Mapping brain maturation and cognitive development during adolescence

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Non-invasive mapping of brain structure and function with magnetic resonance imaging (MRI) has opened up unprecedented opportunities for studying the neural substrates underlying cognitive development. There is an emerging consensus of a continuous increase throughout adolescence in the volume of white matter, both global and local. There is less agreement on the meaning of asynchronous age-related decreases in the volume of grey matter in different cortical regions; these might equally represent loss (‘pruning’) or gain (intra-cortical myelination) of tissue. Functional MRI studies have so far focused mostly on executive functions, such as working memory and behavioural inhibition, with very few addressing questions regarding the maturation of social cognition. Future directions for research in this area are discussed in the context of processing biological motion and matching perceptions and actions.

Introduction
Adolescence represents a major transition that takes place over most of the second decade of human life. It is the final phase of a prolonged pattern of growth and maturation, which have emerged late in the evolution of our species and may confer an evolutionary advantage by providing ample time for the maturation of the brain and its cognitive apparatus before it reaches the full potential of a young adult (e.g. [1–3]). In the shift from a caregiver-dependent child to a fully autonomous adult, the adolescent undergoes multiple changes in physical growth, physiology, and cognitive and emotional skills. As reviewed in the accompanying article by Steinberg [4], the interface between affect, reasoning and decision making, and action is one of the vital elements in adolescent development. This review focuses on current trends in the use of non-invasive techniques for brain mapping to further our understanding of brain–behaviour relationships during this period of human development. This is the first step towards studying the forces present in the subject’s environment and/or genotype that act on the neural substrate underlying complex behaviours of an adolescent.

Recent technological and conceptual advances have dramatically increased our ability to relate structural and functional maturation of the adolescent brain to that of the adolescent’s behaviour. On the technology side, magnetic resonance imaging (MRI) represents a major advance; it allows us to measure \textit{in vivo} subtle inter-individual differences in brain structure and to assess activity in distinct neural circuits from birth to adulthood. The concept of modular organization of the primate cerebral cortex is, arguably, the most fruitful heuristic framework for mapping function onto structure: distinct areas of the cortex specialize in processing different types of information while sharing it via specific neural circuits (reviewed in [5]). In this context, the importance of neural connectivity for smooth communication across specialized brain regions is increasingly recognized. These technological and conceptual advances go hand in hand. Brain mapping provides accurate localization of structural and functional changes in specialized grey-matter regions, as well as the assessment of structural and functional integrity of white-matter pathways that connect them. Put together with the ‘modular-circuit’ view of the primate brain, we can start mapping maturational changes in brain–behaviour relationships during adolescence.

Brain structure during adolescent development
Over the past decade, structural-MRI studies have provided the first comprehensive picture of age-related changes in the volume of grey and white matter of typically developing children and adolescents. These studies provide T1-weighted (T1W), T2-weighted (T2W) and proton-density-weighted (PDW) images of the brain (Box 1).

Box 1. Structural MRI

Contrast in structural MR images is based on local differences in proton density (PD), that is, in the number of hydrogen nuclei per unit of tissue volume, or in either of the following two relaxation times: (i) longitudinal relaxation time (T1); and (ii) transverse relaxation time (T2). Local differences in relaxation times are reflected in the image contrast because, at a given measurement time, the MR signal has already recovered more in regions with a short T1, or decayed more in regions with a short T2. For this reason, tissue with short T1 (white matter) shows a high MR signal and appears bright on T1-weighted images, whereas tissue with long T2 (grey matter) shows a high signal and is bright in T2-weighted images (for details, see [7]; see also Box 2).
Structural images are colour-coded representations of MR signals measured throughout the brain and localized into individual 3D elements of the brain image (voxels). It is then relatively straightforward to apply computational approaches to quantify a variety of morphometric features using fully automatic procedures (see Figure 1; Box 2; reviewed in [6]). In this way, one can measure volumes of grey and white matter in the whole brain and its main subdivisions (e.g. frontal lobe), size or volume of well-demarcated brain regions (e.g. corpus callosum or caudate nucleus), variations in the shape of large (e.g. frontal pole) or small (e.g. cingulate sulcus) morphological entities or variations in the cortical thickness. Voxel-wise comparisons of various age (or clinical) groups are used to assess the ‘density’ of grey and white matter.

The application of the various computational approaches to the morphometry of the adolescent brain has already yielded some interesting insights. In the following section, only results obtained in the most recent or large-sample studies are reviewed; more comprehensive reviews can be found elsewhere (e.g. [7–9]).

**Developmental findings: white matter**

Smooth flow of information throughout the brain depends to a great extent on the structural integrity and maturity of white-matter pathways. In the past, this could be assessed only post mortem (e.g. [10–12]). Although histology provides greater specificity vis-à-vis neural elements changing with age (see Box 3), in vivo assessments of white-matter development provide two major advantages over the post-mortem approach: the potential for collecting large samples and for simultaneous acquisition of behavioural data. To date, one of the largest datasets of MR images obtained in typically developing children and adolescents has been acquired at the Child Psychiatry Branch of the National Institute of Mental Health (NIMH); it comprises a combination of cross-sectional (161 subjects) and longitudinal (329 scans)

**Box 2. Computational analysis of MR images**

A typical image-processing ‘pipeline’ (see also Figure 1 in main text) begins with a linear transformation of a T1W image from the acquisition (‘native’) space to standardized stereotaxic space, such as that of the average MNI-305 atlas [66,67], aligned with Talairach and Tournoux space [68]; note that there is a negligible difference in the overall brain size between adolescent brains and those of young adults (23.4 ± 4.1 years) who constitute the MNI-305 atlas. The next step involves brain-tissue classification into grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF); an automatic classification is achieved by combining information from different types of MR images, namely T1W, T2W and PDW acquisitions [69,70]. The tissue-classification step yields three sets of binary 3D images (i.e. GM, WM and CSF). Each of the binary images can be smoothed to generate probabilistic ‘density’ images. These maps are used in voxel-wise analyses of age- or group-related differences in GM or WM density (see [71] for methodological overview). Another important processing step is a non-linear registration of the subject’s image to a template brain; local differences between the subject and the template are captured in a deformation field. The template brain contains information about anatomical boundaries; this anatomical information can be ‘projected’ onto each subject’s brain using the corresponding deformation field and fine-tuned by combining it with the tissue-classification map [67,72]. In this way, the pipeline provides automatic estimates of regional volumes. Another voxel-wise approach has been developed to quantify individual differences in the 3D anatomy of the cerebral cortex. These include estimates of the cortical thickness [73,74] and the quantification of individual differences in the position, depth and length of the cerebral sulci [75].

**Figure 1. Image-processing pipeline. Top row:** A typical image-processing pipeline begins with a transformation of a magnetic-resonance (MR) image from the acquisition (‘native’) to standardized stereotaxic space; this process generates an image that is ‘registered’ with the template brain. The next step involves voxel-wise classification of brain tissue into three main classes: grey matter (in red), white matter (in white) and cerebrospinal fluid (in green). Each of these binary images (0, tissue absent; 1, tissue present) is then filtered (or smoothed) to generate ‘density’ images; the image of grey-matter (GM) density shown here indicates, at each voxel, the local concentration of GM on a continuous scale from 0 to 1 (the ‘hotter’ the colour, from blue to red, the higher the value of WM density). **Bottom row:** Non-linear registration of the sample image to the template brain allows one to characterize local shape differences; the deformation field quantifies such sample-template differences throughout the brain. By combining non-linear registration with tissue classification, one can segment automatically various brain structures, such as the frontal lobe or the amygdala. Other techniques produce maps of cortical thickness or identify sulci in the subject’s cerebral cortex.
Box 3. Frontal cortex in adolescence: decrease of grey matter or increase in cortical myelination?

A single imaged voxel of cortical grey matter contains several cellular elements including neural cell bodies, axons, dendrites, glia and blood vessels. In the cerebral cortex of an adult mouse, electronmicroscopic analyses yield the following relative volumes: axons 29.3%, dendrites 30.2%, dendritic spines 12.06%, glia 9.5%, cell bodies and blood vessels 13.8%, and extracellular space 5.2% [76,77]. Although it is difficult to estimate the contributions of these cellular compartments to the net MR signal obtained with standard T1W, T2W and PD sequences, it is safe to assume that – on average – about 1/3 of the imaged cortical voxels will give a high ‘white-matter’ signal owing to the magnetic interactions with hydrogen nuclei of the lipids present in the myelin sheath. Such intracortical ‘white-matter’ voxels would, in turn, dilute the ‘grey-matter’ signal from other cellular compartments (e.g. glia, cell bodies). This partial-volume effect could bias classification of brain tissue: an increase in intracortical myelinization would lead to an apparent age-related decrease in the volume of cortical grey matter. Although most investigators have attributed the observed decreases in fronto-cortical grey matter during adolescence to synaptic pruning [78], clearly an alternative explanation exists (also discussed in [22]). Post-mortem studies have documented late myelination in various cortical regions, including the frontal and parietal cortex [10,79,80]. It is therefore possible that the adolescent’s frontal cortex is not losing grey matter but rather gaining myelinated white matter. Recent observations by Zilles and collaborators are consistent with this view; using high-resolution MR imaging and post-mortem histological analysis of the (adult) human cerebral cortex, they could explain up to 80% of variance in T1 relaxation times to myeloarchitecture in deep cortical layers (Zilles et al., unpublished observations).

Figure 2. Age-related changes in white-matter density in (a) the internal capsule, and (b) the left arcuate fasciculus. Thresholded maps of t-statistic values are superimposed on axial (capsule) and sagittal (arcuate) sections through the MR image of a single subject. The images depict the exact brain locations that showed statistically significant (t > 4.0) correlations between white-matter density and the subject’s age (n = 111; age 4–17 yrs). Reprinted with permission from [16]. Copyright (1999) American Association for the Advancement of Science.

In summary, the combination of structural MRI with computational morphometry has already proven useful in describing subtle yet consistent changes in brain structure during adolescence. Very little is known, however, about how such variations in structure relate to those in function. The next section addresses this issue.

Brain function during adolescence

The ultimate goal of research in this area is to understand how the human brain implements behaviour throughout the life span. Two general strategies are used to achieve this goal: (1) perturbation, and (2) correlation. Early brain
lesions are the only model of region-specific perturbations used, albeit in a limited manner, in human developmental studies (see, for example, studies of early frontal-lobe lesions and aggression [e.g. (23)]. On the other hand, advances in MRI have opened up seemingly unlimited opportunities for studying brain–behaviour correlations in typically developing children and adolescents. Two groups of ‘dependent’ variables can be used in this context: (1) quantitative morphometric features, and (2) brain activity.

**Brain–behaviour relationships revealed by computational morphometry**

As outlined in the section on brain structure, computational morphometry provides a rich set of quantitative (structural) parameters that can be related to a function of interest in voxel-wise fashion (e.g. grey-matter or white-matter density; Box 1). Using such voxel-wise correlations in healthy adults, Golestani *et al.* have shown a significant relationship between the subject’s ability to learn novel non-native speech sounds and white matter in parietal regions, especially in the left hemisphere (24). Other studies have shown, for example, a positive relationship between the size of the anterior cingulate gyrus and harm avoidance (25), a larger (anterior) corpus callosum in musicians who had begun musical training before the age of 7 years (26), and a positive correlation between calculation abilities and grey-matter density in the left parietal cortex in adolescents born prematurely (27). In the above studies, the investigators could not determine the direction of these structure–function relationships; it is equally probable that a (pre-existing) variation in the structure could influence performance or that a repeated engagement of a given circuit could change brain morphology. Results of a recent study suggest that repeated use of a given structure could indeed lead to a morphological change detectable with computational analysis of structural MR images; a three-month period of juggling practice led to an increase in grey-matter density in the putative motion-processing region (MT/V5) of the temporal cortex (28). Overall, the above studies provide a proof of principle: quantitative morphometric features can be used as a ‘dependent’ variable in studies of brain–behaviour relationships. One of the appealing features of this structural approach is the ability to study several functions of interest in the same individual, quantify them outside the scanner and, subsequently, interrogate the entire brain vis-à-vis possible structure–function correlations.

**Brain–behaviour relationships revealed by functional MRI**

Functional brain mapping allows investigators to measure – in time and space – neural activity associated with particular sensory, motor and cognitive functions. The most common approach is the use of functional MRI; its high spatial resolution makes this technique ideal for determining where in the brain changes in neural activity

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**Figure 3.** Age-related changes in cortical grey matter. Mixed-model regression plots (grey-matter vs. age) at the following regions of interest: A, precentral gyrus and primary motor cortex; B, superior frontal gyrus, posterior end near central sulcus; C, inferior frontal gyrus, posterior end; D, inferior frontal sulcus, anterior end in the ventrolateral prefrontal cortex; E, inferior frontal sulcus in the dorsolateral prefrontal cortex; F, anterior limit of superior frontal sulcus; G, frontal pole; H, primary sensory cortex in posterior parietal cortex; I, supramarginal gyrus (area 40); J, angular gyrus (area 39); K, occipital pole; L–N, anterior, middle, and posterior portions of STG; O–Q, anterior, middle, and posterior points along the inferior temporal gyrus anterior end. x-axis values are ages in years, and y-axis values show grey-matter volumes. Modified with permission from [22]. Copyright (2004) National Academy of Sciences.
Developmental findings: executive functions and language

Structural MRI findings point to a slightly delayed maturation of the dorsolateral prefrontal cortex (Figure 3E). Regardless of whether such age-related changes reflect loss or gain of tissue (see Box 3), one would expect concomitant variations in brain function. Perhaps this is why the majority of developmental fMRI studies have focused on so-called ‘executive’ functions, such as working memory and response inhibition; integrity of the prefrontal cortex determines, to a large extent, performance on such tasks. Figure 4 provides several illustrative examples of developmental changes in the relevant cognitive abilities. Note that for many of the executive abilities, 10-year old children appear to differ significantly from their younger peers but less so from the older ones.

Are these behavioural observations consistent with the fMRI literature? Unfortunately albeit understandably, the initial fMRI studies were carried out using small numbers of children whose ages spanned this possible ‘10-year divide’. For example, compared with adults, children seemed to show higher BOLD response in the prefrontal cortex during the performance of a verbal working memory task ([34], n=6, age 9 to 11 years; [35], n=6, age 8 to 10 yr). In a study of stimulus–response compatibility ([36], n=8, age 7 to 11 yr), children and adults differed in the BOLD response in the basal ganglia and the hippocampal region (children > adults) and premotor cortex (children < adults); also in this study, several significant correlations was found, across all subjects, between performance and BOLD signal. The latter observation raises an important issue addressed in several subsequent developmental studies: what is the primary source of variance – age or performance of the child? In a study of visuo-spatial working memory ([37], n=23, age 7 to 22 yr), age-related increases in the BOLD signal obtained in the prefrontal and parietal cortex remained even after factoring out inter-individual differences in performance. Similar BOLD increases were also observed in these regions during the performance of tasks involving some form of response inhibition, including the Stroop task ([38], n=30, age 7–22 yr), anti-saccade task ([39], n=36, age 8–30 yr), the stop task ([40]; n=17, age 12–40 yr) and, to a certain extent, during the performance of a go/no-go task ([41], n=19, age 8–20 yr; [42], n=32, age 8–33 yr) and the Eriksen flanker task [42].

The fluency data shown in Figure 4 suggest that children should differ from adults in their ability to engage the relevant neural circuits when generating words. Using a classical verb-generation task [43], Schlaggar et al. [44] matched their subjects either by age (children, age 7–10 yr and adults, age 18–35 yr) or by performance, and revealed that the BOLD response was performance-related in the left inferior prefrontal region and age-related in the putative left premotor cortex. Similar findings were obtained in a large sample using the same analytical strategy ([45], n=95, age 7–32 yr); age-related increases and decreases in BOLD response were identified in 40 cortical regions but in only half of these regions did the difference between children and adults remain after matching the subjects’ performance.

Clearly, future fMRI studies of executive functions need to increase statistical power, either by increasing the number of children in each (one-year) age group or by selecting two groups of children on the opposite side of a ‘dividing line’ established in a separate behavioural study. The confounding effects of age-related changes in performance during the scanning must be taken into account; the above language studies demonstrate the importance of this issue. It might also be helpful to move beyond administration of simple tasks, which might not be taxing enough for an adolescent, and examine (executive) functions in a more complex environment, such as under peer pressure [46].

Developmental findings: social cognition

Let us come back to the structural findings. It appears that, during adolescence, brain maturation continues in the fronto-parietal systems and within the superior temporal sulcus (STS). In addition, age-related changes in white matter continue throughout the brain. Some interesting regional differences exist that could be relevant for processes underlying social cognition. For example, post-mortem observations suggest a significant increase in myelination, in late adolescence, of cortico-hippocampal relay pathways [47], and in vivo findings revealed an increase in white-matter density along the occipito-temporal (ventral) visual pathway (Figure 5a; [48]). During adolescence, high demands are placed not only on the executive systems but also on the interplay between cognitive and emotion-related processes. Such cognition–emotion interactions are particularly crucial in the context of peer–peer interactions and the processing of verbal and non-verbal cues. It is therefore of interest to note that the STS contains a set of regions engaged during the processing of non-verbal cues, such as those carried by eye and mouth movements [49], hand movements [50–52], or body movements [53]; that is, regions involved in processing biological motion (Figure 5b; reviewed in [54]). As suggested by Allison et al. [55], feedforward and feedback interactions between the STS and amygdala may be essential for the discrimination of various facial expressions and for the attentional enhancement of the neural response to socially salient stimuli.

Consistent with such an ‘amplification’ mechanism, Kilts et al. [56] observed significantly stronger neural response to dynamic, as compared with static, facial
expressions of anger in both the STS and amygdala. Although the basic aspects of face perception are in place shortly after birth [57], both the quantity and quality of face processing continues to increase throughout adolescence (e.g. [58–60]). Developmental fMRI studies of face expressions are consistent with this pattern. For example, happy but not sad faces elicit significant BOLD response in the amygdala in adolescent subjects ([61], n = 12, age 13–17 yr). Studies of fearful face expressions suggest that an increase in the BOLD signal in amygdala can be detected in adolescents ([62], n = 12, age 12–17 yr) but it appears to be relatively weak ([63], n = 12, age 8–15 yr). These findings are consistent with recent psychophysical data suggesting that children are less able than adults to recognize fear in human faces (Pollak, personal communication).
Overall, it can be said that brain mapping studies of social cognition during adolescence are in their infancy. Results of the above fMRI studies of face processing are consistent with the electrophysiological evidence ([59]; Figure 5c) of continuous maturation of the relevant neural circuitry and, in turn, the adolescent’s ability to extract quickly the relevant cues from, for example, the face of a peer. The use of ‘biological-motion’ stimuli in future fMRI studies of adolescence will be helpful for the assessment of functional maturation of neural circuits underlying non-verbal communication. Similarly, implementation of paradigms built conceptually on discoveries of action–perception matching systems (Figure 5d; reviewed recently in [64,65]) will further our understanding of neural systems underlying processes such as peer pressure and its variations during adolescence and early adulthood (Fig. 2 in [4]).

Challenges and future directions

Adolescence is a fascinating period of human development: the struggle for identity, choice of friends and first sexual partners, academic routes and vocations are but a few examples of complex behaviours that the brain must implement at the brink of adulthood. Today, we have an extensive range of tools that allow us to measure brain structure and function. This review has emphasized magnetic resonance imaging but there are many other techniques, most notably electro- and magneto-encephalography, that are indispensable for studies of brain dynamics during development. So, where do we go from here?

First of all, multi-modality imaging would facilitate our capacity to integrate information about the maturational status of the same system at different levels; for example, we can assess structural maturation of auditory pathways with high-resolution MRI, magnitude of the functional response to specific auditory stimuli with fMRI, and the temporal dynamics of the same system with electroencephalography. Doing all this in the same subject would provide additional power to explain inter-individual variance in a particular behaviour.

Second, we need to know more about the nature of the structural MR signal. As outlined in Box 3, age-related changes in white and grey matter revealed in several MR studies might reflect variations in multiple cellular elements. To move the field forward, it is essential that parallel in vivo and post-mortem studies are carried out in experimental animals to explain what exactly is changing with age. In this context, implementation of novel MR techniques, such as diffusion tensor imaging and magnetization transfer, should go hand-in-hand with their in vitro validation. This is the only way to clarify, for example, to what extent these techniques measure myelin-specific signals.

Third, investigators using fMRI must take steps towards establishing test–retest reliability of this technique and increasing the statistical power of their studies. This will be quite a challenge: the fMRI environment is unusual and the subject’s repeated experience in the scanner might affect the measurements. Increasing statistical power unfortunately translates into increasing cost, and funding agencies will have to meet this challenge.

Finally, having achieved the above (and possibly more), students of normal and abnormal adolescent development will be in an enviable position to embark on research...
attempting to explain pathways leading to brain mapping ‘phenotypes’. They might join forces with social scientists to map the adolescents’ environment and with geneticists to map their genes. They will also work with mental health professionals to reveal pathophysiology of brain disorders that often start in adolescence, including such serious conditions as addiction, depression and schizophrenia. Although many such studies are already under way, their outcomes will depend crucially on meeting some of the challenges outlined above.

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References

14 Pfefferbaum, A. et al. (1994) A quantitative magnetic resonance imaging study of changes in brain morphology from infancy to late adulthood. Arch. Neurol. 51, 874–887
39 Luna, B. et al. (2001) Maturation of widely distributed brain function subserves cognitive development. Neuroimage 13, 786–793
44 Schlaggar, B.L. et al. (2000) Functional neuroanatomical differences between adults and school-age children in the processing of single words. Science 296, 1476–1479
73 MacDonald, D. et al. (2000) Automated extraction of inner and outer surfaces of cerebral cortex from MRI. *Neuroimage* 11, 564–574
80 Kaes T. (1907) *Die Grosshirnrinde des Menschen in ihren Massen und in ihrem Fasergehalt*, Fischer, Jena
82 Paus, T. et al. (1990) Development of an ability to maintain verbally instructed central gaze fixation studied in 8 to 10 year old children. *Int. J. Psychophysiol.* 10, 53–61
88 Watkins, K.E. et al. (2003) Seeing and hearing speech excites the motor system involved in speech production. *Neuropsychologia* 41, 989–994

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