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Unfolding the Folds: How the Biomechanics of the Extracellular Matrix contributes to Cortical Gyrification

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Abstract. The convoluted human cerebral cortex is one of the key features that allows for an increased neuronal density packing essential for the complex cognitive and socioemotional behaviours man possesses. Nevertheless, the underlying mechanisms involved in cortical folding remained a both intriguing and functionally important enigma. A crucial component known to be involved in the formation and maintenance of all tissues is the extracellular matrix (ECM), providing scaffolds which tie tissues and organs in place. The composition of the ECM in both developing and mature structures is constantly remodelled, degraded and secreted by numerous types of cells, and its role as a source of growth factors and signalling in morphogenesis, migration, and proliferation is increasingly appreciated. Evidence for the differential expression of ECM during gyrification pinpoints its potentially fundamental role in shaping the folds of the cerebral cortex through both mechanical and molecular configurations. This review aims at addressing key ideas, potential directions and discoveries that highlight biomechanics of the ECM during the construction of the cortex cerebral gyrification.

The enlarged folded human cerebral cortex (CC) is considered a key feature for the complex cognitive and socioemotional behaviours man possesses. While structural, molecular and cellular suspects do exist, the underlying mechanisms involved in cortical gyrification in human, as compared to the lissencephalic brains (smooth brain) in rodents, are poorly understood (Fig. 1A). Such question withholds fundamental importance, as structural brain malformations are linked with a range of rare, yet devastating conditions. Malformations of human cortical development (MCD) include disorders of cellular proliferative conditions such as microcephaly (small brain) or megalencephaly (large brain), as well as neural migration and motility defects, as the case in lissencephaly (smooth brain disorder) or subcortical band heterotopia (the formation of double cortex-like bands) (Barkovich et al., 1989; Dobyns, 2010). These conditions are often accompanied by epileptic seizures, intellectual disabilities, and overall reduced life expectancy; and as such they mark the important interaction between tissue architecture and biological functionality (Barkovich et al., 2012; Barkovich et al., 2005; Olson & Walsh, 2002; Reiner & Sapir, 2013).

The CC is a layered tissue in the foremost structure of the brain (the forebrain). Neuronal cell bodies form the grey matter of the brain, a name given due to its considerable darker shade produced by a dense somatic localisation. Beneath the grey matter lies the white matter, wherein fatty substances of the axonal-wrapping myelin sheath are densely compacted, providing a complex axonal wiring network which connects inter and intra regions and the central nervous system (CNS). In general, animals with larger brains have a disproportionally increased surface of the cortical layer, compared to the inner region, albeit rare exceptions were noted in some species (Dehay et al., 2015). This increase is usually manifested as a complex folded surface rather than a smooth balloon-like inflation (Fig. 1A,B).

As in any other structure, corticogenesis involves a grand orchestra of genetic and epigenetic changes through which particular cell lineages are expanded and defined. In addition to the unique cellular composition of each tissue, these programmes specify a mosaic of extracellular matrix (ECM) components that are involved both in structuring and the regulation of these events (Fernandez et al., 2016; Florio et al., 2017). Here we aim to compile the relevant information about ECM characteristics and highlight specific molecules previously hinted to play a role in the expansion and folding of the cerebral cortex; and consolidate this information with mechanical and molecular models describing these folds. Specifically, we will examine how the ECM may actively influence gyrification by (a) promoting cuing agents essential for the documented increase in the number of neural progenitors in gyrencephalic animals; and (b) by introducing both micro and macro scaffold molecules with dynamic physical forces involved in the patterning of the characteristic folds. By aligning the molecular, cellular, and mechanical side by side, we hope to highlight the interplay between those forces in shaping the brain.

Cortical formation, expansion, and gyrification

During early stages of development in both gyrencephalic and lissencephalic mammals, the neural tube generates an epithelia layer of neural stem neuroepithelial cells (NECs) (Gotz & Huttner, 2005). These form tight apical junction and exhibit basal and apical nuclear movements as they undergo mitotic phases, a process also known interkinetic nuclear migration (INM). NECs compose the initial pseudostratified monolayer which undergoes symmetric, proliferative divisions that leads to both the thickening and radial expansion of the neuroepithelium. Differences in the pool of NECs in lissencephalic and gyrencephalic animals already evident at this early stage, as animals of the latter group require an increased proliferation of

neural progenitors. Neurogenesis outsets as NECs start dividing asymmetrically, when NEC division brings about one NEC or an apical radial glial cell (aRGC). aRGCs initially exhibit INM and undergo symmetrical division, and only later switch to asymmetrical division. Due to the downstream lineage proliferation following this divisional switch, new progenitors emerge, which include apical intermediate progenitor (aIP), basal radial glial progenitor (bRGC), or a post mitotic neuron (Fig. 1C). Consequently, the neuroepithelium emerge as a hybrid tissue with progenitors and neurons are spatially segregated, wherein apical progenitors are located near the cortical wall form the ventricular zone (VZ); basal progenitors form an upper subventricular zone (SVZ); and neurons migrate basally and accumulate at the cortical plate (Florio & Huttner, 2014).

In the well-characterised rodent lissencephalic animals model, IPCs give rise to most of the excitatory cells in the cortex (Rauch, 2004) and the sparse bRGCs predominantly generate post-mitotic neurons. However, increased progenitor pool and a relatively lengthy prenatal developmental period in gyrencephalic animals coincide with the formation of a new germinal zones and abundance of bRGCs, which here exhibit significantly greater proliferative behaviours. In fact, progenitors of the gyrencephalic embryo generate an extended VZ and a much thicker SVZ with numerous basal progenitor cells, which in turn separate the inner and outer areas of the SVZ (ISVZ and OSVZ respectively) (Dehay et al., 2015; Li et al., 2017a; Lui et al., 2011; Pollen et al., 2015; Reillo et al., 2011). In contrast to the mouse, most progenitors in the gyrencephalic animal are bRGCs, and the OSVZ bear a conglomerate of cells. As such, the exhibition of OSVZ layer along with the increase in bRGCs in gyrencephalic animals are regarded as crucial in the understanding of brain expansion and convulsions (Fietz et al., 2010; Fietz et al., 2012; Hansen et al., 2011).

From a physical perspective, surface folds emerge due to the mechanical instability generated when an elastic material is under compression (Groenewold, 2001). At low compression forces, the material undergoes a uniform condensation, accompanied by an increase in density and expansion at a perpendicular direction, which results in material strain. Beyond a critical force, the material will exhibit folding and wrinkling to release the compression, without further increase in the average strain. Compression forces and wrinkling can arise internally during differential swelling of polymer gels, due to solvent absorption (Bowden et al., 1998; Cerda & Mahadevan, 2003; Dervaux et al., 2011; Tallinen et al., 2014b; Tallinen et al., 2016; Tanaka et al., 1987). When the outer region of the gel is swelling faster than the interior, this mismatch leads to compression forces and results in periodic wrinkling.

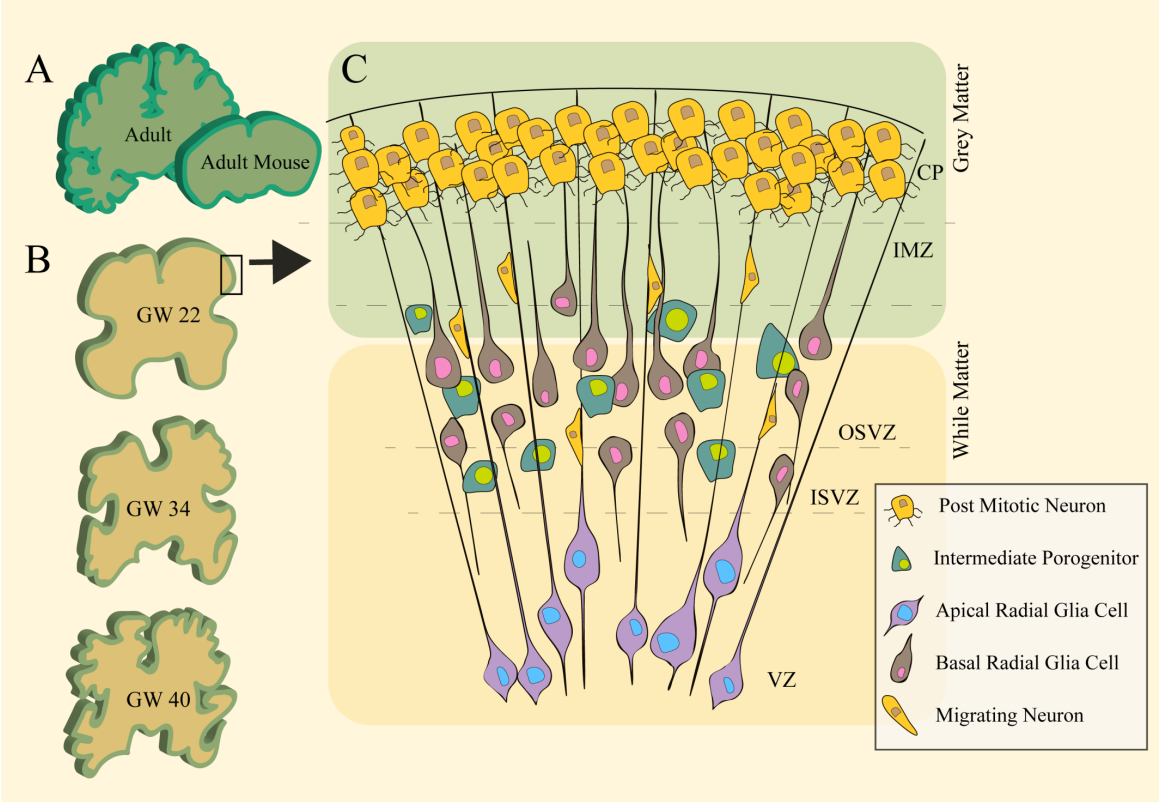

Figure 1. *Corticogenesis in the foetal human brain. A. Schematic gyrencephalic adult human brain and the smooth mouse brain (not drawn to scale). Images adapted from (Tallinen et al., 2016) and. B. folding initiates approximately at gestational week 22 and intensifies onward. C. After NECs initiates asymmetric division, daughters aRGCs form the ventricular zone (VZ) and give raise to additional progenitors such as the IPs, bRGCs and post-mitotic neurons. In humans, the subventricular zone thickens and separates in into the inner subventricular zone (ISVZ) and the outer subventricular zone (OSVZ). aRGCs and bRGCs populate these layers and provide scaffolds for the migration of post mitotic neurons. These reach the cortical plate (CP) through the intermedia zone (IMZ) and populate it in an inside out manner. Image adapted from (Florio et al., 2017).*

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Tallinen et al. tested the idea that tangential expansion of the outer cortical layer in animals with increased cortices creates a compressive stress in relation to its underlying structure, leading to the characteristic cortical wrinkling (Tallinen et al., 2014a; Tallinen et al., 2016). Based on MRI data they constructed a soft hydrogel swelling model with an inner structure mimicking the white matter, and above it a thinner surrounding gel layer. When water allowed swelling of both the outer and inner layer, differential swelling in these constructs produced wrinkling of the outer gel layer, with folds patterns which closely resembled that in the human brain. Furthermore, gyrification-like marks generated over time impressively emulated the structural order in which the folds occur, suggesting that gyrification may be a physically imposed feature. Be that as it may, the modelled differential swelling of the hydrogel to form folds brings about the questions as to what are the molecular components that provide gyrencephalic cortices these physical and mechanical characteristics?

The Extracellular Matrix (ECM)

The idea of an interplay between physical characteristics and biological structure and functionality is a well-established one (Holle et al., 2018). Computation models had not once unravelled forces generated by cells, imposed on them, and that of the ECM surrounding them. Mechanobiology thus proposes a handy approach to understand biochemical and cellular processes constrained by forces they bear and encounter, as demonstrated by the swelling hydrogel model. Albeit the importance of gyrencephalic specific cell lineage proliferation is well appreciated, transcriptomics data highlighted the conceivable role of the ECM in bringing the biomechanical and cellular pieces together. In a seminal paper, Fietz et al. (2012) set themselves to map differentially expressed (DE) genes across each germinal zone of the developing human, compared to that of the mouse (Fietz et al., 2012). The analysis revealed that the most enriched DE genes across the human cortical layers, but not the mice, were related to cell-ECM interactions, ECM secretion pathways, and their corresponding receptors. With regards to the increased proliferation in the human cortex, a cross layers comparisons indicated that the ISVZ and OSVZ maintained expression patterns of the proliferative VZ. The ECM, it is here suggested, presents an only little studied array of functional structures which could tie together the molecular and mechanical processes in gyrification.

The ECM is commonly composed of water, proteins and polysaccharides, yet its precise configuration differs dramatically across tissues. Its composition in both developing and mature structures is constantly remodelled, degraded and secreted by numerous types of cells and enzymes, and its role as a source of growth factors and signalling in morphogenesis, migration, and proliferation is increasingly appreciated. Changes in ECM during development could have a profound impact the physical and cellular architecture of the cortex (Acharya et al., 2014; Barros et al., 2011; Dityatev et al., 2010; Haque et al., 2010; Kim et al., 2016; Lu et al., 2011; Schwartz, 2010).

In brief, ECM molecular members include glycosaminoglycans (GAGs) and proteoglycans, collagens and non-collagenous glycoproteins (Figure 2). GAGs are unbranched polysaccharides consisting of units of a hexosamine and a uronic acid. They possess unique electrostatic properties which provide them with an osmotic pressure; and their negative charge draws water, leading to the swelling of the interstitial spaces in which the GAGs are localised. Among the GAGs most relevant to the developing cortex is the Hyaluronic acid (HA) molecule, which is the only unsulfured GAG (Fowke et al., 2017; Fraser et al., 1997; Long et al., 2018; Miyata & Kitagawa, 2017; Schweitzer et al., 2017; Solis et al., 2012; Toole, 2004; van 't Spijker & Kwok, 2017). Other GAGs form covalent bonds with core proteins and thus form proteoglycans, such as perlecan, neurocan, and aggrecan. These can then form complexes with other proteoglycans, HA, and fibrous proteins, such as collagens, and can regulated molecular motility across the matrix. Finally, considering the highly implicated role of the ECM in dynamic remodelling of biological structures, components that may degrade its structure form an important group. ECM degradation is achieved by proteases called the matrix metalloproteinases (MMPs) and a disintegrin and metalloprotease (ADAMs), with each group consisting of numerous members of overlapping yet specialised targeting capacity (Hummel et al., 2001).

A bridge between the molecular and mechanical: ECM dynamics during cortical folding

With its range of enzymatic and dynamic scaffold agents, the ECM could affect regional mechanical properties such as stiffness, viscosity and density surrounding the cell. Differential expression of the ECM in gyrencephalic animals could help maintain the proliferative capacity certain cell lineages, dictate cellular migratory behaviour, and present a dynamic scaffold with regional-specific mechanical and physical properties.

Past literature supports the idea that genetic programme conserved in gyrencephalic species uniquely introduce pro-mitotic signals that upregulate "progenitogenesis" process in the cortex, and several molecular signals were implicated. FGF signalling, for instance, was found to promote cortical growth by regulating mitotic signals. Interestingly, however, when FGF was overexpressed in lissencephalic animal models it produced an increased brain size (megalencephalic), but not folds (Nonaka-Kinoshita et al., 2013); as was the case of BMP and NOTCH pathways (Reviewed by Fernández et al., 2016; Gaiano et al., 2000; Martynoga et al., 2012). These suggested that the mere increase in the cellular pool was not enough to explain the pressures involved in the folding, and other factors must be involved. However, other studies which looked at changes in the pool of progenitors and their cell cycle could demonstrate folds in mutant mouse brains, for example, with overexpression of beta-catenin (Chenn & Walsh, 2002). An abnormal

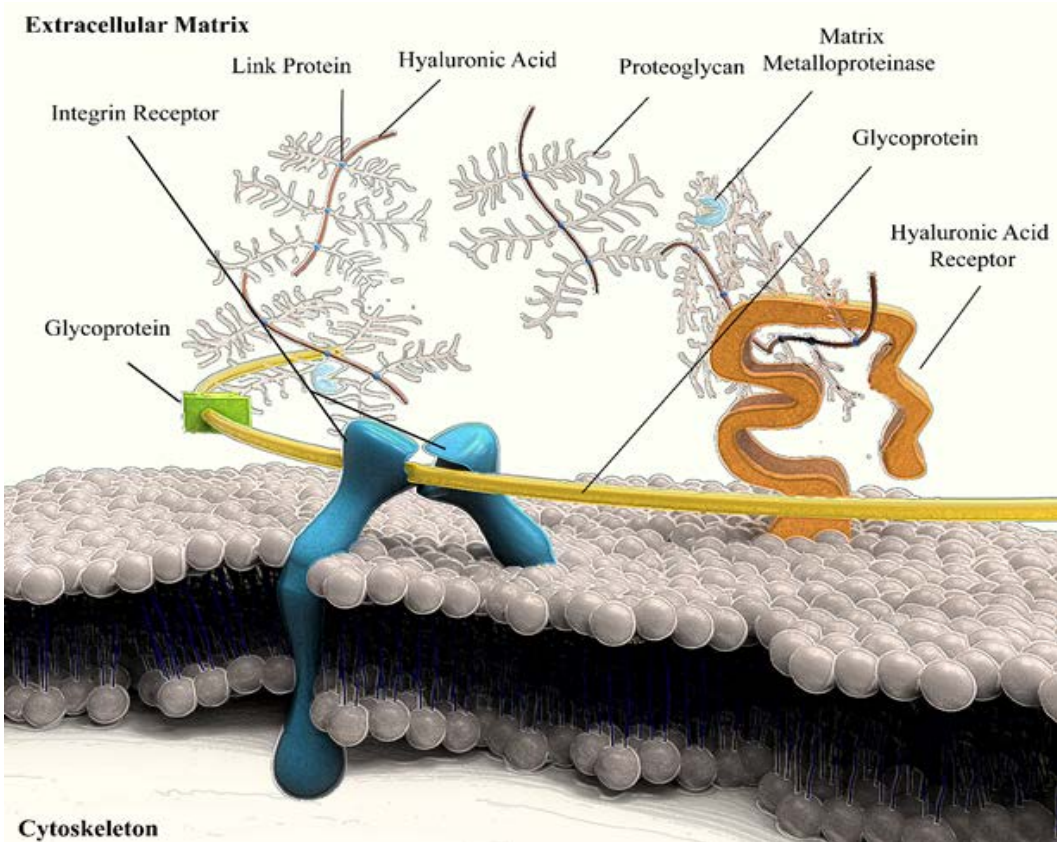

***Figure 2**. Illustration of Extracellular Matrix (ECM) molecules. The ECM is primarily composed of GAGs such as the HA and proteoglycans; with form covalent bonds with GAGs to produce a range of protein complexes. Integrins are membrane embedded receptors which could bind to different ECM compounds, such as collagens and fibronectins, growth factors, laminins, and more. The two main HA receptors are the CD44 and CD168. ECM molecules may be degraded via MMPs which maintain dynamic and responsive environment in the matrix. The extracellular composition of the ECM molecules, as well as their interaction with cells via various receptors, together generate both scaffolds and the signals which in turn could initiate downstream changes in the cell.*

increase in brain size and malformed structures were also observed when programmed cell death was prevented as in case of Caspase 9 deficient mice (Kuida et al., 1998). In addition, overexpression of mutant PTEN in human brain organoids resulted in folds, however such folds were not observed in mouse organoids with the same mutation (Li et al., 2017b). Alternatively, studies have looked at proliferation in specific cell lineages featured in gyrencephalic species (Lewitus et al., 2013; Reillo et al., 2011). By examining progenitors directly associated with the tangential dispersion of radially migrating neurons, such as those identified in the OSVZ, some molecules were found to be involved in the increase of both bRGCs and gyrification. For instance, down-regulation of Trnp1 lead to an increase in IPCs and bRGCs, and notably, an expansion in both surface area and folds of the mouse's cortex (Stahl et al., 2013), and over overexpression of ARHGAP11B elicited large pool of bRGCs accompanied by the emerges folds in the mouse brain (Florio et al., 2015). Nevertheless, how the increase in bRGCs allows for the differential organisation of the cortex remained unclear.

Cell-ECM interactions, may play a role in the precise configuration at which the increased cellular pool is preserved and organised. Reelin is an ECM molecule which has known roles in brain structure (reviews (Folsom & Fatemi, 2013; Honda et al., 2011; Reiner & Sapir, 2005; Sekine et al., 2014). It regulates neuronal migration, and its absence in humans results in lissencephaly (Hong et al., 2000). However, so far it has not be studied from a biomechanics point of view. One of the major groups of ECM regulators are integrins, that are a group of membrane-imbedded receptors which exist in wide variations and can form above 20 different receptor specificities for ECM ligands. By interacting with both ECM and cell surface molecules, integrins can regulate intracellular signal transduction cascades which result in a change to their singling responsiveness, cytoskeleton interactions, and transcription, to name only a few (For a detailed review see Schmid & Anton, 2003). For example, among the α integrin units, $\alpha 6$ is highly expressed in both the VZ and cortical plate (CP), and its full knockout lead to abnormal organization in both the CC and retina of the mouse and alterations in laminar deposition (Georges-Labouesse et al., 1998). Interestingly, Fietz and her colleagues reported that progenitors of the OSVZ retained integrin mediated processes with the basal epithelium in developing ferret cerebral cortex (Fietz et al., 2010). When integrin functionality was interfered, the proliferative capacity of bRGCs was lost, suggesting that mitotic cues provided by the SVZ can be sensed by lineages of distal localisations. Alternatively, it could be argued that integrin-mediated connectivity of OSVZ cells maintain

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their proliferative capacity, at least partially, by exposure to mechanical properties presented by the SVZ.

While an increased cellular pool could support an increase in the upper swelling, another elegant solution is that the expansion at upper layers is achieved via the expression of hydrophilic ECM component before migrating cells have reached their destination. Such process was demonstrated by a recent study showing that the mere exposure of human tissue to specific ECM-related molecules elicited gyrification and was accompanied by alterations to the physical properties of the tissue. Based on existing databases, Long et al. identified the differentially expressed (DE) proteins HAPLN1, LUM, and COL1A2 (collectively termed HLC) as the ECM components most prominently involved in human neocortical expansion (Long et al., 2018). Overexpression of the HLC nearly doubled the gyrification index value in both native foetal human cortical tissues in organotypic slices and, to a lesser extent, in free floating explant cultures. This consequence was not accompanied by any increase in proliferative signals or increased cell population. The study then presented a series of shrewdly designed tests which pointed several noteworthy findings. First, explants derived from ferrets and mouse were not sensitive to the HLC treatment, suggesting that structural changes in response to ECM components required a complementary mechanism unique to humans, rather than that shared with all other gyrencephalic animals. Second, in agreement with mathematical models demonstrating that cortical thickness imposes folding architecture, the authors reported that HLC treatment in thicker CP of the 22-gestational week yielded significantly larger intergyral distances as compared with the thinner CP of the 11-16GW. Finally, CP measurements in treated samples revealed an increase in stiffness prior to the formation of the folds. Further manipulations suggested that the stiffening required a regional accumulation of hyaluronic acid (HA) in the CP. This study suggests that, in addition to its possible role in the expansion of the human cortex and cell lineage specification, the ECM can promote pressures that lead to gyrencephalic arrangement of the cortical tissue. Furthermore, accumulation of HA at the CP could provide a sound explanation as to the increase in swelling of the tissue described in gel models. While evidence for in vitro synthesis of HA in neural progenitors of the rat do exist (Fowke et al., 2017), data exploring genetic programmes of HA synthesis using in vitro human brain models could provide fruitful information about its role in gyrification.

Data recoded by Long et al. raised yet another query as to how progenitor cells may react to the physical alterations generated by stiffening of the CP or other layers. Dynamic pressures introduced by the ECM may be processed by cells via mechano-transduction to elicit biological responses in the membrane, cytoskeleton or the nucleus itself (Miron-Mendoza et al., 2010; Raab & Hancock, 2008). Studies looking at cell-ECM interaction indicated that the sole change in substrate stiffness may affect stem cell lineage commitment (Holle et al., 2018). For instance, Engler and his colleagues famously demonstrate that mesenchymal stem cells (MSC) lineage specificity was widely attentive to the level of tissue elasticity; wherein soft matrix mimicking brain tissue promoted neural progenitor differentiation, whereas a stiffer muscle-like structure produced myogenic cell differentiation (Engler et al., 2006).

Cell migratory behaviours were also shown to be regulated by differential physical preference. In specific, different cell lineages show a particular "stiffness optimum" at which they undergo their maximal motility. This value can be shifted by inhibition of molecular motors and integrin mediated adhesions (Bangasser et al., 2017). The importance of maintaining an adequate neural migration patterns in gyrification was highlighted in numerous studies. For instance, ablation of the cell adhesion molecules fibronectin leucine rich-repeat transmembrane protein (FLRT) 1 and FLRT3 lead to macroscopic cortical sulci in mice. While there were no markers of cell amplification, a discounted intercellular adhesion resulted in faster neural migratory patterns, supporting idea that the rates by which cortical swellings occur could either promote or depress formation of cortical folds (del Toro et al., 2017). Importantly, one of the implicated genes in the smooth brain disorder lissencephaly, the LIS1 gene, is known to have a substantial influence upon the molecular motor dynein, which is widely involved in migratory pathways of the brain. Based on the above, it could be of interest to examine whether LIS1 -/+ mutated cells with an altered dynein behaviour would possess an abnormal stiffness optimum. Likewise, further investigations are required to delineate whether specific cortical progenitors hold their own stiffness optimum, and whether such preferences could coincide with the tangential segregation of the gyrencephalic cortex.

Finally, modelling ECM dynamics across the development of the human cortex could be achieved in new method recently developed by Karzbrun et al. (2018). The paper introduced a 3D miniature brain organoids device called on-chip organoids. The on-chip organoids are limited in thickness, and thereby conform to microscopic limitations and allow live imaging of hitherto obscure developmental events. Using this model, our group could test the mechanical observation produced by previous hydrogel model through biomechanical means. Crucially, the study was able to demonstrate folding in the on-chip organoids, but also a drastically reduced folding patterns in organoids with a LIS1-/+ mutation. Examining downstream consequence of the mutation, transcriptomics indicated that the ECM was the group most affected by manipulation. But what exactly are the mechanical events which could have been mediated by the ECM in healthy organoid and became abnormal in the mutation? We further studied the relationship between material and tissue wrinkling by searching tissue instability phases during the development of the organoids (Karzbrun et al., 2018). We proposed that two opposing forces are involved in generating the typical folds; preferential growth in the periphery which is, in part, due to cell cycle dependent nuclear swelling during the INM; and cytoskeleton contractility in the core, which is based on the adhesion

between the end-feet of the radial glia cells. The preferential growth in the periphery was substantiated by measurements of the nuclear area and kinetics of the INM indicated an increased swelling of nuclei in the outer region of the organoid. The contraction at the core was supported using a range of manipulations at the cytoskeleton contractility levels. Continued cytoskeletal contraction produced stiffness at the core, while long-term contraction inhibition yielded a smoother outer surface driven by a softer core. Laser microdissection separating the inner and outer parts of the organoids, as well as short-term pharmaceutical treatments lead to both the condensation of the outer region wherein nuclei positioned (decrease in the height), while promoting a considerable swelling of the inner surfaces. This suggests that non-uniform swelling of and density of both layers work under mutual compressions. Hypothetically, a process that could promote the integrity of layer tension are the MMPs and their regulators ADAMs presented formerly, which together regulate ECM segregation dynamics throughout the body. Among the DE genes in LIS1-/+ and control organoids, the ADAMTS18 were shown to have an increased activation in early day of the mutated organoid, and at significantly lower proportions at later developmental stage. Where precisely the gene expression was introduced is left to be established; however, ECM proteolytic events could affectively change contractility introduced by the outer and the inner core to manipulate swelling behaviours.

Summary

The main aim of this review was to put together evidence from both molecular, cellular, and mechanical evidence that highlight the little examined role of the ECM in the process of cortical gyrification. Current literature indicates that efforts to delineate the uniquely formed OSVZ in gyrencephalic animals should proceed, and a comprehensive interrogation as to the proliferation and migration of neuronal progenitors must be pursued. Notwithstanding, accumulating evidence highlight the need to characterise the forces, signals, and dynamic remodelling introduced by the ECM over corticogenesis and gyrification. Models of gyrification, albeit controversial in times, are constantly improved, and now include gyrencephalic animal models such as in the ferret and lower primates. Importantly, increased improvements to organoid models in which the human brain development can be examined in health and disease are invaluable in understanding specific human gyrification processes. These together introduce novel techniques by which biological processes form and respond to physical and mechanical considerations. Deciphering of the three dimensional relationship between ECM dynamics, cellular behaviour, and physical properties they promote in the developing tissue would highly facilitate our understanding of neurodevelopment processes in healthy and diseased brains.

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