the exception of humans, primates as a whole standout as having small columns in absolute size, and all primates examined so far including humans, display small columns in primary visual cortex.

The results are tantalizing because they suggest that columns are absolutely smaller in primates compared with other mammals studied thus far. The exception would be humans and possibly some overlap with the gorilla, but more samples will be needed. Even here, the column size in human matches that seen in small brain mammals, but does not exceed it. The data suggests that in the course of hominid evolution columns were getting larger along with the cortex. Of course when considered for brain size, all columns in primates are relatively small.

A dramatic example of the relative and absolute small size of minicolumns in primates is the Siamiri, which has a brain weight many times larger than that of the other small mammals examined, and yet their minicolumns are the smallest measured to date. Compared to the mouse, the brain is about 60x greater and yet it has smaller minicolumns. The complete answer to the question of column size variation, and whether they got smaller in the primate order, is a doable task but will have to await future research that includes large brained land mammals of similar or greater size than that of humans, as well as systematic analysis of many more mammals and primate species including prosimians. The

*Table 1. Comparison of cell columns based on same or similar method of analysis. These areas do not contain data on area V1. In primates V1 is always smaller than found in other mammals so far tested and typically have mean values of ~30um. For a general comparison between other mammals using diverse methods and vertical anatomy, see Buxhoeveden and Casanova, 2002b.*

| Animal | Typical Brain Weights | Minicolumn Size |
|---|---|---|
| **Primates** | | |
| Siamiri | 25gms | 20um |
| OWM | 70-100gms | 30+um |
| Great Apes | 250-500gms | 30-40+um |
| Humans | 1350gms | 40-50+um |
| **Other Mammals** | | |
| Mouse | 0.4gms | ~26um |
| Rat | 2gms | ~40um |
| Rabbit | 10gms | ~40um |
| Cetaceans | 350-3000gms | 25-34um |

especially small minicolumns in area V1 in primates is interesting because vision is a keystone of the initial primate radiation. Could the re-organization that occurred in primate visual cortex have affected the organization and hence size of columns in other regions as well? Finally, the cetaceans are interesting and they demonstrate very small columns in line with those of the primates, but their very thin cortex and unique aquatic evolution make direct comparisons to land mammals difficult.

## Column size and brain size: Functional implications?

If larger brains contain more ontogenetic units and more cortical regions, this creates a target rich environment for additional columns to establish reciprocal connections with. Thus, large cortex may be better able to assimilate additional columns compared to smaller brains because they are being placed in an environment that has an abundance of cells, columns, and cortical regions. Presumably there are more target areas for the new columns to connect with and to receive input from. The implication is that the process of encephalization would proceed more slowly in a small brain and become easier as the brain enlarged.

There may be some relationship between processing complexity and column size. This is a model that could be tested but it would have to be done in the context of the total number of columns in a given brain. Small columns may be an indication of enhanced processing complexity based on increased interconnectivity between them. Or it could at least be representative of functional specialization. Some of the rationale for this is derived from the comparison of minicolumn size in primary visual cortex above (Peters and Yilmaz, 1993). The increased complexity is attained by having more columnar interconnections, more cells, and greater density of cells per column. This is assisted by the increased length (cortical depth) of the columns in primate brains that permits more cells to be placed in a narrower unit. Added to this is the fact that the total cortical volume devoted to V1 is much larger in primates, resulting in a huge increase in the total number of processing units. The approach taken by evolution of the primate brain is to have more column units, which increases the number of interconnection and the ability of each column to process more specific information. The alternative is to have fewer columns with more intrinsic connectivity and less interconnectivity. The combination of having smaller cell columns and more cortex devoted to a particular function, results in an enhancement of the resolution (based on narrower columns that 'break down' the input into more discrete properties), and it also allows more interconnectedness between these more specialized units.

Gustafsson (2004) proposes several scenarios that could lead to narrow columns. However, it must be noted that these arguments are based on a set number of already existing ontogenetic columns. One stems from neural network theory where self-organizing networks, columns in this instance, are formed when lateral feedback synaptic strength is a function of lateral distance as shaped by the Mexican hat model. If the inhibitory synaptic strengths increase the columns become narrower while the reverse is also true (Favorov and Kelly, 1994a,b; Gustafsson, 1997). This can be expected to occur during development. It is also possible for columnar organization to emerge without the usual lateral excitatory-inhibitory feedback mechanism. A basic organization can be laid down before the lateral feedback connections are developed so that when they do arise, they fine-tune or maintain the columnar organization. Others have reported that neural columns would be narrower if levels of nitric oxide (NO) were reduced so that given the same stimulus drive the column size varied according to the level of NO (Gally et al., 1990; Krekelberg and Taylor, 1996). It is also found to be involved in the metasynaptic organization of the frontal cortex in primate, but had no effect in visual cortex.

Finally, the ability to add more columns and connect to more regions enhances the opportunity for variability in larger brains. The variation in column size and brain size seems especially noticeable in human brain. How much of this is relative needs to be clarified and it remains to be seen whether animals with small columns and a small cortex have relatively less variation in the size of the columns and cortex than do large brained primates.

## Summary

The process of normal encephalization cannot be the cause for a narrowing of cell columns. If this were the case, then minicolumns would have become progressively smaller in the millions of years of evolution which is counter to the evidence and which would hit a biological wall at some point since there must be a limit to how small a minicolumn can be. Cell density and column size across mammals is similar enough (though not identical) to demonstrate that as cortex enlarged by adding ontogenetic units, the 'new' units assumed the general size configuration of the host brain. A Darwinian model of cortical evolution would reflect incremental changes with a balance between the selective pressures for more columns on the one hand, and more afferents on the other. The result would be additional columns of similar size so that the presence of more columns results in a larger cortical area. At any one time the addition of 'new' columns can be expected to be limited with little or no change in mean column or cortical size. It can even be predicted that the process of adding new columns is so gradual that it would be difficult to measure significant differences from one generation to another.

Even though the horizontal spacing of minicolumns is a rather simplistic measure, differences found at this level represent profound changes in cortical development and organization. Changing the size of narrow vertical units (minicolumns) affects the relationship between columns and afferents, and alters the intrinsic

anatomy and physiology (Gufstasson, 2004; Seldon, 1981a). While the individual size of any given minicolumn varies according to extrinsic and intrinsic factors, the total number of cell columns is determined during corticoneurogenesis, so the *overall* number, and therefore the *mean* size of the columns, cannot change, provided their integrity remains intact.

The process of encephalization that occurred in mammalian evolution is thought to arise from the addition of more ontogenetic units which is the basis for increased cortical surface area (Rakic and Kornac, 2001). Ontogenetic column number determines cortical surface area, whereas cortical cell numbers within them account for cortical depth (above). Since surface area has increased a thousand-fold (comparing mouse to human), while cortical depth has only increased around 3-4 times, the major impetus for cortical enlargement has been the addition of new ontogenetic units. Therefore, it can be expected that the addition of more ontogenetic cell columns should normally result in an increase in cortical surface area and white matter. However, this is based on the increase in number of columns of *similar size*. If the additional columns were to become smaller or larger, then this would alter the expected outcome in proportion to that change.

In summary, the size of minicolumns in adult cortex is at least partly the outcome of the number of ontogenetic units formed during development. If a significant number of additional columns are produced in one region the effects will be different than if additional columns occur simultaneously in several *interconnected* regions, where the cortico-cortical connections from each will help sustain the presence of the additional neurons. One can see how the distribution of synaptic connections can change as well. For example, if interconnected regions both incur a significant increase in ontogenetic columns, but not in thalamic input, then the ratio of thalamic to cortico-cortical input will presumably undergo change. The thalamic input, which is constant in number, will have to be distributed to more column units thereby lowering the number of inputs per column, whereas the number of cortico-cortical inputs will not decrease, and may even increase in one area if there is a disproportionate growth between the two regions. Furthermore, the number of intrinsic connections may also maintain their numbers as described above, which would result in a relative decrease of thalamic input compared to intrinsic and long distance connections. This is a theoretical concept that assumes all other factors are constant, but it demonstrates potential re-configuration of cortex due to changes in the numbers of ontogenetic units

## Conclusions and Hypotheses

The elegance of the ontogenetic column lies in its explanatory power across a wide range of topics in brain evolution, comparative neuroanatomy, and anomalies of the brain (Buxhoeveden et al, 2006a,b, 2004; Casanova et al., 2003). The mechanisms described by the radial unit hypothesis are powerful tools in general neurobiology and especially so in the field of paleoneurology, and it is hoped that future work will further consider the potential applications associated with the radial unit hypothesis.

1. The ontogenetic unit is the main genetic determinant for the size of the cortex and is the template upon which later neurological events act. Thus it is a pertinent morphological and physiological object for the study of brain evolution.
2. The mutational events that initiate new columns and cells link developmental processes to re-organization and encephalization.
3. From the perspective of micro-vertical columns, it would seem that reorganization can occur without a demonstrated increase in brain size. This means that in hominid evolution it would not have been necessary for the hominid cortex to demonstrate significant enlargement from that of apes to prove it had undergone reorganization.
4. The result of these processes is to enhance heterogeneity in the configuration of the cortex, both across and within species.
5. It may be easier to induce increases in cortical size in a larger brain than a smaller one. Cortical enlargement proceeds faster in larger brains until constrained by other factors (i.e., pelvis, white/grey matter ratio, metabolics, etc).
6. There may be more variability among minicolumns in larger brains due to the increase in number of regions and regional specialization.
7. Cell columns may have become absolutely smaller in the evolution of the primate order. On the other hand, columns in humans are the largest among primates and may reflect both significant increases in additional minicolumns and in afferent input coming into those columns.
8. Smaller minicolumns may represent a reorganization that favors increase complexity based on maximizing specificity and enhanced resolution.
9. Rather than making the argument for a clone-like homogeneity of the cortex, the micro-vertical organization of cortex is a template upon which cortical heterogeneity is played out, one that can result in diverse modular configurations in the adult animal.

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