Chapter 13
The Minicolumnopathy of Autism

Manuel F. Casanova

Abstract The organization of the cerebral cortex is centered around a modular construct. The smallest module capable of information processing is the minicolumn. Recent studies on minicolumnar morphometry using either pyramidal cell arrays or the gray level index (GLI) suggest distinct abnormalities of this structure in several psychiatric conditions including schizophrenia, dyslexia, and autism. More specifically, minicolumns in autism as compared to controls seem thinner and more numerous. An increased number of minicolumns indicates the supernumerary division of periventricular germinal cells. A reduction in size of pyramidal cell somas within affected minicolumns suggests a bias towards shorter corticocortical connectivity. Compartmentalization of the minicolumn indicates that the majority of the deficit is found within the peripheral neuropil space. This compartment includes, among other things, many of the inhibitory elements of the cerebral cortex and provides the so-called "shower curtain of inhibition" to the minicolumn. Laminae studies indicate that in autism the peripheral neuropil defect extends the width of the cerebral cortex. A possible explanation to the above described minicolumnar abnormalities is the heterochronic division of germinal cells. Neuroblasts generated from heterochronic divisions of germinal cells can give rise to heterotopias and dysplastic cortical lesions. Once the radially migrating neuroblasts (future pyramidal cells) reach the cortex they develop asynchronously from tangentially dividing neuronal elements (interneurons). The resultant excitatory/inhibitory imbalance may provide for seizures and sensorimotor abnormalities

Keywords Minicolumns • Cerebral cortex • Autism spectrum disorders • Interneurons • Pyramidal cells

The known neuropathology of the different entities comprising syndromic autism strongly suggest an onset during brain development. The percentage of individuals showing an autism phenotype in many of these conditions is exceedingly high. Different series suggest that 25–50 % of all patients with tuberous sclerosis meet

M.F. Casanova, M.D. (✉)
Department of Psychiatry, University of Louisville, Louisville, KY, USA
e-mail: manuel.casanova@louisville.edu

M.F. Casanova, I. Opris (eds.), *Recent Advances on the Modular Organization of the Cortex*, DOI 10.1007/978-94-017-9900-3_13

criteria for an autism spectrum disorder (ASD). According to some series the frequency is even larger for the Lujan Fryns syndrome (mental retardation, X-linked, Marfanoid body habitus) and the Smith-Lemli-Opitz syndrome (mental retardation and an inborn error of cholesterol synthesis). The commonality among many syndromic cases appears to be a migratory abnormality where neuroblasts fated to form part of either cortex or brainstem either fail to reach their normal target areas or reach the same and are desynchronized in their development from other cellular elements already in place. Syndromic cases with migratory abnormalities exhibit subependymal nodular heterotopias, cluster of neuronal cells within the white matter, and a variety of cortical malformations. Although the above mentioned cases are the result of genetic conditions (including *de novo* mutations), exogenous factors such as viral infections (e.g., cytomegalovirus) and even cocaine during gestation may alter cellular divisions of the germinal matrix thus providing for similarities in both neuropathology and clinical presentations.

Abnormalities of neuronal migration are intimately related to malformations of the cerebral cortex. Malformations during brain development, also called dysplastic changes, are usually manifested as cortical thickening or thinning, blurring of the gray-whiter matter junction and a variety of histological findings, e.g. effacement of laminar patters, minicolumnar morphometric abnormalities, malpositioned neurons (supernumerary neurons in the molecular layer and white matter). In this regard the pathology observed in the cerebral cortex is secondary to processes impinging on its formation, e.g. germinal cell divisions, migration of neuroblasts to the cortical plate. All of the previously observed dysplastic changes have been reported in both syndromic and idiopathic autism (Casanova et al. 2013). The significance of the findings lays in their capacity to explain some of the phenomenology in autism spectrum disorders, e.g., medically refractory seizures and sensory abnormalities.

This chapter will focus on certain aspects of cortical dysplasia in ASD as revealed by minicolumnar morphometry. Vertical aggregates of cells forming closed circuits were first described anatomically by Lorente de Nó (1938): “All the elements of the cortex are represented in it, and therefore it may be called an elementary unit, in which, theoretically, the whole process of transmission of impulses from the afferent fiber to the efferent axon may be accomplished”. According to Mountcastle, the minicolumn is the smallest element of information processing within the cerebral cortex (Mountcastle 1998). Recent electrophysiological studies reveal that sensory processing at the level of the minicolumn modulates the expression of higher cognitive functions (Opris et al. 2013). Differences in minicolumnar morphometry between hemispheres have been used to explain cerebral dominance for the language regions of the brain (Buxhoeveden et al. 2001). Since this difference appears to be specific to our species (not present in non-human primates), it may be a putative speciation event relating language to cytoarchitectonic features of the brain (Buxhoeveden et al. 2001). Defects in minicolumnar morphometry may therefore be present in psychiatric conditions such as ASD which are defined by language abnormalities.

13.1 Minicolumnar Morphometry in Autism Spectrum Disorders

The first study on minicolumnar morphometry in autism spectrum disorders sampled nine cases and an equal number of age-matched controls (Casanova et al. 2002a, b, c). All of the specimens were collected and processed by Drs. Thomas Kemper and Margaret Bauman. There were no abnormalities for any of the cases at gross examination. Four of the nine autistic cases were macrocephalic with brain weights more than two standard deviations above the means for their corresponding ages. The medical records detailed little information as to whether the abnormal brain weights were due to postmortem swelling, an artifact, or a real phenomenon. These cases had been cut midsagittally, freezing one hemisphere and leaving the other for microscopic examination. In order to avoid shrinkage artifacts, brains were embedded in celloidin. Sections were cut at 35 μm and Nissl stained. Every 20th section was collected and for each 100th section and adjacent slide was stained for myelin using the Loyez method. Previous reports on the pathology of these cases used a Zeiss comparison microscope and offered subjective assessments of findings when viewing simultaneously side-by-side anatomically matched slides. In this patient population, Bauman and Kemper indicated the presence of reduced neuronal size and increased cell density in the amygdala, hippocampal complex, subiculum, entorhinal cortex, medial septal nuclei, and mammillary bodies (Bauman and Kemper 2005).

Bauman and Kemper reported few cortical findings in this series. Most prominent among these were an indistinct pattern of lamination in the anterior cingulate gyrus and a minor malformation in one case of the orbitofrontal cortex (Bauman and Kemper 1987; Kemper and Bauman 1998). Subjective appraisal of the slides (whole hemisphere coronal sections) made it difficult to draw firm conclusions about the cerebral cortex. It is in this regard that we attempted relative quantitation by using computerized image analysis and implementing an algorithm based on the Euclidian minimum spanning tree. Images from lamina III in three cortical regions (Brodmann areas 9, 21, and 22) were digitized and cells reduced to points using lines such that the total length of all lines was minimized. Minicolumns were identified as vertical clusters of large neurons delimited on either side by cell-sparse areas. Imaginary lines through the sparse areas partitioned the field into polygonal regions thus defining minicolumnar segments. Descriptive statistic of minicolumnar morphometry included columnar width (CW), peripheral neuropil space (NS), interneuronal distance (MCS), and compactness (RDR). Results from this study revealed that minicolumns in ASD were narrower with a mean CW of 46.8 *vs*. 52.8 μm in the control brain. Both the peripheral neuropil space and compactness were reduced in autism.

Results from this first study revealed that minicolumns in ASD are of reduced width with a significant portion of the abnormality accounted by a diminution of the peripheral neuropil space. The lateral compartment of the minicolumns, the peripheral neuropil space, is the conduit, among other things, for inhibitory circuit

projections. Previous researchers have called this compartment of the minicolumns: "a shower curtain of inhibition" or a "strong vertically directed stream of inhibition" (Szentágothai 1978; Mountcastle 1997). This inhibitory compartment sharpens the functional borders of the minicolumn and increases their definition or discreteness (DeFelipe 1999; Favorov and Kelly 1994a, b; Szentágothai 1978). The primary source of this inhibitory effect stems from the action of double-bouquet and basket cells. Double-bouquet cell axons arrange themselves in repeating vertical patterns between 15 and 30 μm apart depending on cortical area examined (DeFelipe 1999). It is thought that the vertical descent of double bouquet cells across laminae acts as a buffer by inhibiting dendritic terminals belonging to excitatory (pyramidal) cells of neighboring minicolumns. A defect in these inhibitory elements could cause the signals being processed in the core of the minicolumn to suffuse into adjacent minicolumns. The resultant avalanche of activity could help explain the significant prevalence of seizures in ASD.

An interesting possibility worth considering is what would happen in ASD if thalamic fields retain the same area dimension while minicolumns are smaller? The result for ASD would be an increased number of minicolumns innervated per thalamic afferent than in the normal brain. Alternatively, the failure to assimilate additional minicolumns into a thalamic field would impel these processing units to establish connections with functionally dissimilar sets of thalamic neurons (Favorov and Kelly 1994a, 1994b). In the later instance, the failure of the system to assimilate the additional minicolumns would result in cortical noise; that is, supernumerary units of activity that overtax the system (Casanova et al. 2002a, b, c).

Individual cells when depolarized cannot produce gamma activity. This fast oscillation, in the gamma range, is responsible for creating the unity of conscious perception. Only thalamic modulation of neuronal networks can provide for intracortical gamma activity (Sukov and Barth 2001; Macdonald et al. 1998). Because interneurons can help synchronize neuronal discharges and some exhibit fast spiking activity, they are important mediators of gamma activity. Lack of integration among separate specialized local networks (a binding failure) may account for a weak central coherence in autism spectrum disorders. Several laboratories have recently reported a disorder of binding related gamma EEG oscillatory activity in autism spectrum disorders (Grice et al. 2001; Sokhadze et al. 2009; Baruth et al. 2010).

The same patients and regions of interests reported by Casanova et al. (2002a) were examined for descriptive parameters of the Gray Level Index (Casanova et al. 2002b; Schlaug et al. 1995). According to this method a fractional area of Nissl-stained objects was computed (profiles of 11 pixels 110 um wide). Images were smoothed with the resultant profiles leading to the analysis of its peaks and troughs. The method produced measurements of peak width distance and a verticality index. The verticality index quantified the degree of columnar organization relative to the mean of the entire sample. The overall statistical test revealed significant differences between autistic patients and controls and between hemispheres. There was no significant age dependency between factors. Follow-up

univariate tests showed significant diagnosis-dependent effects in feature distance. No significant differences were evident in overall verticality.

Results from the latter two studies using different algorithms indicate the presence of vertical cellular structures in the cerebral cortex of individuals with autism spectrum disorders that are packed more closely together and more regularly spaced than in controls (Casanova et al. 2002a, b). The results equally applied to all areas examined (Brodmann areas 9, 21, 22) in both hemispheres. The findings suggest a developmental defect of the nervous system.

A third study on minicolumnar morphometry in ASD was carried in an independent sample as an international effort sponsored by the Autism Tissue Program (Casanova et al. 2006a, b). Different laboratories were charged with collecting samples, constructing photomicrograph montages, and performing the computerized image analysis. The results were made available to all of the participating researchers before the codes were broken and the data analyzed statistically. The patient population consisted of six age-matched pairs of ASD subjects (DSM-IV-TR and ADI-R diagnosed). Tissue specimens consisted of full coronal sections embedded in celloidin and cut at 200 μm. Gallocyanin-stained sections were used to identify cortical areas M1, V1, frontal association cortex, and S1 (Brodmann areas 4, 17, 9, and 3b). Sections were delineated with a stereology workstation and photographed with a digital camera at 40X. The Virtual Slice module of the StereoInvestigator was used to assemble digitized photomicrographs into one mosaic. Computerized image analysis of minicolumnar morphometry in Laminae II through VI was performed with algorithms previously described in the literature (Casanova and Switala 2005). A threshold function eliminated the smaller cellular elements (interneurons) and allowed the researchers to concentrate on measurements provided by pyramidal cells. Minicolumnar width was reduced in autism spectrum disorder individuals as compared to controls. Mean neuron (soma) and nucleolar size was reduced in ASD, while neuron density (based on a point process model) in autism exceeded the control group by 23 %.

The findings reported in the international study on minicolumnar morphometry in ASD reproduced previous findings (Casanova et al. 2006a). In this study the feature extraction properties of the program were corrected for minicolumnar fragments, curvature of the tissue section, and were adapted to 3D proportions (stereological modeling). The smaller minicolumns per given brain region translates into increased numbers when corrected for 3D quantitation. The smaller minicolumns and their overall increase in total numbers translated into an increased neuronal density. However, the basis for the increase cellular density remained conjectural, e.g., the presence of smaller supernumerary minicolumns, an increase in the total number of cells per minicolumn, or both. A subsequent analysis based on a Delaunay triangulation addressed the aforementioned concerns.

The Delaunay triangulation parcellates points by joining them with edges forming triangles. The edges satisfy the criteria of an “empty circle” property where for each edge we can find a circle containing the edges’ endpoints but no other points within the same. Owing to the clustering of cells within vertical arrangements, the Delaunay triangulation demonstrates a bimodal distribution of

edges between cells in the same minicolumn (intracluster) and edges between cells in neighboring minicolumns (interclusters). The Delaunay triangulation indicated a significant reduction in the edges of intercluster distances but not within intracluster differences. Increased neuronal density in this series was due to the presence of supernumerary minicolumns, otherwise the total number of neurons (pyramidal cells) per minicolumn was normal (Casanova et al. 2006a).

Minicolumns in autism, although smaller in size, are increased in total numbers as compared to neurotypicals. Furthermore within each minicolumn a reduction of both neuronal soma and nucleolar size biases connectivity towards shorter connections. Casanova et al. (2006a) concluded that, "Just et al. (2004) have subsumed the evidence for a lower degree of information integration in autism under the rubric of the "underconnectivity theory". However, the term may prove to be a misnomer when applied to shorter intra-areal connections (arcuate or u fibers). In autism, an increase in the total number of minicolumns requires a scale increase (roughly a 3/2 power law) in white matter to maintain modular interconnectivity (Hofman 1985). This additional white matter takes the form of short-range connections which makes up the bulk of intracortical connections." Dysfunction of long projections translates into complex abnormalities within widely distribute networks. Some authors have suggested that a "dysexecutive syndrome" in autism could possibly result from the frontal lobe's complex pattern of connectivity. The widely distributed network of connectivity of the frontal lobes accounts for the phenomenon of diaschisis where executive cognitive deficits may become apparent in lesions distant to the anterior cortical region (Mesulam 2002; Casanova et al. 2006b).

The international group that produced the Casanova et al. (2006a) study also expanded on previous findings by examining the topographical distribution of the autistic minicolumnopathy (Casanova et al. 2006b). Tissue embedding and processing was identical as before but the number of sampled regions of interest increased to include Brodmann areas: 10 (frontopolar), 11 (orbitofrontal), 9 (dorsolateral prefrontal), 4 (primary motor), 3b (primary sensory), 43 (frontoinsular), 44 (ventrolateral), 24 (anterior cingulate), and 17 (primary visual). The sampling included areas of the cortex representing paralimbic, heteromodal association, unimodal association, and primary areas. The study found an interaction of diagnosis and region for peripheral neuropil space. *Post hoc* analysis revealed significant differences for the frontopolar region (area 10) and the anterior cingulate gyrus (area 24). The role of the frontopolar cortex in executive functions and of the anterior cingulate gyrus in the analysis of socially salient information suggests that involvement of these areas may provide a correlate to some of the more salient clinical manifestations of autism.

The initial results of a minicolumnopathy in autism has been reproduced in an independent sample by Buxhoeveden et al. (2006). The study included two autistic subjects with an average age of 22 years and 5 controls whose average age was 35 years of age. Two of the controls were embedded in paraffin, cut at 20 μm and stained with a silver impregnation method. The other subjects within this study were cryoprotected, cut at 80 μm and Nissl stained. The significance of this study is arguable given the salient limitations imposed by the limited number of

participants, lack of age matched controls, and differences in processing of tissue as well as staining. Despite all of this, the study reproduced previous findings. The average minicolumnar width reported in Casanova et al. (2002a) study was 46.8 μm for 9 autistic subjects and 52.8 μm for 9 controls, compared to results in Buxhoeveden et al. (2006) of 45.5 μm and 56.2 μm in autistic and controls respectively.

Many of the aforementioned studies on minicolumnar morphometry in ASD focused on elucidating changes in lamina III as the columnar nature of pyramidal cell arrays is easily discernible in supragranular layers. In deeper laminae the arrangement of pyramidal cells in relation to the central axis of the minicolumns is more variable. For this reason photomicrograph mosaics from the Casanova et al. (2006b) study were used to analyze with computerized imaging methods the minicolumnar width at the supragranular, granular, and infragranular levels. Images were smoothed with a Markov-Gibbs random field and used a Gibbs energy function to find the gray level that minimized the difference in intensity between each pixel and its surrounding neighbors. We then optimized the gray level value to increase the contrast between neurons and background. Images obtained by the previous steps were segmented by thresholding to produce binary images. The individual neurons were then identified using a region growing algorithm. Minicolumns were recognized with a line tracing method that grouped cells into columnar structures by finding the shortest cell-to-cell paths from one end of the layer to the next. Results of the study corroborated again previous findings of reduced minicolumnar width in ASD but expanded the same to be inclusive of supragranular, granular and infragranular layers. The reduction was accounted by findings within the peripheral neuropil space.

The peripheral neuropil space of minicolumns contains, among other anatomical elements, the interneurons and inhibitory projections that help frame the activation of modules by an inhibitory surround (Buxhoeveden and Casanova 2002). A diminution of the peripheral neuropil space across the different cortical layers probably reflects involvement of a shared anatomical element. It seems possible that the abnormality belongs to inhibitory elements suggesting that individuals with ASD have a defect in the inhibitory surround of minicolumns. Proof for this supposition has been obtained from studies of tactile resolution and habituation to stimuli (Tommerdahl et al. 2007; Tannan et al. 2008) and others using a lateral masking paradigm to assess visuospatial processing information (Keita et al. 2011).

Surround or lateral inhibition is a common feature of cortical modules. They are easily recognized in sensory regions where an excitatory receptive field is surrounded by an inhibitory area or areas. Probably the best known examples of cells organized in center surround fashion are located in the retina and the lateral geniculate nucleus. The presence of surround inhibition allows for contrast detection. Neurons with classical surround inhibition respond best to a stimulus applied to its central receptive field but less well as the stimulus activates the surrounding areas. An abnormality of lateral inhibition in the brains of autistic individuals would affect how the individual processes information, specifically why do they seem to

examine individual elements of a figure but fail to acquire the complete picture of the same.

Besides a minicolumnopathy, the brains of autistic individuals evidence an effacement of the normal lamination pattern, variation in neuronal density, and gyral malformations (Schmitz and Rezaie 2008). The described defects suggest an abnormality during brain development. These malformations or dysplasias define a disturbance of cellular proliferation, migration, and cortical organization that starts long before a person is born. A recent study used cortical width as a proxy measure of dysplasia (Hustler et al. 2007). The study reviewed the histologic findings in 8 ASD individuals and an equal number of controls in three different regions of eulaminate cortex (BA7, 9, and 21). Findings revealed an increased number of cells in both lamina I and subplate region of ASD individuals. A later study using the same patient population evaluated the boundary of the gray and white matter by computerized image analysis (Avino and Hustler 2010). The results indicated the presence of supernumerary cells beneath the cortical plate probably the result of a defect of cell migration or failed apoptosis within the subplate region. Studies by Wegiel and colleagues (2010) suggest that defects of neurogenesis and neuronal migration account for described dysplastic changes.

A recent study by our group attempted to identify the nature of the dysplastic process (Casanova et al. 2013). The study analyzed celloidin-embedded and Nissl stained full coronal sections of 7 autistic (ADI-R diagnosed) and an equal number of age/sex matched controls. Sections were scanned and manually segmented. Digitized images were analyzed with an algorithm using Laplace's equation to measure cortical width. Results of the study revealed multiple circumscribed regions of dysplastic cortex distributed throughout the whole brain of ASD individuals. Described defects varied greatly in overall size and location but were most abundant within the frontal lobes. Microscopic assessment of dysplastic regions revealed and absence of dysmorphic or balloon neurons, and no evidence of gliosis. Affected gyri were not mushroom shaped, nor did they acquire the shape of tubers. There was no evidence of ulegyria. Neuronal morphometry suggested the presence of smaller pyramidal cells and a total reduction in the number of interneurons. The authors concluded that supernumerary minicolumns in ASD are the product of heterochronic divisions of periventricular germinal cells. When these cells are forced to divide and migrate to the cortex they are uncoupled from those that migrate tangentially (interneurons) thus creating an excitatory-inhibitory imbalance.

13.2 Discussion

During corticogenesis progenitor cells located within the ventricular zone provide for symmetric divisions wherein the total number of postmitotic cells will help define the future number of minicolumns within the cerebral cortex. A subsequent wave of asymmetric divisions (following the fortieth embryonic day) provides for

daughter cells that migrate along glial fascicles to the cerebral cortex. During mammalian evolution this process of symmetrical and asymmetrical divisions has resulted in a 1,000-fold increase in cortical surface area (considering the dimensions of the brains of mice and humans) but only a two or three-fold increase in cortical thickness. Putative factors affecting the total number of cells and minicolumns within the cerebral cortex include: (1) the number of founder cells, (2) the duration of the cell-division cycle, (3) the number of successive cell cycles during the period of neurogenesis, (4) the modes of cell division, and (5) selective cell death. The minicolumnar findings from previous studies (Casanova et al. 2002a, b, 2006a) suggest the presence of supernumerary symmetrical cell divisions of periventricular germinal cells providing an increased number of radial units (minicolumns) within the cerebral cortex of individuals with autism spectrum disorders.

Some researchers believe that if neuronal connectivity is kept at a fixed percentage during cortical expansion, then a significant portion of the growth would be devoted to maintaining wiring. This would mean that bigger brains would require increasing axonal lengths and a consequent reduction in neural computational speed. It is this consideration that has driven some researchers to maintain that our brains are almost at their limit for biologic intelligence (Hofman 2001). Encephalization has therefore provided for increased cortical gray with disproportionate growth in white matter. It has been suggested that each minicolumn is connected to on the order of 1,000 other modules (Casanova 2004). Findings of increased number of cortical minicolumns in ASD would help explain why MRIs studies have reported enlarged gray matter volumes with an even bigger increase in white matter (Herbert et al. 2004).

The increased white matter seen with supernumerary minicolumns takes primarily the form of short-range fibers. The total layout of the connectivity within the brain minimizes total connections costs. Long-range connections incur the penalty of increases in both conduction times and metabolism. A small-world network helps to reach neighboring and distant modules in a small number of steps. A restricted number of longer projections, may help explain why despite larger brains, on average, ASD individuals have a reduction in size of their corpus callosum. Indeed, long commissural projections may serve as a better index of macrocolumnar rather than microcolumnar connectivity (Casanova et al. 2004).

The presence of a minicolumnopathy in autism spectrum disorders distances the condition from classic neuropathology by emphasizing abnormalities in cell assemblies rather than single cells. During development these cell assemblies organize into columnar aggregates. Columns will be active when a given set of features is present in the input. Objects with similar features activate columns in proximity to each other. The unequal distribution of synaptic weights among neurons allow for variability in the output. According to Gustafsson (1997) a wide column that contains many neurons has a broader range of synaptic weights than a narrow one. This feature allows for a greater variability in the processing of objects that activate columns. Gustafsson (1997) believes that narrow columns with fewer cells facilitates discrimination, whereas wider columns facilitate generalization.

The morphometric variability of minicolumns in autism spectrum disorders is very specific. Multiple studies have corroborated that diminished minicolumnar width is associated with major reductions in their peripheral neuropil space. While development of the core compartment of the minicolumn is constrained by the process of radial cell migration and its attendant radially oriented projections, anatomical elements within the peripheral neuropil space is more heterogeneous as to their sources, modes of migration, morphogenesis and synaptogenesis. The large variability of the peripheral neuropil space in humans as compared to other species suggests that genetic and epigenetic influences may act primarily in this compartment (Casanova et al. 2009). This heterogeneity may provide the basis for adapting minicolumns to function within specific networks during both evolution and development.

Variability among the multiple components of the minicolumn may contribute to the fault tolerance among larger networks such as macrocolumns. Variability may allow individual minicolumns to compute different functions within the same module that can be used to their advantage with respect to sensitivity to error. This variability in otherwise redundant circuits is the basis for majority voting circuits (Stroud 1994). In effect plasticity is associate not only with the tuning of synaptic activity states but also with the optimal selection among alternate sub-networks of microcircuits developing within a given context. Competition among networks allow for circuit optimization. Morphometric variability of minicolumns, representing variations in their microcircuitry, may provide the substrate of this competition and the basis for adapting learned behavior to context (Casanova 2008).

It has been said that, "During development, neurogenetic programs interact with epigenetic factors to regulate formation of cortical microcircuit templates, which are then shaped and pruned by differential patterns of sensory activity. Incipient behavioral patterns in turn constrain selection for mechanisms of plasticity, establishing a dynamic, mutually informing loop, a process referred to as the Baldwin effect" (Casanova 2008, p. 357). In this regard the variability in minicolumnar shapes and microcircuitry gives rise to a greater potential for combinatorial activity with overlapping or neighboring networks. For these reasons minicolumnar variability may be a phenotypic character under selection in the truest Darwinian sense.

The constellation of minicolumnar findings reported in this chapter along with other neuropathological findings described in the literature (e.g., abnormalities of gyrification and lamination, heterotopias) indicate that many cases diagnosed as ASD are linked through a cascading chain of events propitiated by disordered periventricular cell divisions. In this regard ASD should be considered a sequence rather than a syndrome. In a syndrome the various relationships between pathological findings are not understood. In ASD one primary defect can account for defects in neurogenesis, cellular migration, and corticogenesis. Like other sequences (e.g., Pierre Robin) there may be multiple known causes for ASD. Nevertheless, neuropathological studies of idiopathic and syndromic autism (e.g., tuberous sclerosis,

Ehlers-Danlos syndrome, congenital cytomegalovirus) all evidence an injury of the germinal cell matrix (Casanova et al. 2013).

The presence of a minicolumnopathy and corresponding defects in surround inhibition has promoted a possible intervention based on repetitive transcranial magnetic stimulation (rTMS). This technique offers a non-invasive method of altering patterns of brain activity. TMS operates based on Faraday's Law of induction that describes how a changing magnetic field procreates the flow of electrical current in a nearby conductor. Studies have shown that low frequency rTMS increases the activation of inhibitory circuits probably through the mechanisms of long-term depotentiation (Hoffman and Cavus 2002). We have hypothesized that the presence of double bouquet cells that bear a perpendicular geometrical relationship to the cortex makes them likely targets for induction by low frequency rTMS (Sokhadze et al. 2009). "Slow" rTMS in this regard would help restore the inhibitory tone of the cerebral cortex that my group has tested as a reduction in excess gamma band activity. We have also reported on the positive effects of rTMS on clinical and behavioral questionnaires and a visual attention task employing Kanizsa illusory figures (Sokhadze et al. 2009). Thus far we have found that in individuals with ASD gamma activity does not differentiates between target and non-target stimuli. Following rTMS, individuals with ASD showed significant improvement in their discriminatory activity between relevant and irrelevant stimuli. We have also noted significant reductions in irritability, repetitive behaviors, and response to error monitoring and post-error correction as a result of rTMS (Sokhadze et al. 2012).

References

Avino TA, Hustler JJ (2010) Abnormal cell patterning at the cortical gray–white matter boundary in autism spectrum disorders. Brain Res 1360:138–146

Baruth JM, Casanova MF, El-Baz A, Horrell T, Mathai G, Sears L, Sokhadze E (2010) Low frequency repetitive transcranial magnetic stimulation (rTMS) modulates evoked-gamma frequency oscillations in autism spectrum disorder (ASD). J Neurother 14(3):179–194

Bauman ML, Kemper TL (1987) Limbic involvement in a second case of early infantile autism. Neurology 37(Suppl 1):147

Bauman ML, Kemper TL (2005) Structural brain anatomy in autism: what is the evidence? In: Bauman ML, Kemper TL (eds) The neurobiology of autism, 2nd edn. Johns Hopkins University Press, Baltimore, pp 121–135

Buxhoeveden DP, Casanova MF (2002) The minicolumnar hypothesis in neurosciences. Brain 125:935–951

Buxhoeveden DP, Switala AE, Litaker M, Roy E, Casanova MF (2001) Lateralization of minicolumns in human planum temporale is absent in nonhuman primate cortex. Brain Behav Evol 57(6):349–358

Buxhoeveden DP, Semendeferi K, Buckwalter J, Schneker N, Switzer R, Courchesne E (2006) Reduced minicolumns in the frontal cortex of patients with autism. Neuropathol Appl Neurobiol 32:483–491

Casanova MF (2004) White matter volume increase and minicolumns in autism. Ann Neurol 56 (3):453

Casanova MF (2008) The significance of minicolumnar size variability in autism: a perspective from comparative anatomy (ch. 16). In: Zimmerman A (ed) Autism: current theories and evidence. Current clinical neurology. The Humana Press, Totowa, pp 349–360
Casanova MF (2013) The minicolumnopathy of autism spectrum disorders (ch. 3.7). In: Buxbaum JD, Hof PR (eds) The neuroscience of autism spectrum disorders. Academic, Oxford, pp 327–333
Casanova MF, Switala AE (2005) Minicolumnar morphometry: computerized Image analysis. In: Casanova MF (ed) Neocortical modularity and the cell minicolumn. Nova Biomedical, New York, pp 161–180
Casanova MF, Buxhoeveden DP, Switala AE, Roy E (2002a) Minicolumnar pathology in autism. Neurology 58:428–432
Casanova MF, Buxhoeveden DP, Switala AE, Roy E (2002b) Neuronal density and architecture (Gray Level Index) in the brains of autistic patients. J Child Neurol 17:515–521
Casanova MF, Buxhoeveden DP, Brown C (2002c) Clinical and macroscopic correlates of minicolumnar pathology in autism. J Child Neurol 17:692–695
Casanova MF, Araque J, Giedd J, Rumsey JM (2004) Reduced brain size and gyrification in the brains of dyslexic patients. J Child Neurol 19:275–281
Casanova MF, Van Kooten IAJ, Switala AE, Van Engeland H, Heinsen H, Steinbusch HWM, Hof PR, Trippe J, Stone J, Schmitz C (2006a) Minicolumnar abnormalities in autism. Acta Neuropathol 112:287–303
Casanova MF, Van Kooten IAJ, Switala AE, Van Engeland H, Heinsen H, Steinbusch HWM, Hof PR, Schmitz C (2006b) Abnormalities of cortical minicolumnar organization in the prefrontal lobes of autistic patients. Clin Neurosci Res 6:127–133
Casanova MF, Trippe J, Tillquist C, Switala AE (2009) Morphometric variability of minicolumns in the striate cortex of Homo sapiens, Macaca mulatta, and Pan troglodytes. J Anat 214 (2):226–234
Casanova MF, El-Baz AS, Kamat SS, Dombroski BA, Khalifa F, Elnakib A, Soliman A, Allison-McNutt A, Switala AE (2013) Focal cortical displasias in autism spectrum disorders. Acta Neuropathol Commun 1:67. doi:10.1186/2051-5960-1-67
DeFelipe J (1999) Chandelier cells and epilepsy. Brain 122(10):1807–1822
Favorov OV, Kelly DG (1994a) Minicolumnar organization within somatosensory cortical segregates, I: development of afferent connections. Cereb Cortex 4(4):408–427
Favorov OV, Kelly DG (1994b) Minicolumnar organization within somatosensory cortical segregates, II: emergent functional properties. Cereb Cortex 4(4):428–442
Grice SJ, Spratling MW, Karmiloff-Smith A et al (2001) Disordered visual processing and oscillatory brain activity in autism and Williams syndrome. Neuroreport 12:2697–2700
Gustafsson L (1997) Inadequate cortical feature maps: a neural circuit theory of autism. Biol Psychiatry 42:1138–1147
Herbert MR, Ziegler DA, Makris N, Filipek PA, Kemper TL, Normandin JJ, Sanders HA, Kennedy DN, Caviness VS Jr (2004) Localization of white matter volume increase in autism and developmental language disorder. Ann Neurol 55(4):530–540
Hofman MA (1985) Neuronal correlates of corticalization in mammals: a theory. J Theor Biol 112(1):77–95
Hofman MA (2001) Brain evolution in hominids: are we at the end of the road? In: Falk D, Gibson KR (eds) Evolutionary anatomy of the primate cerebral cortex. Cambridge University Press, Cambridge, pp 113–127
Hoffman RE, Cavus I (2002) Slow transcranial magnetic stimulation, long-term depotentiation, and brain hyperexcitability disorders. Am J Psychiatr 159:1093–1102
Hustler JJ, Love T, Zhang H (2007) Histological and magnetic resonance imaging assessment of cortical layering and thickness in autism spectrum disorders. Biol Psychiatry 61:449–457
Just MA, Cherkassky VL, Keller TA, Minshew NJ (2004) Cortical activation and synchronization during sentence comprehension in high-functioning autism: evidence of underconnectivity. Brain 127(8):1811–1821

Keita L, Mottron L, Dawson M, Bertone A (2011) Atypical lateral connectivity: a neural basis for altered visuospatial processing in autism. Biol Psychiatry 70(9):806–811

Kemper TL, Bauman ML (1998) Neuropathology of infantile autism. J Neuropathol Exp Neurol 57(7):645–652

Lorente de Nó (1938) Cerebral cortex: architecture, intracortical connections, motor projections. In: Fulton JF (ed) Physiology of the nervous system. Oxford University Press, Oxford

Macdonald KD, Fifkova E, Jones MS, Barth DS (1998) Focal stimulation of the thalamic reticular nucleus induces focal gamma waves in the cortex. J Neurophysiol 79:474–477

Mesulam M-M (2002) The human frontal lobes: transcending the default mode through contingent encoding (ch. 2). In: Stuss DT, Knight RT (eds) Principles of frontal lobe function. Oxford University press, Oxford, pp 8–30

Mountcastle VB (1997) The columnar organization of the neocortex. Brain 120(4):701–722

Mountcastle VB (1998) Perceptual neuroscience: the cerebral cortex. Harvard University Press, Cambridge, MA

Opris I, Santos L, Gerhardt GA, Song D, Berger TW, Hampson RE, Deadwyler SA (2013) Prefrontal cortical microcircuits bind perception to executive control. Sci Rep 3:2285

Schlaug G, Schleicher A, Zilles K (1995) Quantitative analysis of the columnar arrangement of neurons in the human cingulate cortex. J Comp Neurol 351(3):441–452

Schmitz C, Rezaie P (2008) The neuropathology of autism: where do we stand? Neuropathol Appl Neurobiol 34:4–11

Sokhadze EM, El-Baz AS, Baruth J, Mathai G, Sears L, Casanova MF (2009) Effects of low frequency repetitive transcranial magnetic stimulation (rTMS) on gamma frequency oscillations and event-related potentials during processing of illusory figures in autism. J Autism Dev Disord 39(4):619–634

Sokhadze EM, Baruth JM, Sears L, Sokhadze GE, El-Baz AS, Casanova MF (2012) Prefrontal neuromodulation using rTMS improves error monitoring and correction function in autism. Appl Psychophysiol Biofeedback 37(2):91–102

Stroud CE (1994) Reliability of majority voting based VLSI fault-tolerant circuits. IEEE Trans VLSI Syst 2:516–521

Sukov W, Barth DS (2001) Cellular mechanisms of thalamically evoked gamma oscillations in auditory cortex. J Neurophysiol 85:1235–1245

Szentágothai J (1978) The Ferrier Lecture, 1977: the neuron network of the cerebral cortex: a functional interpretation. Proc R Soc Lond B 201:219–248

Tannan V, Holden JK, Zhang Z, Baranek GT, Tommerdahl M (2008) Perceptual metrics of individuals with autism provide evidence for disinhibition. Autism Res 1:223–230

Tommerdahl M, Tannan V, Cascio CJ, Baraneck GT, Whistle BL (2007) Vibrotactile adaptation fails to enhance spatial location in adults with autism. Brain Res 1154:116–123

Wegiel J, Kuchna I, Nowicki K, Imaki H, Wegiel J, Marchi E, Ma SY, Chauhan A, Chauhan V, Wierzba Bobrowicz T et al (2010) The neuropathology of autism: defects of neurogenesis and neuronal migration, and dysplastic changes. Acta Neuropathol 119:755–770