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Cortical organization: a description and interpretation of anatomical findings based on systems theory

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Abstract

The organization of the cortex can be understood as a complex system comprised of interconnected modules called minicolumns. Comparative anatomical studies suggest that evolution has prompted a scale free world network of connectivity within the white matter while simultaneously increasing the complexity of minicolumnar composition. It is this author's opinion that this complex system is poised to collapse under the weight of environmental exigencies. Some mental disorders may be the manifestations of this collapse.

Keywords

Minicolumn; Neocortex; Isocortex; Encephalization; Corticalization; Systems theory

Introduction

“[W]e can deduce a basic premise, that an understanding of nervous function requires identifying the elementary units at different levels of organization and understanding the relations between the different levels” [1, p. 4–5].

There is a long standing reductionist approach to neuroscience that promotes the understanding of systems by dismantling and examining their most minute elements. Nicolaus Steno, a mid-17th century anatomist and geologist, once said: “There are two ways only to know a machine: one is that the master who made it should show us its artifice; the other is to dismantle it and examine its most minute parts separately and as a combined unit” [2, p. 1]. The field of complexity theory challenges this approach [3] and sees higher cognitive properties as emergent phenomena arising from the aggregate behaviors of hierarchically arranged modules. Orderliness in life occurs within a hierarchy of structural levels that exhibit uniformity across scales (different sizes). Within this hierarchy, the properties at one level are not completely predicted by those at other levels of organization.

Reductionist interpretations are the constraints of disciplinary boundaries. They argue that we can get Humpty-Dumpty back by gluing its pieces together. According to Denis Noble, the reductionist approach “...is about the naming and behavior of the parts. We reduce each whole to its component parts and define them exhaustively” [4, pp. x–xi]. By way of contrast, systems theory (Greek σύστημα, from σύν “together” and ἵσταναι “to set up”) exhibits no boundaries. This assertion is based on the observation, reminiscent of gestalt theory, that within a defined system the whole is greater than the sum of its parts. In effect,

there is a sensitive dependence on the initial conditions of a dynamic system wherein tiny perturbations lead to major changes of the system itself. Elements within a system interact with each other in a nonlinear fashion giving rise to behaviors that are not obvious from the individual components. Systems are therefore dynamic entities capable of unpredictable interactions with their environment. The term “systems theory” originated in the 1920s out of the need to explain the interrelatedness of organisms within an ecosystem.

Emergent or complex properties tend to be connected together and dependant on each other. When considering the cerebral cortex as a complex system we may highlight the high degree of interconnectedness among its constituent modules and, within a given level, among its emergent properties. According to Harris, “functions that are localized to discrete regions in the brain are not the complex faculties of the mind, but rather more elementary brain operations. The complex faculties are constructed from serial and parallel (distributed) connections among several brain regions [*sic.*, modules]” [5, p. 35]. In this regard the author has argued that all emergent properties of the cerebral cortex are geared towards the single aim of increasing our sociability [6]. The survival of hominids has depended on group cohesion. This has made group cohesion (i.e., socialization) the main target for evolutionary selective forces.

Trade-Offs

The life history of cells can be described in terms of growth, maintenance, reproduction (mitosis), and the acquisition of resources. Life histories can vary dramatically among cells. Each life history results from natural selection pressures that maximize how different mechanisms are used to assure the continued survival of the organism. Due to limited resources the organism must divide the total available energy among different life history needs. The repartition of resources propitiates trade-offs or sacrifices which become more common as resources dwindle. This may be of particular importance to the human brain, an organ that receives 15% of the cardiac output and accounts for 20% of total body oxygen consumption.

Neurons offer a good example of trade-offs: by taking away reproduction (i.e., mitosis) more energy can be allocated to maintenance and therefore to the long term survival of the cell. The difference between a keratinocyte and a neuron is not unlike differences observed at the species level. A bird such as the tree swallow (*Tachycineta bicolor*) that reproduces often has, not coincidentally, a short life-span. This stands in contrast with any of the species of albatrosses that reproduce less but have a longer lifespan. Strategies at different levels of complexity do not differ from one another; rather, they represent different ways of maximizing reproduction. There is constant turnover of neurons, not because cells die and are replaced but because new connections are made, eliminated, and/or strengthened every second.

Adaptive responses help explain the absence of neoplastic process involving neurons. Neuronal elements in cortical tubers and gangliocytomas appear to have little proliferative potential and may be best characterized as hamartomatous in nature. Absence of neoplastic neuronal lesions implies a lack of neuronal stem cells within the neocortex and basal ganglia. Olfactory neuroblastomas (esthesioneuroepithelioma) originate from local stem cells that provide for the continuous replacement of olfactory receptor cells [7]. Circulating stem cells may also help explain the occasional supratentorial primitive neuroectodermal tumors [8]. By way of contrast neoplastic process of glial origin are well known. We may conclude that specialization of neocortical neurons is a fixed process wherein energy has been allocated to information processing to the exclusion of reproduction. Some of the benefits from this specialization, e.g., limiting the number of neuron-based tumors, seem counterbalanced by an inappropriate increase in the prevalence of mental disorders [6].

The Plurality of Neurons

Histology textbooks define the neuron as a cell whose function characterizes the brain as an organ. Neurons have been described as idealized anatomical elements having 3 different components, each bearing on reception, impulse-initiation/propagation, and transmitter release [9]. This is a simplistic idealization for cells that differ among each other in kind and not in degree. Countless types of neurons exist within the brain, each varying from one another in terms of shape, size, location, and neurotransmission [10]. Exceptions to general principles abound for neurons. The axons of some neuronal cell types bear receptive surfaces, occasional dendrites generate an action potential, and some neurons fail to obey Ramón y Cajal's law of dynamic polarization, which states that nervous impulses are received at the dendrites and transmitted via the axon [11]. As a matter of fact, many neurons throughout the animal kingdom lack axons while many others release neurotransmitter-like substances from nonsynaptic areas [12]. It has therefore been argued that the plurality of neuronal types, both in terms of anatomy and physiology, argues against their designation as an "individual" element of the brain, i.e. an element representative of the organ's functions [10]. This stands in contrast to, for example, the liver, where hepatocytes tend to be identical regardless of location.

According to Shepherd and Koch, "No matter how complicated a single neuron may be, it cannot play a role in the processing of information without interacting with other neurons" [13, p. 27]. This interdependence is clearly seen in cell cultures wherein a minimal seeding density (80–300 cells/mm²) is necessary in order for neuronal cells to divide and grow appropriately. A similar conclusion is derived from the work Thomas Sudhof of the University of Texas Southwestern Medical Center. Dr. Sudhof's team of researchers created a mouse that lacks a protein essential for neurotransmitter release [14]. In spite of the fact that the wiring plan for the brain looks normal, in the days following synapse formation there is massive neuronal death. The main lesson from this experiment is that neurons do not live in isolation but, rather, continue to exist because of their close apposition to other neurons. If this interdependence is compromised (e.g., no synaptic transmission) the involved neurons will die.

We may conclude from reviewing the scientific literature that neurons exist only when using as a frame of reference the cellular doctrine of Schwann. In terms of the neuronal doctrine the concept of a neuron appears supported by an empiricist's view that is based on sensory experience, that is, if we take a look at a section of the brain under the microscope we see primarily neurons and glia. The histological techniques that were developed at the turn of the century by Golgi and Nissl impregnated or stained individual cells but made it difficult to visualize them within modular arrangements.

Attempts at validating the existence of neurons as modular elements of information processing are weakened by having to embed the term in question (i.e., neurons) within its operational framework. In order to be understood, an operational definition should end with a statement that requires no further characterization. In the case of neurons this is impossible as you can't define a neuron without invoking its interdependence to other similar elements, in other words, there is no base level where to stop. This is an example of an infinite regress illustrating the implausibility of defining neurons as "individual" anatomical/physiological elements.

Modules

According to Serb and Oakley, "Modules are the distinct processes or units that act cooperatively in an organism, but have a degree of dissociability due to their internal integration. These modules are spatiotemporally bounded with discrete origins, histories,

and deaths through evolutionary time and can be treated as individuals” [15, p. 1159]. In the neocortex the smallest information processing module is the minicolumn [16]. In a concrete way of thinking minicolumns provide for the interconnectedness of higher cognitive functions.

The main function of individual minicolumns is to enhance contrast. Connectivity between modules binds different experiences into a cognitive whole. In this regard contrast enhancement may help explain the significance of color vision. The human eye can distinguish 500 different levels of brightness but, more impressively, about 6 million hues of color. The striate cortex perceives edges but the brain interprets the same as shapes. We hear noise but the brain makes sense of the same as language. The brains of humans are therefore meant to make meaning out of their surrounding environment. Unfortunately, in certain conditions, like autism, this capacity for contrast appears diminished. Several studies suggest that the inhibitory surround of minicolumns (i.e., the ability to make sharper edges) in autism is defective [17]. The overall effect is one of signal amplification and cortex hyperexcitability. Not surprisingly about one third of autistic patients suffer from seizures as they reach puberty [17].

The minicolumn is a vertical aggregate of neurons and their connections. It spans laminae II-VI of the neocortex [18,19]. Constituent cells originate from the germinal matrix surrounding the ventricles early during gestation. The germinal matrix provides a cadre of stem cells divided into well-demarcated columns by glial septa. These proliferative units contain 3 to 5 cells initially but may later expand to include as many as 12. The germinal cells begin dividing before the 6th week of gestation in the human fetal brain with a limited series of symmetrical divisions [20]. The initial division provides for copies of each other and prevents this cell resource from being rapidly depleted. Cell divisions are performed through regular mitosis with resultant daughter cells having an equal lineage to each other. This is followed by a wave of asymmetric germinal cells divisions where generated daughter cells have more restricted developmental capacities [21,22]. Thus, while mother cells retain their original characteristics daughter cells commit to a pathway of differentiation with restricted choices. These daughter cells are now known as multipotent and will give rise to neurons, oligodendrocytes, and astrocytes. Daughter cells that are going to become pyramidal neurons settle in a radial inside-out configuration within the cortical plate. In humans, the symmetrical phase of cell division ends at about the 17th week of gestation. The end result is a cortex comprised of multiple minicolumns each having a core of pyramidal cells surrounded by a peripheral neuropil space rich in dendrite arborizations, synapses, and GABAergic interneurons [23].

The apposition of these cells early during development provides for transitory gap junctions and the possibility of Hebbian learning [24,25]. The resultant string of pyramidal cells and their connections establishes a canonical circuit [26,27] that is repeated throughout the neocortex of all mammalian species thus far examined [28]. (Although “canonical” has been used by multiple investigators to describe the circuitry of the minicolumn, the term does not imply uniformity in cellular composition. Variability in morphometric parameters of the cell minicolumn is evident throughout the cortex primarily as related to its peripheral neuropil space and interneuronal composition [21,27].) Modulation of this circuit is provided by extracortical projections and intracortical inhibitory cells. The radial glial unit is too deeply rooted (conserved) in many different species, in all cortical processing, to be anything but a primordial/ancient unit. Position and connectivity of the primordial circuit is acquired early during gestation. There is a later phase of connectivity provided by pruning, environment, etc.—but the same is not part of the primordial circuit. The latter process helps engender a top-down circuit in contrast to the primordial circuit which is a bottom up one. Cells that migrate to the cortical plate transversely to the radial configuration established by glial/stem

cell projections (see above) constitute a significant proportion of the cortex's interneurons [29]. Indeed, in rodents most, if not all, neocortical interneurons originate in the ganglionic eminence and use this tangential mode of migration. This stands in contrast to the cortical interneurons of humans which originate from the ganglionic eminence as well as the ventricular and subventricular zone, and possibly the subpial granular layer [30,31].

Calvin has proposed that the human cortex has several hundred million minicolumns [32]. With such a large number of minicolumns stochastic behaviors of individual modules cancel each other out and provide for system-wide predictability [3]. The system-like organization of the cortex provides for stability to changes in lower-level modules and the emergence of properties. The behavior of individual elements therefore seems, in some ways, disconnected from the global behavior of the system. The strength of modular arrangements lies in their plasticity. The analogy is to that of a twisted rope where strength is not the result of a single strand but stems from the way strands are woven (or connected) together.

The existence of electroencephalography (EEG) attests to the presence of modular units within the cortex. A dipole from a single neuron is so small as to be impossible to record with scalp electrodes. If neurons were arranged randomly within the cortex, their individual dipoles would cancel each other out. In reality, pyramidal cells and their projections are spatially arranged so as to allow summation of their dipole voltages. Recordings are hindered by the fact that the cortex is folded; however, an approximation of the true waveform is made based on averaging the orientation of individual dipoles, i.e., the equivalent current dipole (ECD) [33].

Information Processing

The modular concept of cortical architecture appears to be founded on a rationalist view that insists that reason apart from experience can be a source of knowledge. In this regard, minicolumns exist within the confines of cortical modularity where neurons are particles in a box resistant (or unimportant) to operational definitions. We consider the minicolumn a fossil, millions of years old, carefully conserved throughout evolution. It is an assembly line where the division and specialization of labor by multiple cells (different neurons) has tremendously increased the efficiency of information transmission. This means that the neuron no longer controls information transmission because they alienate the same from the final product that is being produced. This is in reality the promise of capitalism where the assembly line (or minicolumn) is able to process more information and make its results more readily available to other parts of the central nervous system.

The circuitry for information processing needs to be alike in order to realize the efficiency engendered in assembly lines. Ford used to say that "You can have a model T in any color as long as it is black." Thus, the increase in efficiency during manufacturing is attained through uniformity. By analogy this phenomenon suggests advantages for the commoditization of information transmission/processing by the brain. In other words, information transmission within the brain may be considered and analyzed as a series of economic trades. Because each trade has plusses and minuses we have to think of information processing as something that can be sold rather than freely given. If a ton of steel is the same product regardless of its origin, information should be considered the same regardless of where in the cortex it is generated. Not surprisingly some researchers believe that information processing is the same irrespective of cortical area [34]. This may help explain why emotional information, rather than personal information, processed by the cortex originates from extra-neocortical sites within the limbic system. Even more so, it may help understand synaptic development in terms of game theory with a Hebbian strategy rather than simple gradient detection [35].

Information is transferred through different hierarchical levels of the cortex so that it is acted upon. Otherwise, there would be no intrinsic value on information. Pierre Bourdieu, the late French sociologist, used to say, “What goes without saying comes without saying” [36]. To transfer information is to incur a debt to a center for an answer. Connectivity, in terms of feedback, therefore establishes the dynamics of the cortex. Negative feedback provides for system stability and positive feedback for amplification and possible instability [3]. When a system lacks the modulating influence of feedback, a cascading effect ensues whose growth (hardwired connections) is similar to cancer.

Neurons vs. Minicolumns

Assumptions regarding the existence of the minicolumn are based on the principle of continuity or congruity; that is, that the pyramidal cell arrays that we see in specimens under the microscope developed from a primordial (ontogenetic) structure [37] and that this structure has been conserved across many species [26]. As previously asserted this makes the minicolumn a cellular fossil about the origin of the cortex. Although debatable, this claim is more than an assumption. Chords of pyramidal cells spanning multiple neocortical layers were first observed by the pioneering neuroanatomists of the late Nineteenth Century [38]. Constantin von Economo and Georg Koskinas devoted one section of their book on the cytoarchitectonics of the human cortex to the anatomical motif provided by the vertical arrangements of cells [39]. Since the anatomical motif represented the direction of the white matter fibers of the cortex, the so-called Radii, they named the structure radial arrangements. Rafael Lorente de Nó [40] was the first to propose that the cerebral cortex was composed of elementary operative units. In the 1950's Vernon Mountcastle provided physiological evidence for the columnar organization of the somatic sensory cortex of the cat and monkey [41,42]. In effect, the complexity engendered in the different anatomical components of the cortex, those that have a vertical bias, provide evidence of a design or, alternatively, purpose [43]. The onus of the existence of minicolumns therefore relies on whether the same provides a better argument than accounts based on randomness. In this regard the question requires a similar type of consideration that we provide to other scientific theories like the neuronal doctrine.

The minicolumn could not have been the first or elementary unit of information processing within the brain; it was the neuron. As minicolumns formed, they were so much more effective at information processing that they took over the primordial role.

In terms of cortical circuitry, simplicity should have preceded complexity. Simplicity is based on singular steps of adding one neuron at a time to the cortical plate. This type of circuit is deterministic, not depending on the chance resources of the environment. This canonical circuit required a source of energy, neurons, and a duplicating cycle where similar cells were juxtaposed to each other (a reiterative process may incidentally help explain why pyramidal cells are the most abundant neurons within the neocortex). This view advocates a flat circuit with closely adjacent/short connections far outstripping longer ones¹. The resultant circuit would have to exhibit the characteristics of weak linkage, as seen for example in blind individuals showing activity in the primary visual cortex while engaged in reading Braille [45]. Within this circuit it is unlikely that both the pyramidal cell arrays and interneurons originated together as it would require the emergence of two simultaneous novelties.

¹In some patients with partial seizures, surgically transecting the abnormal cortex may reduce or eliminate the ictal episodes. The procedure is based on interrupting longer (extramodular) fibers to neighboring areas while leaving unaltered shorter (intramodular) connections. The surgical procedure does not appear to impair the function of the transected region [44].

The total number of neurons within a given minicolumn suggests that not all interneurons are constituents of an arbitrarily defined anatomical boundary [46]. There is no basic proportion to the number of interneurons within a given minicolumn. The sole exception is the apparent one-to-one correspondence of double bouquet cells to minicolumns. The cell type has been suggested to derive from ventricular/subventricular zone of GABAergic lineage expressing *DLX1*, *DLX2*, and *MASH1* and migrate radially along with other pyramidal cell progenitors [46,47]. In this regard double bouquet cells may account for the higher proportion of GABAergic cells in primates than in rodents [46,48].

The Primordial Cortical Circuit

A putative characteristic of the primordial (earliest or original) circuit should have been a chain of cells that performed the same elements of information processing in reiterative fashion. The cells should have been the same pyramidal cells that today comprise the cell minicolumn. The same type of cell in different combination would have been able to provide for all necessary responses [17], analogous to the NOR and NAND gates of computation logic, either of which suffices to compute any Boolean function. Signals should have been transferred in laminar fashion (i.e., in parallel lines so as not to interfere with each other) in contrast to turbulent flow. This would be the best way to allocate energy. To power this circuit there was a need for a self-replicating cycle. Furthermore, this cycle would require a measure of variability so as to allow different versions of the circuit to compete for resources. The end result would be a more efficient system at processing signals.

There is no question that this original circuit by itself was not intelligent. But a cyclical process under competitive pressure can induce molecular system to evolve (e.g., RNA Spiegelmann's monsters) [49]. More so, there are suggestions within the literature that this reiterative process of signal processing would have propitiated a columnar organization. Recent studies suggest that neocortical columnarity emerges during evolution from constraints in axonal connectivity imposed by the granular and supragranular layers [50]. Afferent allocortical projections enter the dorsal telencephalon through the superficial marginal zone [51]. These axonal projections are guided by the presence of target cells within the preplate [52]. Projections through the marginal zone are therefore tangential to the apical dendritic bundles of cortical plate neurons which constitute the main receptive fields for these neurons. In the neocortex, afferents are guided by cells in its subplate from where they ascend in a vertical fashion into the cortex [53]. These subplate cells have transient connections to layer IV. After reaching layer IV a "stop" signal allows axons to sprout at this level while simultaneously being repelled from adjacent layers [50,54]. This mechanism may underlie the layer specificity of cortical thalamic innervations [55] and the anatomical basis of macrocolumns [16]. This interdependence is readily seen in layer IV barrels or macrocolumns which hold a one to one correspondence with a facial whisker and barreloids in the thalamus [56].

The Primordial Cortex

Stephan and Andy [57] used hedgehogs and other insectivores as brain models for the initial stage of primate evolution. These animals have a recognizable prefrontal cortex as shown by projections to the area stemming from the dorsomedial thalamic nucleus [58,59]. However, extant species, regardless of their size, are likely to have both ancestral (plesiomorphic) and more recent (apomorphic) specializations. Data from the fossil record indicates that early mammals had small brains and that significant percentage of their forebrains was devoted to the olfactory cortex and bulb [60]. Their cortex was probably parcellated into a couple of dozen areas. Function of these areas may have depended more on connectivity (afferent and efferent) rather than on marked differences in architectural patterns [61].

The basic plan in amniotes required a medial, dorsal, and lateral cortex at the external aspect of the ventricle [62]. The cortex was lissencephalic and the two hemispheres were separated caudally so that the superior colliculi was exposed dorsally [63]. Bigger brains had to increase the total number of cells generated in the ventricular zone and utilize migrational cues that would prove effective over long distances, e.g. Filamin-1, Lis1, and Doublecortin [64,65]. Furthermore an important event was the acquisition of a Reelin-dependent inside-out allocation of cortical cells [66]. The increased brain size was thus due to neocorticalization. This fact is derived from measurements of endocast specimens with the rhinal fissure (the boundary between the neocortex and paleocortex) serving as an anatomical landmark. Overall brain shape became more globular in order to maximize the amount of tissue that could be fitted into the skull [67]. With time the dorsal cortex of reptiles transitioned into the neocortex of mammals and the dorsal and lateral sectors became homologues of the mammalian hippocampus and piriform cortices respectively [68]. In this regard the neocortex of mammals is not necessarily a new structure and some scientists prefer the appellation of isocortex.

Evidence in favor of these homologies is derived from immunocytochemical studies demonstrating cell types expressing *CCK8*, *VIP*, and acetylcholine in supragranular cortical layers. By comparison the same antigenic epitopes are largely absent in reptilian dorsal cortex, mammalian neocortical infragranular layers, and the mammalian hippocampus [69]. Development of the neocortex in mammals therefore appears to occur in two successive waves of migrating neurons; one each for the lower and upper cortical layers (see below) [70,71].

It has long been argued whether mammals have a six-layer cortex. However, by comparison the lamination in the reptilian cortex is similar to layers V and VI of mammals [72]. It has thus been frequently hypothesized that the mammalian isocortex developed as an enlargement of the reptilian dorsal pallium [73]. Upper cortical layers provide corticocortical connections while infragranular layers, reminiscent of the reptilian cortex, kept their “ancestral ties” via connections to the thalamus. The generation of extra cortical neurons required the appearance of an accessory site of proliferation within the subventricular zone (SVZ) and the appearance of an intermediate progenitor population [74]. Throughout evolution many aspects of circuitry were conserved as shown by similarities in the laminar allocation of cells connecting to thalamus, spinal cord, and intracortical regions [75].

Corticalization

It has been hypothesized that corticalization is the result of added germinal cell divisions providing for supernumerary minicolumns [76]. This appears to be the case regardless of whether regionalization of neurons and parcellation of different brain areas follow mechanisms suggested by the diverging protomap or protocortex models [77,78]. When making comparisons among the brains of mice and humans, Rakic’s hypothesis explains why the surface area of the cortex has increased by a thousand fold while keeping its width relatively stable, i.e., a two- or three fold increase. Rakic’s tentative explanation has been tested and proven by studies showing that a single microinjection of Fgf2 into the cerebral ventricles of rat embryos doubles the number of excitatory (pyramidal) neurons generated during cortical development. Diametrically opposed results, a diminished number of pyramidal neurons, were observed in a knockout mouse of the *FGF2* gene [79,80,81]. It is therefore unsurprising that mutations of the fibroblast growth factors (FGF) family of genes seemingly alter, in correlated fashion, both brain size and minicolumnar numbers [82].

Hyperplasia is sometimes a response to injury and occurs in cells that, in many occasions, need to renew or replenish themselves. A significant portion of psychiatric conditions may stem from altered modulating influences of germinal cell division, e.g. hyper- or hypoplasia. Preliminary work on the 22q11 deletion syndrome, also known as DiGeorge or Velo-Cardio-Facial syndrome, suggests that deletion of regulatory cells that control the cell cycle of germinal cells provide for changes in both brain volume and in the specification of cells within different cortical layers [83]. Since different cortical layers provide for defined efferent projections, the end result of altered germinal cell divisions is a modification of the brain's connectivity. It is therefore unsurprising that provoked hyperplasia of germinal cells at defined time points during gestation provides for long-term repercussions on emerging cognitive and motor behaviors (see above) [82].

The overall increase in brain size, observed during corticalization, is manifested by a bias in the gray/white matter ratio. The increased number of minicolumns provides for additional pyramidal cells and a scaled increase in projections traversing the white matter [84,85]. Metabolic and conduction constraints limit the range of these supernumerary fibers resulting in an increased number of U-fibers or arcuate projections while reducing the total number of longer corticocortical connections [85]. Studies in comparative anatomy indicate that despite a faster increase in the volume of the white matter (as compared to gray matter) during corticalization, the cross sectional area of the corpus callosum falls behind overall brain size [86,87]. This means that evolution has proceeded by varying the numbers of minicolumns and finely tweaking the balance of short and long corticocortical connections [88]. It has been postulated that changes in the ratio of short to long corticocortical connections may provide for different cognitive styles [88].

There is limited variability in terms of neuronal and dendritic arbor size as compared to brain size across species [61]. As the cortex enlarged the scope of the dendritic arbor for any given neuron became proportionally smaller adding the possibility of changing the specialization of that given region. The gain in function seems to have limited the size of cortical areas with only a few large ones in mammals. The trend in larger brains has therefore been to increase compartmentalization and reduce global interconnections [89].

Corticalization Gone Bad

Increase brain size and its concomitant number of minicolumns and connections entail compromises in metabolic costs which may explain the recent raise in prevalence of certain mental disorders [6,27]. In effect, human primates have a large cortical surface whose development depends on germinal cells that have a prolonged cell cycle and an extended migratory route for daughter cells to reach the cortical plate. The coincidence of factors predisposes our cortex to derangements. It is therefore not unusual for disparate lesions to manifest similar pathologies such as heterotopia and cortical dysplasia. The resultant disorganization may be the most common cause of intractable epilepsy in children. The next few paragraphs describe some of the lesser recognized manifestations findings suggesting modular abnormalities in several psychiatric disorders. This is a selected review of the literature that expands upon the author's perspective on these conditions. There are multiple other findings and fruitful lines of research that have been obviated due to space limitations [90–93].

AUTISM—Studies of minicolumnar morphometry in autism have shown an increase in the number of modular units [94,95] having a diminished diameter primarily due to a reduction in their peripheral neuropil space. The morphometric defect of the neuropil space extends throughout both the supra and infragranular layers. It has been suggested that the diminished minicolumnar width across the different layers reflects involvement of a shared constituent

among the different laminae (e.g., double bouquet cells) and a defect in the inhibitory surround of these modules [96]. A recent therapeutic intervention using low frequency transcranial magnetic stimulation has been aimed at increasing the surround inhibition of minicolumns in autism [97]. Thus far the trial has provided for a positive outcome based on event-related potentials, induced gamma frequency activity, and behavioral measures.

Parallel arrays of minicolumns enhance computational power at the expense of increasing cortical excitability and decreasing the threshold for aberrant epileptic discharges [98]. This comes from the increased occurrence of contacts points by nerve cell processes without forming typical synaptic contacts. It is believed that some type of transmission occurs at such nonsynaptic sites (emphatic interactions) and appears involved in the oscillation of cortical rhythms. This may result in sleep disturbances or raising the baseline level of cortical hyperexcitability.

Cortical hyperexcitability may affect how well one can stay focused and our attention span. It can affect one's level of irritability and arousal. This impulse ridden individual will be driven by a need for stimulation, self-induced or otherwise. A person whose brain is too noisy is blasted by stimuli that can't be blocked out thus the brain "can't hear itself think" [99]. This overwhelming aversive feeling propitiates mood disorders when the person realizes that he/she is overloaded and is working at the distal edge of his mental capacity. Although an apt correlate to this neurophysiology may be Attention Deficit Hyperactivity Disorder (ADHD) another example may be autism. The overall level of noise affects a person's ability to relate to other people in not been able to gauge the depths of social interaction, being concrete and relying on overlearned behaviors [99].

DYSLEXIA—Recent studies have described a spectrum of minicolumnopathies wherein autism and dyslexia stand at opposite tail ends of the distribution [88,100,101]. When considering brain volume, minicolumnar size, gyrification, gyral window, volume of arcuate fibers, and size of the corpus callosum these condition are diametrically different. As compared to controls, brains of dyslexic patients tend to be smaller and less gyrified (40% of the difference in gyrification being attributed to smaller volumes). Subsequent studies have shown that their gyral window (i.e., aperture for afferent and efferent cortical projections) is broadened and that this change correlates with the size of the corpus callosum [102]. In essence, dyslexic patients exhibit a bias in connectivity favoring longer corticocortical connections at the expense of shorter ones [88].

SCHIZOPHRENIA—Two different studies by our group have analyzed intercellular distances in the cortex of patients with schizophrenia by measuring parameters related to minicolumnar morphometry [90,103,104]. The results showed significant alterations in mean interneuronal distance according to both the lamina and cortical area examined. Otherwise, there were no significant differences in either minicolumnar width or the vertical orientation of the cell minicolumn. The lack of alterations in parameters defining the core constituents of the minicolumn alongside abnormalities in mean cell-spacing suggested a disturbance in lamination, and pathology within the modulating action of lamina specific innervations by the monoaminergic system. It is therefore noteworthy that according to epidemiological studies the onset during development of lamination coincides with the time window (i.e., second trimester) of vulnerability to schizophrenia [105].

ALZHEIMER DISEASE AND PARAPHRENIA—Several studies relate tau positive neurons to abnormalities of intrinsic cortical connectivity. Based on qualitative observations, medial temporal lobe structures such as the entorhinal cortex and/or subiculum appear to be either the first or the principal region affected by pathology in both Alzheimer disease and paraphrenia. Structural MRI has also found volume reductions of several medial temporal

regions [106]. These structures serve as a gateway between the hippocampus and other areas of the cortex. Since tangles are selective for corticopetal neurons [107–110], regions receiving projections from the entorhinal/subicular regions would themselves exhibit pathology based on their corticocortical connectivity. Such a stepwise progression has been observed in Alzheimer's disease. Here, tangles stereotypically begin in the entorhinal cortex and spread to the posterior parahippocampal gyrus and then to the frontal and occipital cortices [111,112,113].

Descriptive models have been proposed to explain the pathological spread (entorhinal cortex → hippocampus proper/subiculum → frontal → occipital lobes) and clinical heterogeneity of AD based on stage, compensation, and subtype of degenerative changes. One of them, called the phase model may facilitate understanding of a restricted tauopathy by addressing the distribution of lesions. This model assumes bilateral neuropathological change [114], originating in either subiculum and/or entorhinal cortex [113]. Pathology then spreads in a step-wise fashion following the origin and termination of corticocortical connections. Thus far, a rostral spread seems most likely, an orthograde or caudal distribution (entorhinal cortex → parahippocampus) has not been proven [113]. Individual differences explain little of the total variance: duration of illness is the most important variable [114].

Propagation of neurofibrillary tangles occurs in small clusters that register across the supragranular and infragranular layers [111]. Several authors have suggested that the resultant arrangement of affected neurons provides for a minicolumnopathy wherein corticopetal neurons are selectively affected [115,116]. In essence, neurofibrillary tangles target the *locus minoris resistentiae* of the minicolumn, primarily its efferent component. Damaging a few neurons nullifies the action of the minicolumns as a whole. The cascading damage may help explain the rapidly deteriorating course of the condition.

Conclusion

This article elaborates on the opinion of the author regarding how information processing within the cortex involves a highly orchestrated ballet with the canonical circuit of the minicolumn playing the role of the leading ballerina. As elegant as this process may be, many costly mistakes can happen. Some of these aberrations are the result of working with a system that is taxed in terms of resources. An increased number of minicolumns (as with corticalization) exponentially increases the metabolic demands and the intrinsic bias in terms of short to long corticocortical connections. Several psychiatric conditions (see above) may be the result of functional and anatomical minicolumnar derangements.

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