

BRAIN

Imaging the Growing Brain

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Introduction

When does your brain stop growing? A simple answer is: never.

Of course, the most dramatic growth happens in the womb. During the short period of nine months, the initial “mother” cell gives rise to over 100 billion nerve cells, and a brain that weighs about 400 grams when a child is born. As the child learns to walk and talk, her brain continues to grow, reaching the size of 1,200 grams by the time she is four years old; this is only about 200 grams less than an adult. But it does not stop there.

Over the next 10 to 15 years, until the child becomes a young adult, the brain growth continues: it now affects different brain compartments in a slightly different way. For example, the thickness of the different regions of *cerebral cortex* changes between 5 and 18 years of age at different paces, with the regions important for reasoning, planning and social communication maturing last. The white matter containing the pathways that connect the different brain regions continues to mature as well during this period. In boys, the volume of white matter increases sharply during adolescence, perhaps under the influence of the rising levels of the sex hormone, testosterone. In girls, changes in white matter seem subtler and may reflect a process called myelination, by which axons gain additional layers of a fatty substance called myelin, which makes them conduct nerve impulses faster.

What happens next? Does the brain of an adult stop growing? Not really.

It seems that experience continues to shape our brains even in our early 20s. For example, if you are trying to learn how to juggle three balls and you practice every day for two months, the parts of your cerebral cortex that are tracking the moving balls grow. Although we do not know which cells are growing, it is likely that all the additional brain activity in this brain module, specialized for tracking movement of visual stimuli, elicits a cascade of events leading to a structural change in this region. However, this is not permanent – if you stop juggling, it is gone a couple of months later.

Finally, what about the “aging” brain? Does it grow or shrink?

This seems to depend on where in the brain we look and whose brain we look at. For example, older professional musicians playing in an orchestra are possibly gaining, and certainly not losing, grey matter in the *cortical region* that may be engaged repeatedly during their work, such as frequent sight-reading of musical scores. This observation suggests that the brain structure continues to be plastic and amenable to experience even later in life.

How do we know all this? To a great extent, the above knowledge was gained through the use of magnetic resonance imaging (MRI) to visualize the living brain in healthy participants, from infancy, through childhood and adolescence into adulthood. MRI is a powerful non-invasive technique that allows us to take detailed 3-dimensional pictures of the brain in less than 15 minutes. These are then analysed using various computational algorithms that quantify, automatically and precisely, many different features, such as thickness of the cerebral cortex, volume of grey and white matter or properties of major white-matter pathways. The widespread availability of magnetic resonance (MR) scanners and the relative ease of acquiring structural images of the brain makes MR an ideal tool for large-scale studies of brain development and the various factors that may influence it, both in relation to an individual’s genes and her environment. The emerging discipline of “population neuroscience” provides laboratory-based research to the field. Measuring the human brain on a population level allows us to study the complexity of human existence and the circumstances, whether psychological (e.g., early life stress) or biological (e.g., nutrition), under which we grow.¹ I will now describe in more detail the basic principles of MRI, the use of computational tools to quantify the brain growth and a few conceptual issues related to the interpretation of findings obtained with these techniques.

MRI: Basic principles

For imaging brain structure, the most common acquisition sequences include T1-weighted (T1W) and T2-weighted (T2W) image *diffusion-tensor images (DTI)* and magnetization-transfer images (MT). The T1W and T2W images are typically used for quantifying the volume of grey and white matter (both global and regional), and estimating the cortical thickness or other morphological properties of the cerebral cortex, such as its folding. Using DTI and MT imaging, one can assess different properties of white matter, again both globally and regionally. The various features of brain structure that can be extracted from these four types of images are described below. In addition to the above sequences, less common but often even more informative acquisitions include T1 and T2 relaxometry (i.e., measurement of the actual relaxation times)² *magnetic resonance spectroscopy (MRS)*.²

For imaging brain function, the most common MR parameter to measure is the blood oxygenation-level dependent (BOLD) signal. The BOLD signal reflects the proportion of oxygenated and deoxygenated blood in a given brain region at a given moment. A strong correlation between the amount of synaptic activity and regional cerebral blood flow is the reason why the BOLD signal is a good, albeit indirect, measure of brain “function.”³ In the majority of *functional MRI (fMRI)* studies, one measures changes in BOLD signal in response to various sensory, motor or cognitive stimuli. Therefore, only brain regions that are likely to respond to such stimuli can be examined using a given paradigm.

Structural MRI: Measuring the brain growth

As pointed out above, the different acquisition sequences capture various properties of grey and white matter and, in turn, provide a wealth of information that can be extracted from the images using an ever-growing array of computational algorithms. Here I provide an overview of the most common techniques used in developmental studies:

Computational analysis of high-resolution structural brain MR images (typically T1W and T2W images) is used to extract in a fully-automatic fashion two types of measurements: (1) Voxel- or vertex-wise features derived for each X, Y and Z (i.e., three-dimensional) location (e.g., grey- and white-matter “density” maps, cortical thickness, cortical folding); and (2) Volumetric measures (volumes of grey or white matter in particular brain regions, or the area of specific brain structures, etc).

Density maps are generated by (1) registering T1W images with a template brain (e.g., the average MNI-305 atlas);⁴ (2) classifying the brain tissue into grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF); and (3) smoothing the binary 3-D images (i.e., GM, WM and CSF) to generate 3-D maps of GM/WM density. These maps are then used in voxel-wise analyses of age- or group-related differences in GM or WM density.⁵

Cortical thickness can be measured, for example, using FreeSurfer; this is a set of automated tools for reconstruction of the brain cortical surface.⁶ The local cortical thickness is measured based on the difference between the position of equivalent vertices in *pial* and grey/white surfaces. Local estimates of cortical folding can be obtained by measuring, for every point *x* on the cortical surface, the area contained in a small sphere centred at *x*.⁷

The volume of brain tissues (grey matter or white matter) can be estimated by registering images to a labeled template brain on which lobes have been defined traced by an expert. One can then count the number of grey and white matter voxels belonging to a given anatomical region, such as *frontal lobe*.^{8,9} More sophisticated algorithms are often developed to segment small structures with poorly defined boundaries, such as *hippocampus amygdala*.¹⁰

In addition to the density maps and volumetric measurements of white-matter structures, such as the *corpus callosum*, two other techniques are used to evaluate structural properties of white matter: diffusion tensor imaging (DTI) and magnetic transfer (MT) imaging. Using diffusion tensor imaging, one can estimate local differences in the magnitude and directionality (fractional anisotropy) of the diffusion of water in the extra-cellular space around the axons. It is assumed that fractional anisotropy varies as function of structural properties of white matter, such as *myelination* and fiber arrangement of a given white-matter tract.^{11,12}

The magnetization transfer ratio (MTR) is another measure employed for the assessment of white-matter properties; it provides information on the macromolecular content and structure of the tissue.¹³ Given that the macromolecules of myelin are the dominant source of MT signal in white matter,^{14,15} one can use MTR as an index of myelination. Note, however, that myelin is not likely to be the sole factor influencing MTR.¹¹

The above techniques provide a wealth of information about structural properties of the human brain. Work described in the reviews by Durson¹⁶ and Giedd¹⁷ used some of these approaches to chart brain development from childhood to adolescence.

Interpreting brain images

A number of conceptual frameworks have been put forward to interpret some of the findings reviewed above vis-à-vis underlying neurobiology. Unfortunately, the indirect nature of the available measures makes it very difficult to verify the validity of some of these propositions.

Cortical grey-matter and synaptic pruning

It is the case that MR-based estimates of the volume of cortical GM and cortical thickness appear to decrease during adolescence. This has been often interpreted as an indication of “synaptic pruning,” a process by which “redundant” synapses overproduced in the early years of life are being eliminated.¹⁸ The initial evidence for accelerated synaptic pruning during post-natal development came from post-mortem studies by Huttenlocher, who described a decrease in the number *dendritic* spines in the human cerebral cortex during childhood and adolescents.^{19,20} But these studies were limited by the low number of specimens available for the different stages of human development. A more definite evidence of synapse elimination during adolescence was provided by studies carried out by Rakic and colleagues in non-human primates.^{21,22} Using electron microscopy, they observed a dramatic decrease in the number of synapses in the monkey visual cortex during puberty, whether expressed as a number of synapses per neuron or per cubic millimetre of neuropil (unmyelinated nerve fibers) (about a 45% loss). But it is unlikely that this decrease in synaptic density translate into a decrease in cortical volume. Bourgeois and Rakic²¹ commented that “changes in the density of synapses affect very little either the volume or surface of the cortex because the total volume of synaptic boutons ... is only a very small fraction of the cortical volume” and concluded that “... a decline of synaptic number during puberty should have a rather small effect on the overall volume of the cortex.”²¹

If the number of synapses per se is unlikely to change the cortical volume/thickness than what other cellular elements could affect it? As discussed in detail elsewhere,²³ age-related variations in (cortical) grey matter observed in vivo with MRI could be related to the variations in neuropil (60% of the mouse cortex), which consists of dendritic and axonal processes. It is also conceivable that the apparent “loss” of grey matter reflects an age-related increase in the degree of myelination of intra-cortical axons. The higher the number of myelinated fibres in the cortex, the less “grey” the cortex would appear on regular T1-weighted images. Such a “partial-volume” effect could result in an apparent loss of cortical grey-matter.

White matter and myelination

Given the well-documented histology-based increase in the degree of myelination during the first two decades of human life,²⁴ it is perhaps not surprising that any changes in the volume or “density” of white matter revealed by computational analyses of T1-weighted images are attributed to changes in myelination. Again, assumptions based on previous knowledge are influencing interpretation of new data. Quite often, articles reporting age-related changes in myelination have merely measured volumes of white matter. We have shown a clear example of dissociation between age-related changes in the volume of white matter during adolescence and changes in magnetic transfer ratio (MTR), an indirect index of the amount of myelin in white matter.²⁵ Although white-matter volume increased with age during adolescence among males, MTR values decreased, thus indicating a decrease in the amount of myelin in the unit of volume.²⁵ If not increases in myelin, what could be driving the observed increase in white-matter volume during male adolescence? Our tentative answer is that this may be due to changes in axonal caliber. The larger the caliber, the fewer axons fit in the same unit of the imaged volume, producing a relative decrease in the myelination index.²⁶ Although more work is needed to confirm this initial observation, it serves as a reminder that most of the MR sequences from which inferences are often drawn are not specific enough to interpret MR-based findings as reflecting a single neurobiological process, such as myelination.

Brain images and causality

The use of structural and functional neuroimaging provides a powerful tool for the study of brain maturation and cognitive development during adolescence. In addition to the need to keep in mind the many specific challenges associated with the interpretation of structural and functional findings discussed in the previous section, one also needs to be cautious about the general meaning of “brain images.” In particular, we should not confuse a manifestation with a cause.

Observing a difference between children and adolescents in the size (or activation) of a particular structure simply points to a possible neural mechanism mediating the effect of age on a given behaviour; it is not the cause of this behaviour. For example, a stronger activation of the ventral *striatum* during the performance of a reward task by adolescents, as compared with adults, should not be interpreted as causing the adolescent’s reward-seeking behaviour; it merely indicates possible age-related differences in the probability of engaging this structure during this particular task. In this sense, neuroimaging-based assessment should be treated in the same

way, and at the same level, as any other quantitative phenotype describing cognitive, emotional, endocrine or physiological characteristics of an individual. To look for causes of a given behaviour and its higher or lower probability during adolescence, we need to turn our attention to the individual's environment and his/her genes.

Role of genes and environment in shaping the brain

It is clear that both genes and experience influence many structural features of the human brain. In a special issue on genomic imaging, published by Human Brain Mapping,²⁷ a number of articles reported high heritability of regional volumes of grey matter estimated from twin studies carried out in adults, as well as in children and adolescents. At a single-gene level, several previous reports revealed differences between (adult) individuals with different allelic variations in brain morphology.^{28,29}

Findings of genetic influences on brain morphology are often seen as the consequence of a direct effect of the genes on brain structure, perhaps occurring as early as in utero. But it is also possible, in fact quite likely, that these effects are mediated by the different level of functional engagement of given neural circuits in individuals with different genes and experiences. Several studies have confirmed that a repeated (functional) engagement of a particular neural circuit leads to changes in its structural properties, which can be detected in vivo with MR (e.g., in musicians;^{30,31} London taxi drivers;³² bilingual subjects;³³ initially inexperienced jugglers³⁴). Although determining directionality of such structure-function relationships is impossible in the majority of current studies (with the exception of the juggler study), the existing animal experimental literature confirms the possibility of experience impacting brain structure.³⁵

Overall, there is an increasing body of evidence that challenges a simple, deterministic view of genes influencing the brain directly and, in turn, the individual's behaviour. As indicated by a number of studies on the effect of experience on brain structure, MRI-derived anatomical measures may very well reflect a cumulative effect of the differential experience (behaviour) rather than the other way around. This point speaks directly to the issue of biological determinism. Quite often, we view developmental changes in brain structure as (biological) prerequisites of a particular cognitive ability. For example, the common logic assumes that cognitive/executive control of behaviour emerges in full only after the prefrontal reaches the adult-like level of structural maturity. But given the role of experience in shaping the brain, it might also be that high demands on cognitive control faced, for example, by young adolescents

assuming adult roles due to family circumstances, may facilitate structural maturation of their prefrontal cortex. This scenario, if proven correct, will move us away from the passive view of brain development into one that emphasizes active role of the individual and his/her environment in modulating the “biological” (e.g., hormonal) developmental processes.

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