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Spherical harmonic analysis of cortical complexity in autism and dyslexia

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Abstract

Alterations in gyral form and complexity have been consistently noted in both autism and dyslexia. In this present study, we apply spherical harmonics, an established technique which we have exapted to estimate surface complexity of the brain, in order to identify abnormalities in gyrification between autistics, dyslexics, and controls. On the order of absolute surface complexity, autism exhibits the most extreme phenotype, controls occupy the intermediate ranges, and dyslexics exhibit lesser surface complexity. Here, we synthesize our findings which demarcate these three groups and review how factors controlling neocortical proliferation and neuronal migration may lead to these distinctive phenotypes.

Keywords

Cerebral cortex; Gyral window; Gyrification index; Minicolumn; Neurogenesis

Introduction

The human cerebrum, unlike that of the lissencephalic mouse, is a highly gyrified mass of tissue, with the neocortex alone containing over 27 billion neurons [1]. The majority of this ontogenetic divergence between mouse and human lies not within the radial extension of laminae but in an increase numbers of minicolumns. While the laminar phenotype has been adaptively constrained across time such that divergence since our last common ancestor appears to be relatively minor, novel tissue construction and novel behaviors have partially arisen from the addition of columnar units of pyramidal cells, minicolumns, through the prolongation of radial glial proliferation and the subsequent increase in total neurogenesis [2].

Because the brain is an interconnected system of nodes, altering the total number of neurons in this system necessitates neuritic accommodation in order to maintain functional interconnectivity amongst a bourgeoning population of cells. While some have referred to this developmental tendency as a “save wire” approach (Component Placement Optimization or CPO), one might also think of it as adhering to a Principle of Least Effort (PLE), implying not that the brain is evolutionarily predestined to develop in such a

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conservative fashion but that conservation is the most probable outcome in a system which utilizes varying yet limited energy outputs to achieve its means [3,4]. In short, the physical and chemical nature of the biological system tends to constrain phenotypic variance to that which is most functionally feasible or probable and not necessarily that which is most advantageous [5,6]. By altering the number within a population of neurons one may subsequently alter how their neurites and synapses ultimately develop. Thus, by creating heterochronies between tissues, new emergent properties can arise.

By altering how the system communicates within itself, one may expect to see a continuum of behavioral phenotypes that correlates with general phenotypes in connectivity. In an earlier publication, we proposed that when placed upon a continuum of minicolumnar density and total cerebral volume, developmental dyslexia and autism spectrum conditions appear to occupy extremes of this neuroanatomical distribution [7]. Autism resides at one end of the continuum, exhibiting reduced minicolumnar width and neuropil spacing, suggestive of increased total minicolumnar number as compared to controls. This has been further supported by recent evidence showing that autism is not characterized by alterations in absolute cortical thickness but by the enlargement of overall cortical surface area, as would be predicted by lateral expansion of the progenitor population [8]. Dyslexia, on the other hand, lies at the opposite end of this morphological distribution and can be identified by increased minicolumnar width and neuropil spacing, suggestive of a total minicolumnar decrease [9,10]. Likewise, there are macroscopic correlates to these two phenotypes, reflective of their underlying cerebral morphometries. To investigate this, we have previously studied the gyral window in both of these conditions, which is a plane in the neocortex through which fibers connect to the underlying white matter [11,12,13]. When fiber tracts are altered due to varying numbers of neurons within the system, such as has been proposed for autism and dyslexia, one expects to see alterations in gyrification and the size of the gyral window in relation to the amount of gray matter [14]. In relation to its minicolumnar density, autism is characterized by greater levels of gyrification and reduced gyral window size [14]. Dyslexia meanwhile presents with the opposing phenotype, while controls occupy the intermediate ranges [9,15,16].

Dyslexia is a reading disorder most commonly defined by deficits in the phonological decoding of words [17,18]. In this condition, higher order comprehension is not directly deficient but is instead prevented by a lower order impediment in the deciphering of phonological information. While reading ability is the only criterion which determines diagnosis, individuals with dyslexia often present with other deficits and specific learning disabilities, suggesting universal abnormalities in brain development [19]. In contrast, autism is identified not by a single trait but by a combination of complex traits, specifically abnormalities in socialization/communication and restricted or repetitive patterns of behavior [20]. Both dyslexia and its counterpart, hyperlexia, can co-occur with autism, although the latter with greater frequency [21].

While our team and others have investigated neocortical development of these conditions on numerous levels, ranging from microscopic to macroscopic, in this current study we have applied a reliable technique which measures the relative surface complexity of the brain in autism, dyslexia, and age- and sex-matched controls. Here we report further evidence of the intimate relationship between corticogenesis and gyrification, utilizing spherical harmonics to determine the precise 3D forms of our experimental and control brains.

Experimental Procedures

The spherical harmonics are a set of complex-valued functions defined on the unit sphere; however, linear combinations of spherical harmonics of positive and negative degree form a set of real-valued harmonics, also called tesseral harmonics:

$$Y_l^m(\theta,\phi)=\begin{cases} c_{lm}P_l^{-m}(\cos\theta)\sin m\theta & ,-l\le m<0 \\ c_{l0}P_l(\cos\theta) & ,m=0 \\ c_{lm}P_l^m(\cos\theta)\cos m\theta & ,0<m\le l \end{cases},$$

where P_l^m is the associated Legendre function of degree l and order m, P_l is the Legendre polynomial of degree l, and c_{lm} is a constant normalization factor. SH form a basis for a certain class of functions: Given any real-valued $f(\theta, \phi)$ such that the surface integral $f^2 d\theta d\phi$ is finite, there exist constants b_l^m such that

$$f=\sum_{l=0}^{\infty}\sum_{m=-l}^{l} b_l^m Y_l^m$$

almost everywhere.

Raw data comprised T1-weighted MRI of the brains of 13 individuals with autism (aged 8 y–38 y, mean 22.5 y), 16 with dyslexia (aged 18 y–40 y, mean 28.2 y), and 31 neurotypical comparison participants within the same age range (for description of participant selection, MRI protocol, and image processing, see [12,13,16]). Several participants' data were removed from our previous datasets due to inadequate image quality for the purposes of this analysis. Triangular mesh representations of the cerebral cortical surface in scanner-based, RAS coordinate system were mapped to the unit sphere using an attraction-repulsion algorithm. Mesh topology was preserved, so that the transformed meshes triangulated the sphere. This mapping defined three scalar functions on the sphere: $R(\theta, \phi)$, $A(\theta, \phi)$, and $S(\theta, \phi)$, each of which was represented as an SH series. Truncating the series at a particular maximum SH degree L_{max} provides an approximation to the cortical surface that incorporates greater detail as L_{max} is increased (Figure 1). We computed a shape index, s, for each surface by summing the truncation error as L_{max} ranged from 1 to 65, inclusive.

Results

Results show that the shape index varied significantly by diagnostic category ($F_{2,57} = 142.4$; $p < 0.0001$). Autism exhibited a greater level of surface complexity, mean $s = 279$ (95 % confidence interval [255, 305]), dyslexia presented within the lower ranges of our three groups, mean $s = 99.5$ (95 % confidence interval [91.8, 108]), while controls occupied the median ranges, mean $s = 181$ (95 % confidence interval [171, 192]). This suggests that these three groupings display variances in overall gyral complexity: autism exhibits the greatest degree of complexity, controls a moderate degree, and dyslexia presents with a comparatively lesser degree than the other groups (Figure 2).

Discussion

Gyrogenesis, or the processes which give rise to the convolutions of the brain, begins following neurogenesis within the prenatal encephalon. Primary gyrification of the more prominent gyri and sulci occurs through weeks 20–28 of gestation in humans, while

secondary gyrification occurs postnatally [22]. Rates of proliferation within the fissures of the brain may be higher within the concavities of the proto-gyri than the superficial or convex portions, suggesting that asymmetric rates of proliferation across the surface of the developing cerebrum promote aspects of mechanical folding [23,24]. In humans, mapping of local growth patterns during the time of primary gyrification reveals a particular intensity of growth within the formations of the pre- and postcentral gyri, as well as the opercula, the latter comprising the superior temporal gyrus, the pars orbitalis, the pars opercularis, and the pars triangularis [25].

Autism and developmental dyslexia are conditions with extremely complex etiologies. While it is easy to become overwhelmed by the sheer breadth of research topics available, certain fundamental characteristics are noted consistently within the neocortices of these conditions which may help guide scientists towards key effectors underlying their phenotypes: 1) abnormalities in gyrification, 2) abnormalities in total cell count suggestive of proliferative aberration, 3) migratory aberrations, and 4) alterations in cerebral connectivity [13,15,26,27,28,29]. As our present study reconfirms, there exists abnormalities in gyrification within autism and dyslexia. Autism exhibits an increase in total surface complexity reflective of a more complex gyral phenotype, while dyslexia presents with lesser gyral complexity as compared to both autistics and controls.

While abnormalities in gyrification certainly indicate abnormalities in underlying cerebral connectivity as has generally been the focus of many gyrification studies, e.g., different arcuate fiber patterns, the gyral phenotype itself may pinpoint earlier aberrative local growth patterns, as work by Rajagopalan et al. [25] suggests. As their study reveals, an intensity of growth underlying the central and opercular gyri occurs during primary gyrification in humans.

Suggestive of proliferative disturbance during this 20–28 week prenatal time period, both autism and developmental dyslexia present with abnormalities of gyrification within these specific areas [27,30,31]. Abnormalities in gyrification of these areas suggests not only aberrations within fiber tracts but within the gross forms of the gyri themselves and the proliferative phenotypes which gave rise to them. If at the heart of a significant portion of cases of autism and dyslexia lie abnormalities in proliferation of the cortical plate, then these locations, the gyri surrounding the central sulcus and sylvian fissure, may be vulnerable points within the human cerebrum in general. These abnormalities not only support evidence of atypical neurogenesis in the two conditions but also give us a chronological indication of when these phenotypes are developing, highlighting the prenatal period in both conditions.

We do not propose that focal areas are targeted in autism and dyslexia while others are left unaffected; instead we suggest that deviations in development are not homogenized across the cortical plate and areas like the precentral gyrus, the postcentral gyrus, and the operculum may serves as useful indicators of the same. Measures of overall surface complexity, as we've applied here, are a complementary approach to investigating individual gyri. Current evidence shows that autism presents with compaction of neocortical minicolumns in the face of normal or above-average total brain volume [10]. Likewise, cortical heterotopias, dysplasias, and thickening of the supependymal layer within the idiopathic forms are indicative of increased proliferation and disruption of neuronal migration, similar to that seen in the syndromic autistic condition, Tuberous sclerosis [32]. Autism's linkage not only with mutations in *Tuberous Sclerosis Complex 1/2* but also with mutations in the tumor suppressor gene, *Pten*, further tie its etiology to corticogenesis and macrocephaly [33,34].

Our work has also revealed neocortical abnormalities in dyslexia, namely that of widely spaced minicolumns, increases in gyral window size, and a smaller total cerebrum [13,15]. Genetics research has pinpointed various decrease-of-function haplotypes linked to dyslexia such as *Dyslexia susceptibility 1 candidate 1* and *KIAA0319*, products which have suggested involvement in migration of supragranular neurons to the cortical plate and in aspects of cell-to-cell signaling [35,36]. Similar to autism, brains from individuals with developmental dyslexia display periventricular heterotopias and laminar dysplasias, suggesting that reduced cell density within the condition may partly find its roots in the misplacement of cells [37]. Reduced cerebral volume likewise suggests premature differentiation of neuronal populations, leading to an early reduction in the progenitor pools and subsequent deviations in gyral development [38].

Both conditions express gyral abnormalities: as determined by spherical harmonics, autism is characterized by overall greater surface complexity while dyslexia presents with reduced complexity as compared to controls. Gyral abnormalities also exist within the primary gyri, which pinpoint the prenatal time period as a risk period for development of these conditions. Deviance in the development of primary gyri suggest that proliferative abnormalities underlie autism and dyslexia, as rates of proliferation are key effectors in determining gyral form. Heterotopic and dysplastic cells also highlight the proliferative and migratory aberrations which overlap these conditions. Ultimately, atypical gyral complexity is a prime indicator of abnormal cortical development. Proliferation and cell motility share numerous molecular similarities and are both vulnerable targets to epigenetic and genetic disruption [39].

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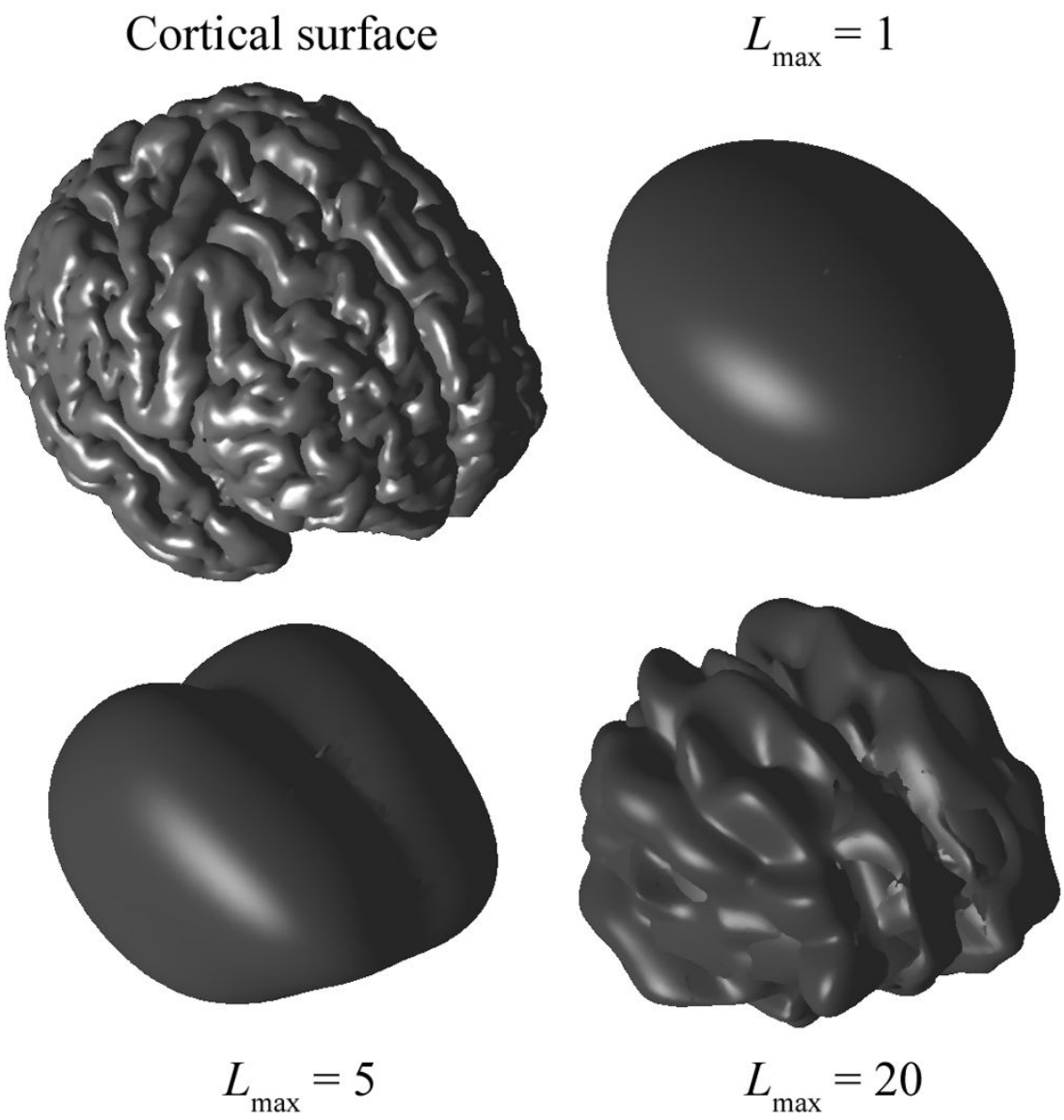

Figure 1.
As the maximum spherical harmonic degree L_{max} increases, finer details appear in the reconstruction, which more closely approximates the original shape.

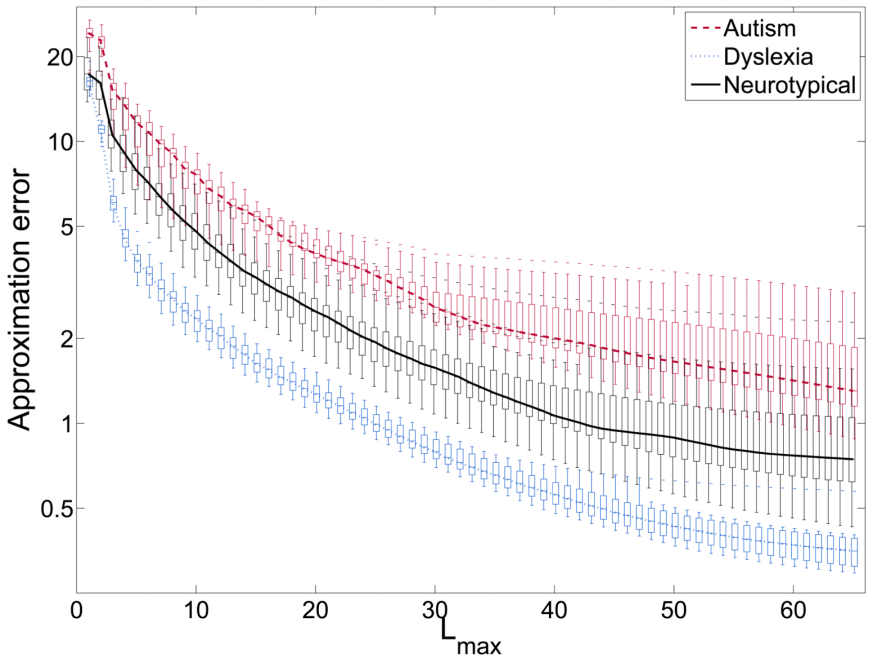

Figure 2.

Box plots show the range of approximation error in our sample for L_{max} from 1 to 65, inclusive. For any fixed L_{max}, the approximation was most accurate in dyslexia, less so in the neurotypical case, and least accurate in autism. We conclude that the brain in autism has more structure at higher spatial frequencies (i.e., finer scales), while the brain in dyslexia has less, consistent with prior measurements of cortical folding in the two conditions [12,13].