GROWTH PATTERNS IN THE DEVELOPING HUMAN BRAIN DETECTED USING CONTINUUM-MECHANICAL TENSOR MAPPING

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ABSTRACT

We report the first, spatially-complex, 4-dimensional quantitative maps of growth patterns in the developing human brain, detected with a tensor mapping strategy that provides growth pattern information with greater spatial detail and sensitivity than previously obtainable in brain imaging studies. By repeatedly scanning children (age: 3-15 yrs.) across multi-year time intervals (up to 4 years), a rostro-caudal wave of growth was detected at the *corpus callosum*, a fiber system that relays information between brain hemispheres. Children aged 6-15 consistently displayed a localized peak of rapid growth at the callosal *isthmus*, which innervates temporo-parietal cortices that primarily support associative thinking and language function. Growth rates at the isthmus were attenuated after puberty. An opposite dynamic pattern was found between ages 3 and 6, with most rapid growth in frontal and pre-frontal callosal networks that regulate the planning and organization of new actions. Rates and profiles of tissue growth, elimination, shearing and dilation are visualized in 3 dimensions, revealing the magnitudes, gradients and principal directions of growth throughout the dynamically changing brain. Focal growth of the callosal *isthmus* and its temporo-parietal projection fields contrasted sharply with a rapid, spatially-localized loss of gray matter in subcortical systems. Dynamic brain maps therefore offer a powerful new means to (1) map growth patterns in an individual child, and (2) gain insight into the complex dynamic processes that affect regional anatomy in the healthy and diseased brain.

Introduction

The dynamic nature of growth and degenerative disease processes mandates the design of sensitive strategies to detect, track and quantify structural change in the brain in its full spatial and temporal complexity [1]. We report the creation of the first, high-resolution, 4-dimensional quantitative maps of growth patterns in the developing human brain. Both regressive (tissue loss) and progressive (tissue growth) processes are characterized, with a strategy that allows growth patterns to be mapped in an individual child. By repeatedly scanning the same children (aged 3-15 years) across very short and very long time-spans (2 weeks to 4 years), a rostro-caudal wave of growth was detected at the *corpus callosum* (Fig. 1). Peak growth rates in regions of the *corpus callosum* that connect linguistic and association cortices of the two brain hemispheres were found consistently after the age of 6. These foci of fastest growth were similarly localized, but attenuated, after puberty.

Continuum-Mechanical Tensor Maps. Time-series of high-resolution 3-dimensional magnetic resonance imaging (MRI) scans were acquired across large time-spans from young normal subjects (ages: 3 to 6; 6 to 7; 7 to 11; 8 to 12; 9 to 13; and 11 to 15 years) at intervals ranging from 2 weeks to 4 years. Next, pairs of scans were processed to determine patterns of structural change across the interval between the two scans. A battery of specialized 3D

image registration [2], intensity-correction [3] and pattern recognition [4] algorithms were applied to mutually align the scans for further processing. Registered scans were histogram-matched (i.e. their intensity distributions were equalized). Next, an image matching algorithm [5,6,7] was used to compute a 3D elastic deformation vector field [5,6,7], which reconfigures the anatomy at the earlier time-point into the shape of the anatomy of the later scan. From this transformation, local rates of tissue dilation, contraction and shearing were calculated. The biological validity of the resulting anatomical transformation was guaranteed by forcing a large system of anatomical surface boundaries to match exactly. These included multiple structural, functional, and tissue type boundaries in 3 dimensions, including the callosum, caudate, cortex and ventricles ([6,8]; see Figs. 2-6). Deformation processes recovered by the image matching algorithm were then analyzed mathematically with vector field operators [7] to produce a variety of *tensor maps* (Figs. 1-4, 6(e),(f)). These maps reflect the magnitude and principal directions of tissue dilation or contraction, and the local rates, divergence and gradients of the growth processes detected in the dynamically changing brain. The resulting growth maps reveal striking systematic trends (Fig. 1), as well as directional biases in the profiles and local characteristics of growth and tissue loss.

Growth Patterns. Maps of local growth rates (Figs. 1-4, 6(e),(f)) revealed the complexity and regional heterogeneity of tissue growth, pruning and maturation, even at this comparatively late period of brain development. In subjects scanned at the ages of 6 and 7, 7 and 11, 8 and 12, 9 and 13, and 11 and 15, highest growth rates were consistently attained in temporo-parietal systems which are functionally specialized for language, and for understanding spatial relations (Fig. 2). In contrast to the near-zero maps of change recovered at short time intervals (2 weeks; Fig. 3, *lower panel*), growth maps spanning large time intervals (4 years; Fig. 2, and Fig. 3, *upper panel*) showed complex and heterogeneous patterns of change. For example, in one subject scanned at ages 7 and 11 (Fig. 2, *top panel*), comparative stability of splenial and rostral fiber systems of the *corpus callosum* contrasted sharply with rapid focal growth at the callosal *isthmus* (up to 80%). Although global measurements indicated an overall 22.4% increase in mid-sagittal callosal area during the 4-year time-span (from 527.6 mm^2 to 645.6 mm^2), these global values disguise the complexity of local growth patterns. Local growth is as high as 80% (Fig. 2, *top panel*), a feature which may not be apparent with conventional volumetric descriptors.

Foci of Fastest Growth. A focus of extreme growth at the callosal isthmus was detected consistently in the other subjects tracked between 6 and 15 years (Fig. 2). In a girl scanned exactly one year apart aged 6 and 7, extreme growth (up to 85%) at the callosal isthmus contrasted sharply with a comparatively quiescent region in the more rostral systems that innervate frontal and pre-frontal cortex. Although a degree of individual variation was expected in the dynamics of growth, the isthmus provided a localized and consistent focus for the fastest growth at these ages. Intriguingly, when a 4-year growth map was generated for a slightly older child (11-15 years, *bottom panel*), growth rates were correspondingly reduced in every region. Nonetheless, growth patterns at the isthmus and splenium (commonly defined as the posterior fifth of the callosum) were still more rapid than in the more rostral callosum. Peaks of 20-25% growth locally contrast with near-zero change in the *rostrum* and *genu*. In an analysis of gray matter at the cortex [9], we recently observed a localized gray matter loss in frontal cortex that persists in normal subjects throughout adolescence even into adulthood. Gradual quiescence of growth at the rostral callosum around puberty may therefore be a precursor to a prolonged regressive process of gray matter loss through adolescence into adulthood in the frontal circuits it innervates.

Control Experiments. Several near-zero maps of change were recovered at short time intervals. Fig. 3 shows typical maps from a subject scanned at age 8, and exactly 4 years later at age 12. The same subject was then scanned once again 2 weeks later (aged 12). Negligible change at short time intervals (Fig. 3, *lower panel*) contrasted with a highly heterogeneous map of growth across the 4 year time-span (Fig. 3, *top panel*). Growth rates again achieved their highest rates in the associative and linguistic networks that cross at the callosal isthmus.

To expand the age range covered (Fig. 1), a subject was scanned at age 3 and exactly three years later aged 6, and growth patterns were mapped (Fig. 4). A focus of peak growth rates (60-80% locally) was found throughout the anterior *corpus callosum*, in the frontal circuits that help to sustain a vigilant mental state and regulate the organization and planning of new actions. The extremely rapid rates of local growth are consistent with metabolic studies using positron emission tomography [10], which show an extraordinary doubling of the rates of glucose metabolism in frontal cortex between the ages of 2 and 4, with frontal metabolic rates remaining at 199% of their adult values throughout the 3-8 year age range. Between the ages of 3 and 6, when language function and associative thinking are not yet fully developed, growth rates at the isthmus were more quiescent (Fig. 4; 0-20% growth). The later patterns of growth in the isthmus, however, were found consistently in all subjects in the 6-15 age range, and may reflect fine tuning of language functions known to occur late in childhood.

Lobar, Ventricular, and Caudate Patterns. To better understand whether regressive processes (tissue loss) could be mapped at the same time as rapid growth, maps of additional systems were made. In the 7-11 year old subject (Fig. 2, *top panel*), maps of lobar growth spanning the same time period (Fig. 5(a)) revealed relatively pronounced (2-6 mm) temporo-parietal and pre-frontal enlargement. A similar pattern was found in the 9-13 year old subject (Fig. 5(c),(d)). Somatosensory, motor and occipital brain regions were comparatively stable, with near-zero maps of change in all brain regions at short time intervals (2 weeks; Fig. 5(b)). Up to 50% *loss* of tissue volume was detected at the caudate head (Fig. 6(e), (f)). This tissue loss was highly-localized, and contrasted with a 20-30% growth of the adjacent internal capsule, for which a separate surface model was made, and a 5-10% dilation of the superior ventricular horn. Gross volumetric measures confirmed an overall 60 mm^3 tissue loss at the caudate head, although these global measures disguise the regional complexity of the change. This example helps illustrate how tensor maps distinguish local growth patterns (Fig. 6(e)) from bulk shifts, such as global displacements of the adjacent cerebral ventricles (Fig. 6(a),(b)). 3D vector displacement maps (Fig. 6(b),(d)) emphasize that both global and local displacements may be required to match modeled anatomical elements across time. The 3D deformation field, however, encodes the patterns of local anatomical dilation and contraction, and its values are unaffected by global displacements. Maps of local 3-dimensional growth are therefore not critically dependent on how well scans are initially aligned, and can define growth at arbitrary 3D points in the local anatomy (Fig. 6(e)). Figure 6(f) indicates the anatomical context and regional complexity of the growth and regressive processes in the time-span covered by the scans. The foci of tissue loss corroborate the hypothesis that pruning processes occur during this developmental stage [11], and suggest that these processes can be tracked in an individual child.

Discussion. In this paper, we report the detection of striking and spatially complex patterns of growth and tissue loss in the developing human brain. A rostro-caudal wave of peak growth rates (Fig. 1) was identified in

the *corpus callosum*, with several surprising characteristics. Fiber systems that mediate language function and associative thinking grew more rapidly than surrounding regions across time spans before and during puberty (6 to 7, 7 to 11, 8 to 12, and 9 to 13 years), and were found to be attenuated shortly afterwards (11 to 15 years; Fig. 2, *bottom panel*). Detailed maps of these processes reveal fine-scale directional patterns in the rates of anatomical change, as well as regional biases in the magnitudes, gradients and complexities of growth processes at both the local and systemic levels. In a developmental context, the ability to delineate both the progressive and regressive processes of late development reveals their considerable local complexity and regional characteristics.

The rapidity of tissue elimination in regions of the basal ganglia, while surrounding regions display equally rapid patterns of growth, suggests that the rates of complementary regressive and generative processes are dynamically balanced to maintain the necessary equilibrium in overall cerebral volume. While progressive changes were found in association cortices of the temporo-parietal junction (Fig. 5), regressive changes were found in the caudate head (Fig. 6), suggesting increased processing efficiency in systems that support the programming and execution of learned motor behavior. While an overall equilibrium in growth rates is maintained at the *whole brain* level, prominent foci of rapid growth and tissue elimination can be identified. In particular, the callosal and lobar growth maps (Figs. 2-5) reveal rapid temporo-parietal systemic growth. This suggests that even during the relatively late developmental phase of 6 to 15 years of age, different cortical fiber systems differ substantially in the rates of the myelination processes that serve to accelerate neuronal signal transduction [12].

Callosal growth exhibits surprising temporal complexity: a massive perinatal *loss* of callosal axons, lasting from the 35th gestational week to the end of the first post-natal month [13,14] leads to a restricted pattern of callosal connections [15], with a topographically specific organization of callosal fibers in relation to the cortical regions they connect. Anterograde tracer studies indicate that perisylvian fibers from superior temporal and parietal cortex, which relay information from critical language and association areas, cross mainly in the *isthmus* (Figs. 2, 3). Fast-conducting, large diameter (>3 μm) fibers are concentrated in the posterior midbody and isthmus, while slower-conducting, thinner, and more lightly myelinated fibers are found at the *genu* [16], connecting pre-frontal regions implicated in maintaining mental vigilance, and in the regulation and planning of new actions. Rapid growth in temporo-parietal systems (Figs. 2, 5) suggests that cortico-cortical networks supporting rapid associative relay and language functions may myelinate more extensively [12] and over more prolonged periods than rostral fiber systems, with a growth spurt that spans the 6 to 15 year age range (*cf.* Fig. 2, *all panels*). Intriguingly, the age range where growth rates are markedly increased in linguistic regions of the callosum (6-13 years) also appears to be followed by a period where growth rates are drastically reduced (11-15 years; Fig. 2, *bottom panel*). This temporal pattern may coincide with the ending of a well-known critical period for learning language, which has been consistently noted in studies of second-language acquisition, including sign-language, and in isolated children not exposed to language during early development (reviewed in [17]). These studies have shown that the ability to learn new languages declines rapidly after the age of 12, as does the ability to recover language function if linguistic areas in one brain hemisphere are surgically resected. Peak growth rates in linguistic regions of the callosum, as well as their attenuation around the age of puberty, may reflect the conclusion of critical period for the learning of language.

Although the callosal *isthmus* carries fibers that project to Wernicke's language area and the parieto-temporo-occipital

junction, it also innervates regions of temporal and parietal association cortex that are implicated in our understanding of spatial relations, as well as in abstract mathematical thinking. We recently found that the same temporo-parietal fiber system, crossing at the callosal *isthmus*, degenerates most rapidly in early-stage Alzheimer's Disease [18], providing corroborative evidence for an early atrophic phase when progressive neuronal loss and perfusion deficits are most marked in temporo-parietal association cortices and their commissural projection systems. Consequently, associative networks which exhibit the latest growth spurts developmentally may be among the first to degenerate in dementia. Whether or not this is the case, the developmental age range examined here is likely to be a critical period for the acceleration of signal transduction in the networks that support both associative thinking and language function.

Convenient recovery of dynamic and spatially-detailed 3-dimensional measures of dilation, contraction or shearing of anatomic regions, including information on local growth rates and their directional characteristics, may offer a powerful framework to analyze and monitor the complex patterns of structural change during brain development and dynamic disease processes. Spatially complex maps of anatomical change may offer advantages in tracking the effects of therapeutic interventions in patients with tumor growth, dementia, active lesions, and traumatic brain injury. The ability to map the local dynamics of growth in an individual child may be advantageous in both scientific and diagnostic settings. These approaches will be applied to wider normative subject and patient populations to generate powerful quantitative descriptors of developmental and disease processes, based on increasingly sensitive imaging strategies, and based on dynamic rather than static criteria.

Methods

3D ($256^2 \times 124$ resolution) T_1-weighted fast SPGR (spoiled GRASS) MRI volumes were acquired from young normal subjects (mean age: 8.6±3.1 yrs.) at intervals ranging from 2 weeks to 4 years. For each scan pair, a radio-frequency bias field correction algorithm was applied to both scans to eliminate intensity drifts due to scanner field inhomogeneity. The initial scan was then rigidly registered to the target using automated image registration software [2] and resampled using chirp-Z (in-plane) and linear (out-of-plane) interpolation. Registered scans were histogram-matched and a preliminary map of differences in MR signal intensities between the two scans was constructed. These difference maps help to determine whether structural change has occurred in dementia [1], and can support calculations of cerebral volume loss [19]. Using difference maps as a first step, more complex tensor models of structural change, computed here, map local patterns of differences or change in 3 dimensions, but also calculate rates of tissue dilation, contraction and shearing. To facilitate this, a high-resolution surface model of the cortex was first automatically extracted [4] from each of the mutually registered histogram-matched scans. 3D digital anatomical models, based on parametric surface meshes [5,6], were then made to represent a comprehensive set of deep sulcal, callosal, caudate and ventricular surfaces at each time-point [7]. Surface models based on manually-digitized data were averaged across multiple trials (N=6) to minimize error [8]. These model surfaces provided anatomic constraints for an elastic image registration algorithm [5,8]. This algorithm calculates a 3D vector deformation field, with $384^2 \times 256 \times 3 \approx 0.1$ billion degrees of freedom, which reconfigures the anatomy at the earlier time-point into the shape of the later scan. Landmark points, surfaces, and curved anatomic interfaces were matched up in the pair of 3D image sets. The deformation field required to match the surface anatomy of one scan with the other was extended to the full volume using a continuum-mechanical model based on the Cauchy-Navier operator of linear elasticity [7,20,21]. The resulting system of 0.1 billion second-order elliptic partial differential equations was solved by successive over-relaxation methods, with multi-grid acceleration [5,7], on a standard radiologic workstation. Artifactual differences which might arise due to differences in how surfaces were parameterized in each scan were compensated for, by using a field of Christoffel symbols to modify the form of the differential operators which act on surfaces during the anatomical transformation [7].

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Figure Legends

Fig. 1. *Growth Patterns in the Developing Human Brain Detected from the age of 3 through 15 years.* A rostro-caudal wave of peak growth rates is detected in a range of young normal subjects scanned repeatedly across multi-year time spans (up to 4 years). In a subject scanned at age 3 and exactly 3 years later aged 6 (*far left*), a striking focus of peak growth rates (60-80% locally) was found throughout the anterior *corpus callosum*, in frontal circuits that sustain a vigilant mental state and support the regulation and planning of new actions. Growth rates at the *isthmus*, where associative fibers cross, were more quiescent (0-20% growth; *far left panel*). Regions of greatest growth are indicated (*red colors*) for each subject, distinguishing them from regions of little or no growth (*blue colors*). In subjects scanned at the ages of 6 and 7, 7 and 11, 8 and 12, 9 and 13, and 11 and 15, highest growth rates were consistently attained at the callosal isthmus, in temporo-parietal systems which are functionally specialized to support associative thinking and language function. Intriguingly, the same topographic pattern of growth is observed in a child scanned at age 11 and then exactly 4 years later aged 15, but growth rates are everywhere reduced (*far right*).

Fig. 2. *Mapping Dynamic Patterns of Brain Development.* Complex patterns of growth are detected in the *corpus callosum* of 5 young normal subjects. The first map (*top panel*) illustrates structural change occurring in the 4-year period from 7 to 11 years of

age. The effects of the transformation are shown on a regular grid ruled over the reference anatomy and passively carried along in the transformation that matches it with the target. The color code shows values of the local Jacobian of the warping field, which indicates local volume loss or gain. Patterns of contractions and dilations are emphasized, revealing their regional character. A strikingly similar pattern was observed in all children scanned, with the callosal *isthmus* as a prominent focus (*red colors*) where highest growth rates were achieved. Note the attenuation of growth rates after puberty, in an 11-15 year old child (*bottom panel*).

Fig. 3. *Mapping Anatomical Change over Very Long and Very Short Time Spans*. The top panel shows the pattern of growth at the *corpus callosum* of a young normal subject scanned aged 8 and again, exactly 4 years later, aged 12. Callosal growth is dramatic, with peak values occurring throughout the posterior midbody. The pattern of growth contrasts with the near-zero maps of change observed between scans acquired over a 2-week interval (*lower panel*).

Fig. 4. *Rostral Growth and its Principal Directions in A Younger Child*. The top panel shows the extreme rates of growth in the anterior *corpus callosum* of a child scanned age 3, and again exactly three years later, aged 6. In view of subject motion, pediatric imaging data (especially longitudinal data) from this age range is extremely rare. Highest growth rates are attained in the frontal and pre-frontal fibers of the *rostrum* and *genu*. These interhemispheric fiber systems transfer information necessary to sustain mental vigilance and support the planning and organization of new actions. The bottom panel shows directional biases in these growth processes. The deformation required to match the anatomy of the earlier scan with the later one is applied to a grid of spheres that are passively carried along in the anatomical transformation. Again, they are color-coded to indicate local volumetric gain. Red colors denote greatest local growth, while blue colors denote minimal change. The growth tensor is the 3x3 matrix of the spatial derivatives (rate of change) of the 3D displacement vectors. Local volume change is the determinant of this matrix; visually this is just the volume of the deformed mesh cells relative to the undeformed volume. The principal directions of change are simply the 3 orthogonal directions where the changes in deformation are greatest. They correspond to the axes of an ellipsoid produced from applying the deformation to a small sphere. These principal directions are seen to vary in different callosal regions, with an outward radial expansion of tissue in rostral regions. Characterization of more subjects will be required to confirm whether this early growth spurt in anterior callosal regions is related to acquisition of completely new skills between infancy and childhood.

Fig. 5. *Patterns of Lobar Growth*. In a subject scanned at age 7 and again exactly 4 years later at age 11, dramatic growth is found in temporo-parietal regions (*red colors*, (a)). All brain regions are stable in a control experiment (*blue colors*, (b)) where scans acquired 2 weeks apart are analyzed. In a 4-year interval for a 9-13 year old subject (c), a similar pattern of diffuse growth is found, most pronounced in temporo-parietal regions. Digital overlay of models of the cerebral cortex at each time-point (*arrows: 9,13, panel* (d)) also indicate growth in temporo-parietal regions. Also notice how growth at the callosal *isthmus* (Fig. 2, in the 7-11 and 9-13 year old subjects) is accompanied by diffuse growth in its (temporo-parietal) lobar projection zones (*panels* (a), (c), (d), *this figure*).

Fig. 6. *3D Patterns of Deep Nuclear Tissue Loss are Detected, and Distinguished from 3D Displacements of the Adjacent Ventricular Surfaces*. Tensor maps of growth distinguish local growth from global displacements of anatomy occurring in the same interval. The 3D patterns of displacement vectors required to match models of ventricular anatomy (a) at an earlier time-point (7 yrs.; *red colors*) with their counterparts at a later time-point (11 yrs.; *yellow colors*), are shown (b), with their magnitude coded in color. Greater displacement at the lateral surface of the occipital horn (*yellow arrows*), contrasts with the stability of its medial surface and caudal tip (*blue colors*). Across the same time interval (7-11 yrs.), 3D displacement vector maps (c,d) show the deformation required to reconfigure models of the caudate head at the earlier time-point into its shape at the later time point. Stability of the caudate tail (*blue colors*, (d)) contrasts sharply with dorsolateral regression of the caudate head and ventromedial progression of the internal capsule. These surface deformations are used to derive a volumetric deformation field (*vectors*, (c)), from which local measures of 3-dimensional tissue dilation or contraction can be quantified (e). In a smaller region selected for detailed analysis (*green square, inset*, (e)), a local 50% tissue *loss* was detected at the caudate head, as well as a 20-30% growth of the internal capsule and a 5-10% dilation of the superior ventricular horn. Visualization (f) of these maps in a convenient graphical format indicates the anatomical context and regional complexity of the growth and regressive processes detected during the period spanned by the two scans.

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